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The clinical diagnosis and management of urinary tract infections in children and adolescents

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ABSTRACT
Urinary tract infections (UTI) are one of the most common and serious bacterial infections encountered by paediatricians and primary care physicians. Although the diagnosis and management of UTI appear simplistic, they remain among the most contentious issues in paediatrics. In part, UTI controversies stem from the absence of classic clinical symptoms, inappropriate urine specimen collection, modified urinary tract imaging recommendations, and diverse treatment and prevention strategies. Recently published guidelines and large clinical trials have attempted to clarify UTI diagnostic and management strategies. In this manuscript, we review the diagnosis and management of acute and recurrent UTI in the paediatric and adolescent populations.

Urinary tract infection morbidity
Urinary tract infection (UTI) is characterised by pathogen invasion and replication in the urinary tract. UTI affects nearly 2% of boys and 8% of girls in the first 7 years of life [1,2]. As a result, UTI is the second most common bacterial infection in children after otitis media [2–4]. In young children, UTI has a peak in incidence in infancy and a second peak in the toddler toilet-training years. The incidence of UTI also increases during adolescence. One in five women will develop a UTI during her lifetime [1,5]. Each year in the United States, children and adolescents diagnosed with UTI account for more than one million outpatient clinic visits, over 500,000 emergency department encounters, and 50,000 hospital admissions [1,6]. Since 2000, the number of inpatient and outpatient encounters for management of UTI has steadily increased [7,8]. In 2013, aggregate hospital charges for inpatient UTI management exceeded US$630 million [9].

Of children and adolescents who develop a UTI, 12–30% will develop subsequent infections [10–12]. Acute UTI can lead to kidney injury, bacteraemia, urosepsis and even death. Complications of long-term UTI include hypertension, proteinuria, renal scarring and renal insufficiency [13]. To date, no treatment strategy has proven effective in preventing UTI sequelae [14]. Moreover, antibiotic resistance in uropathogenic bacteria has been increasing [15–17]. Thus, antibiotics are becoming less effective in preventing and treating UTI [18,19].

Pathogenesis of urinary tract infections
The urinary tract, which extends from the urethral meatus to the kidneys, is considered a sterile environment and resistant to bacterial colonisation. The major defence against invading pathogens is complete bladder emptying during urination. Additional innate defences which prevent UTI include barrier formation by urothelial cells lining the lower and upper urinary tract, the unidirectional flow of urine, urothelial mucous production, alterations in the urinary ionic composition, and the secretion of antimicrobial peptides and proteins that limit bacterial attachment or directly kill invading uropathogens [20–22].

Escherichia coli is the most common bacterial pathogen responsible for UTI and accounts for 85–90% of cases. Uropathogenic E. coli (UPEC) are thought to originate from the faecal flora, spread across the perineum, and invade the bladder through the urethral opening. Bacterial attachment to the urothelium and internalisation are essential in establishing UTI. If UPEC attach to the urothelium and undergo internalisation, they trigger a host inflammatory response which results in the production of distinct inflammatory mediators. This response is followed by the activation of innate immune responses.
cells and proteins which migrate to the infectious focus and facilitate eradication of the invading bacteria. Tissue damage following UTI is the result of this inflammatory response [23,24].

**Clinical presentation of urinary tract infections**

Cystitis, or infection of the lower urinary tract (i.e. bladder), traditionally presents with urinary urgency, frequency, dysuria or foul-smelling urine. In contrast, pyelonephritis, or infection of the upper urinary tract (i.e. kidney), is often associated with more severe or systemic symptoms, including fever, back pain, flank pain or vomiting. In infants and young children, these symptoms are often absent or difficult to identify. Fever may be the only symptom. Currently, the American Academy of Pediatrics (AAP) recommends that UTI be considered in any infant or child aged between 2 months and 2 years presenting with fever with no identifiable source of infection [25,26]. In addition to fever, infants and young children with UTI can present with irritability, poor feeding, vomiting or failure to thrive. In toddlers and young children, regression to urinary incontinence in previously toilet-trained children, prolonged fever, suprapubic tenderness or significant abdominal pain should raise the suspicion of UTI (Table 1). In severe situations, ascending infections may result in bacteraemia and present as the systemic inflammatory response syndrome or overt urosepsis [1]. Urosepsis is defined as the presence of the systemic inflammatory response syndrome plus evidence of an infectious aetiology. Septic shock, urosepsis plus hypotension, is uncommon unless urinary tract obstruction is present or the child is otherwise compromised [27].

