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The Diagnosis, Evaluation and Treatment of Acute and Recurrent Pediatric Urinary Tract Infections

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Abstract

Urinary tract infection is one of the most common bacterial infections encountered by pediatricians. Currently, the diagnosis and management of acute urinary tract infection and recurrent urinary tract infection in children remains controversial. 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 urinary tract infection in the pediatric population.

Keywords

Urinary Tract Infection; Pyelonephritis; Nephrology; Urology; Diagnosis; Management

The Socioeconomic Impact of Urinary Tract Infection

Urinary tract infection (UTI) is the second most common bacterial infection in children, only after otitis media [1–3]. Estimates on the cumulative incidence of UTI in American children indicate that up to 180,000 of the annual birth cohort will be diagnosed with a UTI by 6 years of age (3–7% of girls and 1–2% of boys) and 12–30% of these children will develop recurrent UTI [4–6]. Children diagnosed with UTI account for over 1 million annual office visits, 500,000 emergency department visits, and over 50,000 hospital

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admissions. Since 2000, the number of inpatient and outpatient encounters for UTI management has steadily increased [7, 8]. In 2013, aggregate hospital charges for inpatient UTI management exceeded $630 million [9].

In attempt to offset this increase in UTI clinical encounters and rising hospital charges, physicians need to promptly recognize, evaluate, and appropriately treat a suspected UTI. Appropriate and timely evaluation minimizes morbidity, excessive testing, treatment delay, and/or unnecessary hospitalization. UTI in children is of concern because it can be associated with acute mortality (i.e. urosepsis) and/or chronic medical problems like renal scarring, hypertension, and chronic renal insufficiency [7].

UTI Definition and Pathogenesis

An infection of the lower urinary tract is referred to as cystitis while infection of the upper urinary tract is referred to as pyelonephritis (Table 1). *Escherichia coli* (*E. coli*) is the most frequent bacterial pathogen responsible for cystitis and pyelonephritis accounting for 85–90% of cases. Uropathogenic *E. coli* (UPEC) are thought to originate from the fecal flora, spread across the perineum, and enter the bladder through the urethra. The pathogenesis of UPEC mediated cystitis has been extensively investigated both from the host and pathogen perspective, and we refer the interested reader to recent reviews on this topic [10–12]. Bacterial attachment to the urothelium and internalization are essential in establishing cystitis. As bacteria attach to urothelium and undergo internalization, they trigger a host inflammatory response that results in the production of distinct inflammatory mediators. This response is followed by the activation of innate immune cells and proteins that migrate to the infectious focus and facilitate eradication of the invading bacteria. Tissue damage following UTI is the result of this inflammatory response [13, 14].

Proposed antibacterial mechanisms limiting uropathogen attachment and invasion include barrier formation by uroepithelial cells, unidirectional flow of urine, regular bladder emptying, mucous production, the urinary and gastrointestinal microbiome, alterations in the urinary ionic composition, and the production of antimicrobial proteins that limit bacterial attachment or directly kill invading uropathogens [15–17].

Clinical UTI Presentation

Cystitis typically presents with lower urinary tract symptoms – including dysuria, urgency, and frequency. Pyelonephritis is often associated with more severe or systemic symptoms including fever, back/flank pain, and vomiting. Ascending infection may result in bacteremia and clinically present as the systemic inflammatory response syndrome or overt septic shock (urosepsis). Part of the challenge in diagnosing and treating UTI in children is the inconsistent nature and vagueness of the presenting illness. Additionally, children often have a difficult time articulating their ailments and symptoms [18]. The symptoms of frequency, urgency, and dysuria that are highly suggestive of UTI in an adult are often absent in children.