**Paediatric populations at increased risk of urinary tract infections**

Although all children and adolescents are susceptible to UTI, some have a heightened risk.

**Table 1.** Commonly encountered UTI symptoms by age group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Common symptoms</th>
<th>Less common symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns, infants</td>
<td>Fever</td>
<td>Vomiting, Irritability, Jaundice, Failure-to-thrive</td>
</tr>
<tr>
<td>Young children (not toilet-trained)</td>
<td>Irritability, Abdominal pain, Suprapubic tenderness</td>
<td>Foul-smelling urine, Haematuria</td>
</tr>
<tr>
<td>Older children (toilet-trained)</td>
<td>Cystitis: Dysuria, Voiding dysfunction: Incontinence, Frequency, Pyelonephritis: Fever, Vomiting, Dysuria, Abdominal or flank pain</td>
<td>Haematuria, Foul-smelling or cloudy urine</td>
</tr>
</tbody>
</table>

(A) **Neonates and infants:** In the first few months of life, infants are at increased risk [28,29]. This susceptibility has been attributed to an incompletely developed adaptive immune system [29]. Under the age of 1 year, the incidence of UTI is greater in boys than in girls. However, after 1 year of age, girls are much more likely to develop a UTI than boys [28,30].

(B) **Circumcision:** In uncircumcised boys, the incidence of UTI is increased in the first year of life. This is partly because the foreskin harbours higher concentrations of uropathogens which can invade the urethral meatus and lead to UTI [28,31]. In 2012, the AAP updated its policy statement on circumcision, stating that current evidence supports the benefits of circumcision for reducing the risk of UTI and that these benefits justify universal access to the procedure for those who wish it [32].

(C) **Constipation and bowel dysfunction.** When there is constipation, the stool bacterial load increases and may increase the risk of UTI. Moreover, a stool-filled colon may compromise bladder emptying and increase the risk. Exclusion of constipation or bowel dysfunction is strongly recommended by several professional societies in any child with febrile and/or recurrent UTI. Treatment of constipation is necessary [28,33].

(D) **Anatomic and functional urinary tract anomalies.** Infections associated with urinary tract abnormalities often appear in children under 5 years of age. Congenital and acquired kidney and urinary tract anomalies (CAKUT) or impaired bladder emptying (i.e. neurogenic bladder) can result in urine stasis or obstruction, decreasing the clearance of invading pathogens (Table 2). Elevated bladder pressure stemming from poor bladder drainage can cause secondary vesicoureteral reflux (VUR) and increase the potential risk of renal damage associated with an ascending infection [34]. It is important to identify urinary tract anomalies early because, if uncorrected, they may serve as a reservoir for bacterial growth or recurrent infections [25].

(E) **Spinal cord disorders.** Children and adolescents with myelomeningocele or who experience spinal cord injury typically have/develop neurogenic bladder which increases the risk of UTI. These patients often perform intermittent catheterisations, which can further increase the UTI risk when performed incorrectly [35–37].

(F) **Sexual activity.** In female adolescents and young women, the risk of UTI correlates with sexual activity. A similar risk has not been demonstrated in young men.

**Table 2.** Anatomical and functional anomalies associated with increased risk of UTI.

<table>
<thead>
<tr>
<th>Lower urinary tract anomalies</th>
<th>Upper urinary tract anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior urethral valves</td>
<td>Cystic kidney disease</td>
</tr>
<tr>
<td>Ureterocoele</td>
<td>Ureteropelvic junction obstruction</td>
</tr>
<tr>
<td>Vesicoureteral reflux</td>
<td>Duplicated kidney collecting system</td>
</tr>
<tr>
<td>Ectopic ureter</td>
<td>Neurogenic bladder</td>
</tr>
<tr>
<td>Neurogenic bladder</td>
<td>Bladder outlet obstruction</td>
</tr>
</tbody>
</table>
Positive leucocyte

Urine microscopy,

Urine microscopy,

Positive leucocyte

Nitrite 53 (15–82) 98 (90–100)

Leucocyte esterase 83 (67–94) 78 (64–92)

Test Sensitivity (range) % Specificity (range) %

Table 3.

**History and physical examination**

In addition to identifying the child’s symptoms, the medical history should include questions regarding symptom duration, drinking and voiding habits, stooling patterns, and any complicating factors, including sexual history. In addition, the medical history should include questions on the number of previous UTIs, age of first UTI, prior episodes of febrile or non-febrile UTI, documented malformations of the urinary tract (typically identified on pre-natal or post-natal imaging), previous surgery and family history of UTI [1,39,40].

A complete physical examination is required to exclude sources of fever, especially when no other source is apparent. The European Urology Association and the European Society of Paediatric Urology highlight that, in addition to searching for signs of fever, the physical examination should look for signs of constipation, palpable or painful kidney(s), a palpable bladder (stigmata of spina bifida or sacral agenesis) or genital disorders including phimosis, labial adhesions, vulvitis, post-circumcision meatal stenosis or cloacal malformations [39].

**Urine sampling**

Accurate UTI diagnosis relies upon identification of the clinical symptoms described above (Table 1) in conjunction with positive laboratory testing [41]. To establish the diagnosis of a UTI, positive laboratory testing includes (i) urinalysis indicating the presence of infection (pyuria or bacteriuria) and (ii) a positive urine culture growing at least 50,000 colony-forming units (CFU)/mL of a uropathogen from an appropriately collected urine specimen [25,26]. Obtaining an appropriately collected urine specimen before the administration of antibiotics is one of the fundamental barriers to the accurate diagnosis of UTI. Clinically, there are four methods of collecting urine, each with its own benefits and challenges. The easiest way is to collect it in a plastic bag attached to the perineum. However, given the high risk of contamination, such specimens are unreliable and unacceptable for diagnosing UTI. The only value of such a specimen is to rule out UTI [25,26]. More appropriate methods include clean-catch midstream samples, transurethral bladder catheterisation or suprapubic aspiration (SPA) [25,26,41].

To date, the most reliable method of collecting urine for precise culture results in infants and non-toilet-trained young children remains controversial [42]. SPA and transurethral bladder catheterisation are unlikely to yield a contaminated growth result and are strongly recommended by the AAP [25,26]. Unfortunately, these methods are invasive, unpleasant to children, stressful for families, and are not always practical as routine procedures in the primary care office setting. In the NICE, Italian and Royal Children’s Hospital (RCH) Melbourne guidelines, clean-catch urine specimens are proposed as the preferred collection method in young children in terms of convenience and diagnostic accuracy [40,43–45]. In comparison with SPA, the sensitivity of clean-catch urine specimens for diagnosis has been calculated to range from 75 to 100% and the specificity from 57% to 100% [40].

**Evaluation of urine specimens**

Urine culture is the standard method of diagnosing UTI. Urine culture results should be considered contaminated if there is growth of more than one organism, growth of a typical skin organism or low CFU counts. If such circumstances and if there is still a high suspicion of UTI, urine culture should be repeated [41]. Unfortunately, it takes at least 18 h to detect bacterial growth and 48–72 h to identify which antibiotics would be appropriate. Thus, when deciding whether to initiate empirical antibiotic therapy, clinicians routinely rely on their clinical index of suspicion and the results of urinalysis.

The urine dipstick results that receive the most attention for UTI diagnosis are biochemical tests to detect the presence of nitrites or leucocyte esterase (as a surrogate marker of pyuria). The urine nitrite test is not a sensitive UTI marker in children (Table 3). The conversion of dietary nitrates to nitrites by enteric Gram-negative organisms in the urine requires approximately 4 h [46]. Therefore, negative nitrite test results have little value in ruling out UTI. Moreover, not all urinary pathogens reduce nitrates to nitrites. The presence of urinary nitrites is helpful when the result is positive, as it is highly specific (i.e. few false positive results) [47]. In contrast to urinary nitrites, the sensitivity of the leucocyte esterase test is 94% when used in the context of a clinically suspected UTI (Table 3). However, positive leucocyte esterase results should be interpreted with caution as false positive results are common. Other conditions besides UTI are associated with leucocytes in the urine and include Kawasaki disease, hypercalciuria, appendicitis, glomerulonephritis or even heavy exercise. Therefore, the detection of pyuria by no means confirms the diagnosis of UTI [1].
Microscopic examination of a centrifuged urine specimen can also assist diagnosis of UTI. Microscopy, especially with a threshold of ten white blood cells per high-power field, has been considered more reliable to predict UTI in children <2 years of age by the NICE, Italian and RCH Melbourne guidelines [40,43–45]. However, the AAP highlights that a recent meta-analysis did not confirm the advantage of microscopy over a positive leucocyte esterase on urine dipstick testing [25]. Additionally, the visualisation of bacteria in a fresh uncentrifuged urine specimen combined with a gram stain is also considered a reliable, rapid test to identify or exclude UTI [48]. Hoberman and Wald reported that the positive predictive value of pyuria and bacteriuria is as high as 84.6% [49]. Because of its low sensitivity, negative urine microscopy does not rule out UTI. As with all laboratory testing, the choice of test may lead to a trade-off between false positive and false negative results [30].