Young children with UTI can present with irritability, poor feeding, vomiting, failure to thrive, or jaundice [19–23]. Currently, the American Academy of Pediatrics (AAP)

recommends that UTI be considered in any infant or child between two months and two years of age presenting with fever without an identifiable source of infection [24]. In toddlers and young children, regression to incontinence in previously toilet-trained children and significant abdominal pain should raise suspicion for UTI. Suprapubic tenderness and presence of fever for more than two days are also strong predictors of UTI. Older children may present with the "classic" symptoms of UTI – dysuria, frequency, abdominal or flank pain, and fever [18–20].

UTI Risk Factors

Although all children are susceptible to UTI, there are specific circumstances that alter UTI risk.

(A) *Neonates and infants*: In the first few months of life, infants are at a higher risk for UTI. This susceptibility has been attributed to an incompletely developed immune system [25, 26].

(B) *Circumcision*: Since the 1980s, studies have shown an increased frequency of UTI in uncircumcised boys during the first year of life [27–29]. In 2012, the AAP revised its policy on circumcision stating that current evidence supports the benefits of circumcision including UTI risk reduction, and that these benefits justify universal access to this procedure for families who choose it[18].

(C) *Fecal colonization and constipation*: Most UTI results from fecal-perineal-urethral retrograde ascent of uropathogens. In the setting of constipation, the stool bacterial load increases and may contribute to increased UTI risk. Moreover, a stool-filled colon may compromise bladder emptying and increase UTI risk. The treatment of constipation can lead to UTI reduction [20, 25].

(D) *Functional urinary tract disorders*: An inability to empty the bladder, as in the case of dysfunctional elimination syndrome or neurogenic bladder, frequently results in urinary retention, urinary stasis, and inadequate uropathogen clearance. Chronically elevated bladder pressures, secondary to poor emptying, may also cause secondary vesicoureteral reflux (VUR) and increase the potential risk of renal damage associated with pyelonephritis [30].

(E) *Anatomic Anomalies of the Urinary Tract*: When abnormalities of the urinary tract result in obstruction or urine stasis, children are predisposed to UTI due to inadequate clearance of uropathogens (Table 2). Infections associated with urinary tract abnormalities often appear in children younger than 5 years of age. It is critical to identify these abnormalities early because if uncorrected, they may serve as a reservoir for bacterial growth and recurrent UTI [25, 31].

(F) *Systemic Disorders*: Diabetics patients, immunocompromised patients (HIV/AIDS, solid organ transplant recipients), and patients with sickle cell anemia have increased UTI risk [32–35].

(G) *Spinal Dysraphism*: Patients with myelomeningocele typically have neuropathic bladders which increase UTI risk. These patients routinely perform clean

intermittent catheterization, which, when correctly performed, may result in asymptomatic bacteruria (ABU) but serve to reduce the risk for symptomatic (febrile) recurrences (i.e pyelonephritis) [36, 37].

(G) *Sexual Activity*: Sexual activity has been recognized as a risk factor for the development of UTI in young women [38, 39]. Although the exact relationship between sexual activity and UTI is unclear, the proposed mechanism is direct transfer of bacteria from the bowel or vagina to the urethral meatus during sexual intercourse [40].

(H) *Immune response*: The innate immune response provides front-line defense against microbial insult and leads to subsequent activation of the adaptive immune system. Alterations in innate immune mechanisms *may* predispose patients to UTI, lead to uroepithelial tissue destruction, parenchymal scarring, or overwhelming infection [15]. Polymorphisms in genes encoding pattern recognition receptors, cytokines, and transcription factors associated with the innate immune response are associated with childhood UTI predisposition [12].

UTI Definition and Diagnosis

The most recent AAP clinical practice guidelines suggest that UTI diagnosis requires *both* (A) urinalysis demonstrating evidence of pyuria and (B) urine culture demonstrating the presence of >50,000 colony forming units/mL of a single uropathogen. These guidelines stress the importance of delineating a true febrile UTI indicative of pyelonephritis from simple cystitis or asymptomatic bacteriuria [24].