### Treatment of acute urinary tract infections

Prompt treatment should be initiated once the diagnosis of UTI has been confirmed or if there is high clinical suspicion. The aim of treatment is to relieve the symptoms, avert complications and prevent renal scarring [10]. Treatment should include 7–14 days of antimicrobials according to local sensitivity patterns. NICE guidelines recommend antibiotic therapy for 7–10 days [45]. The latest AAP guidelines did not reach a consensus on duration of treatment: the committee states there is insufficient evidence that directly compares 7-, 10- and 14-day courses of antibiotics and suggest that a 7–14-day course is sufficient [25,26]. In both the AAP and NICE guidelines, oral or parenteral antibiotics were found to be equally effective. If a child is ill and unable to tolerate oral antibiotics, a course of parenteral antibiotics for 2–4 days followed by oral antibiotics is sufficient [25,26,45], this is important for any child with pyelonephritis because an oral antibiotic may not be retained long enough to be systemically absorbed.

### Imaging after the initial urinary tract infection

Several professional societies recommend a renal and bladder ultrasound (RBUS) following the first febrile UTI in infants and young children (Table 4) [25,26,41,43,45,50]. The purpose of the RBUS is to detect anatomical anomalies that require further evaluation, including additional imaging or urological consultation. It also provides an evaluation of the renal parenchyma and an assessment of renal size that can be used to monitor kidney growth. In today’s era, the detection of actionable findings is relatively low as the wide-spread use of pre-natal imaging has reduced the prevalence of unsuspected CAKUT [25,26,51].

Previously, the same professional societies recommended that all children with a febrile UTI should undergo a voiding cystourethrogram (VCUG) to evaluate for the presence of VUR. However, in the last decade these societies modified their stance on VCUG imaging because only a small number of children ultimately require surgical correction of VUR (Table 4) [25,26,41,43,45,50]. Delaying a VCUG until recurrence of UTI avoids VCUG testing in approximately 90% of children with a first febrile UTI. Moreover, limiting the initial VCUG to children with recurrent febrile UTI increases the likelihood that high-grade VUR will be detected [1].

Nuclear renal scanning with technetium-labelled dimercaptosuccinic acid (DMSA) is a sensitive test for detecting acute pyelonephritis. A systematic review showed that 57% of children with an initial febrile UTI have findings on DMSA consistent with acute pyelonephritis. Furthermore, it was demonstrated that 15% of these children will have renal scarring on follow-up renal scan [52]. Currently, DMSA scans are not recommended as a part of routine evaluation in infants and children with their first febrile UTI as the findings rarely affect acute clinical management (Table 4) [53]. If a DMSA is undertaken, it should be performed in the acute phase of UTI to optimise screening for acute pyelonephritis or 4–6 months after completion of UTI treatment to assess for renal scarring [54,55].

### Treatment and prevention of recurrent UTI

The rate of recurrence of UTI is high, occurring in up to 80% of school-age girls. Recurrence is usually encountered within 6 months. Children who experience recurrent UTI suffer significant morbidity, including chronic urinary symptoms, abdominal pain, urinary incontinence.

### Table 4. Management and diagnostic evaluation of a first febrile UTI in children aged 2–24 months: published Nephrology Society guidelines [53].

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Ultrasound</th>
<th>VCGU</th>
<th>DMSA</th>
<th>Antibiotic prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>National institute for health and care excellence</td>
<td>Atypical UTI, &lt;6 months of age</td>
<td>Yes</td>
<td>No, unless &lt;6 mo of age with positive US or atypical UTI</td>
<td>Yes &gt;6 mo post-atypical UTI</td>
</tr>
<tr>
<td>American academy of paediatrics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italian society of paediatric nephrology</td>
<td>Yes</td>
<td></td>
<td>No, unless abnormal US or risk factors</td>
<td>Yes &gt;6 mo post-UTI if abnormal US or VUR</td>
</tr>
<tr>
<td>Kidney health Australia – caring for Australians with renal impairment</td>
<td>Yes, if no prenatal RBUS, &lt;3 mo of age, or atypical UTI</td>
<td>No, unless abnormal US</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Canadian paediatric society</td>
<td>Yes</td>
<td></td>
<td>No, unless abnormal US</td>
<td>No</td>
</tr>
</tbody>
</table>
nausea, vomiting and malaise. These experiences can have a significant negative impact on their well-being. Moreover, recurrent UTI can lead to renal scarring which can ultimately lead to hypertension, proteinuria and renal insufficiency. The incidence of post-pyelonephritis renal scarring depends on many patient factors. Data from the international registries of end-stage renal disease (ESRD) show that populations at serious risk of chronic kidney damage are children, predominantly boys, with significant congenital abnormalities of the kidney and urinary tract, particularly hypodysplasia [56,57]. In contrast, the risk of ESRD after UTI in otherwise healthy children remains anecdotal [53].

The treatment of recurrent UTI is the prompt administration of antibiotics as described above for children with a first febrile UTI. Antibiotic therapy should be based on prior positive urine culture results and local antibiotic resistance patterns. Therapy duration should be guided by clinical severity, but in general is limited to 14 days. There is no evidence supporting prophylactic antibiotics after a single febrile UTI (Table 4). Other aspects of recurrent UTI treatment and prevention are directed towards the underlying aetiologies. Patients and caregivers should be instructed on proper hygiene – the perineum in girls and the foreskin and glans in uncircumcised boys. To minimise bacterial burden, the circumcised penis should be washed gently with soap and water. With an uncircumcised penis, the foreskin can be gently retracted and the whole penis washed with soap and water [58].

Normal bladder and bowel habits must be established and constipation should be aggressively treated when clinically apparent. Additional measures to prevent recurrent infections are necessary on a case-by-case basis and may require subspecialty consultation with a paediatric urologist or nephrologist [1].

**Antibiotic prophylaxis and prevention of recurrent UTI**

The use of prophylactic antibiotics in recurrent UTI evokes strong opinions in paediatric academic circles. Evidence regarding the value of continuous antibiotic prophylaxis (CAP) in recurrent UTI prevention has been obtained almost exclusively in the setting of VUR and remains largely inconclusive. Several recent large-scale studies have demonstrated a statistically significant benefit of CAP in preventing recurrent UTI. Craig et al. suggest that CAP with trimethoprim–sulfamethoxazole (TMP–SMX) was associated with a modest reduction in UTI in patients aged 0–18 years over a 1-year period, but VUR status was unknown for 17% of the study participants [17]. In contrast, Garin and colleagues noted that CAP and grades I–III VUR did not significantly influence UTI recurrence or renal scarring in children aged 3 months to 18 years over a 1-year period [15]. In the Swedish Reflux Study, the incidence of recurrent UTI and renal scarring were reduced in girls with grades III–IV VUR on CAP versus placebo over 2 years [59,60]. The recently completed Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial established that prophylactic TMP–SMX significantly reduces the risk of recurrent UTI in patients aged 2–71 months with grades I–IV VUR. The benefit of antibiotic prophylaxis was particularly evident in females, in those with febrile index UTI and those with bladder and bowel dysfunction. The use of prophylacticTMP–SMX was associated with increased rates of antibiotic resistance in children with breakthrough UTI in the RIVUR study [61].

**Conclusion**

UTI is a common problem in paediatric and adolescent patients with the potential to produce long-term morbidity. One of the clinical challenges of diagnosing UTI is its vague presenting symptoms, especially in young children. Thus, a high index of suspicion is appropriate when a young child presents with fever. Although the gold standard for diagnosing a UTI is urine culture, clinicians routinely rely on their clinical suspicion and the results of the urine dipstick test. Antibiotic therapy for febrile UTI in young children should last 7–14 days and be based on the urine culture results. The appropriate work-up after a UTI in young children and infants includes an RBUS. Children with renal scarring after an acute UTI should be followed long-term for signs of hypertension and renal insufficiency.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**Notes on contributors**

**Lindsey Korbel** is a pediatrician with an interest in antibiotic stewardship and urinary tract infections.

**Marianella Howell** is a Pediatric Nephrologist with interests in preventing acute kidney injury, progression of kidney disease, and scarring.

**John David Spencer** is an associate professor of Pediatrics and Pediatric Nephrologist who is interested in the kidney and bladder’s innate immune defenses against uropathogens.

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