The method of appropriate urine collection from young children has been extensively debated. In the most recent guidelines for children <2 years with a presumed UTI, the AAP recommends transurethral bladder catheterization or a suprapubic aspirate since these collection methods are less likely to yield a contaminant [24]. Unfortunately, these methods are stressful, invasive, and not always feasible in the primary care setting. The National Institute for Health and Care Excellence (NICE) and Italian guidelines propose clean catch urine as the method of choice for young children [41, 42]. No organization supports urine collection by a bag affixed to the perineum, as this collection method is associated with high rates of false-positive results. The only utility of a bagged urine specimen is to rule out UTI [24]. The method of urine collection for UTI diagnosis, the role of the urinalysis, and interpretation of the urine culture have been previously thoroughly reviewed by Bitsori *et al* in this journal [18].

Acute UTI Treatment

Prompt treatment should be initiated once the diagnosis of UTI has been confirmed. If the child is febrile and deemed appropriate to receive empiric treatment prior to urine culture results, antibiotic treatment should be implemented. Treatment should include 7–14 days of antimicrobials according to local sensitivity patterns. In regards to treatment duration, NICE guidelines recommend antibiotic therapy for 7–10 days [42]. In the latest AAP guidelines, a consensus could not be reached regarding duration of treatment, as there is insufficient evidence that directly compares 7, 10, or 14-day courses of antibiotics. Therefore, the AAP

suggests that a 7–14 day course is sufficient [24]. 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 [24, 42]. There is no evidence supporting prophylactic antibiotics after a single febrile UTI.

Imaging After the Initial UTI

The "bottom-up" approach

In the age of "ALARA" (as low as reasonably achievable), physicians must judiciously utilize imaging to decrease the adverse events associated with radiation exposure. In 1999, the AAP recommendations for imaging after an initial febrile UTI were extensive and included renal and bladder ultrasound, voiding cystourethrography (VCUG) or radionuclide cystography in all children younger than two years of age [43]. This approach became widely known as the "bottom-up" algorithm because it begins with the diagnosis of VUR. In these guidelines, the AAP was vague concerning the use of ^{99m}Tc-DMSA. However, the American Academy of Family Physicians advised this test after treatment of UTI to determine if permanent renal scarring occurred. This approach exposed children to many invasive radiologic examinations [44]. Since 1999, a vast amount of research has been done to demonstrate that the amount of imaging performed in these children can be safely reduced, and that the children most at risk for renal scarring can still be identified.

In the latest AAP UTI guidelines, VCUG is no longer recommended after the initial UTI. However, renal and bladder ultrasound is still recommended. Ultrasound is non-invasive and poses no radiation risk to the child. Moreover, a renal ultrasound is useful to screen for renal abnormalities like as hydronephrosis. If the child does have hydronephrosis, the underlying cause may need to be determined by utilizing further imaging modalities such as VCUG or MAG-3 renal imaging [42]. The AAP modified its stance on VCUG imaging after first febrile UTI because only a small number of children ultimately require surgical or medical treatment for VUR. Delaying a VCUG until UTI recurrence avoids VCUG in approximately 90% of children with a first febrile UTI. Thus, if a VCUG is performed, the likelihood that a child has high-grade VUR is greater as children at highest risk of febrile UTI recurrence are those with clinically significant VUR.

The NICE guidelines also recommend that all children younger than 6 months undergo an ultrasound within 6 weeks of the infection. However, the NICE guidelines differ in that ultrasonography is not recommend in children older than 6 months with an uncomplicated febrile UTI [42]. To add to the confusing aspect of UTI imaging, subsequent studies have both disputed and upheld these guidelines. For example, Ristola and Hurme conducted a retrospective review of a cohort of 672 patients younger than 3 years of age with UTI. According to their data, if the NICE guidelines had been applied to their cohort, 59 patients with VUR would have been missed and 13 of these eventually underwent surgical anti-reflux surgery [45]. In contrast, Deader *et al* demonstrated that the vast majority of renal anomalies demonstrated on what they deemed "inappropriate" ultrasounds were of little significance, thereby concluding the NICE imaging guidelines are safe and appropriate [46].

The “top-down” approach

The “top-down” approach is another method that has been proposed in the evaluation of children with acute pyelonephritis. Ultrasonography is limited by its ability to detect renal abnormalities as 60% of VUR and 50% of renal scan abnormalities can be missed with ultrasound. [47–49]. In contrast, DMSA scan has been shown to be highly sensitive and specific in identifying acute pyelonephritis. In a systematic review study, it was shown that 57% of children with an initial febrile UTI have findings on DMSA consistent with acute pyelonephritis. Further, it was demonstrated that 15% of these children will have renal scarring on follow up renal scan [50]. The idea behind the “top-down” approach is that one can identify patients at risk for renal scarring and avoid VCUG in children that have low-grade VUR. It has been shown that by utilizing this method, children with low-grade reflux may be missed. However, these children typically have VUR that resolves or never causes renal damage. Although DMSA scan is more costly than VCUG or ultrasound, Pohl and Belman have shown that the “top-down” approach is less expensive than the “bottom-up” approach [51].

Overall, there is no one approach that can be advocated as the “best” imaging approach after a single febrile UTI. All of the recently published guidelines agree that VCUG is no longer indicated as a first-line imaging study after initial UTI. The role of ultrasound is still not well defined. Although ultrasonography remains the least invasive imaging modality, it will not identify every episode of VUR or renal scaring. However, it will identify more severe cases of dilating reflux, renal scarring, and other serious anomalies such as ureteropelvic junction obstruction or severe bilateral hydronephrosis.

Recurrent UTI and Recurrent UTI Risk Factors

When evaluating a child with a complaint of recurrent UTI (rUTI), defined as 2 discrete UTI episodes (Table 1), the pediatrician or primary care physician should carefully adhere to the aforementioned principles of accurate UTI diagnosis. As noted, this can be a challenging task as UTI diagnosis occurs in a variety of clinical settings and complete records are not always available. Nonetheless, review of prior dipstick urinalysis (UA) results and urine culture results in the context of patient history, physical examination, and urinary tract imaging forms the cornerstone of rUTI management.

The same risk factors described for UTI apply to patients with rUTI, albeit data supporting their specific roles are limited. An observational study implicated patient age (3–5 years), white race, and higher grades of VUR in UTI recurrence. In contrast, lower VUR grades, gender, and antimicrobial prophylaxis were not associated with rUTI risk [52]. A prospective study in patients with grade III-IV VUR associated female gender with UTI recurrence [53].

Recurrent UTI History and Physical Exam

When obtaining a history from a patient with rUTI, attention should be directed toward presenting symptoms and signs of illness – particularly if UTI are associated with fever. Additional steps should be taken to review the presence of UTI risk factors described above.

Many patients with rUTI have underlying bowel and/or bladder dysfunction, and rUTI may be the presenting sign of this condition [54]. Thus, the clinician evaluating a patient with rUTI should take a careful history of voiding and stooling behaviors. Parents should be carefully questioned about medication usage including laxatives, osmotic agents, stool softeners, or enemas. A history of straining during bowel movements, visibly hard stool, or painful or blood-streaked stool is also a sign of bowel dysfunction. Any prior abdominal imaging should be reviewed to determine if the child has a history of fecal retention. Important indicators of neurogenic bowel dysfunction that also need to be screened for are history of Hirschsprung disease or underlying anatomic condition such as anorectal malformations.

A thorough physical exam of a child with rUTI should primarily be focused on the abdomen and pelvis. The physical examination may demonstrate stigmata of constipation such as palpable stool and/or anal fissure. Flank/abdominal tenderness or a palpable abdominal mass may be the first evidence of a hydronephrotic kidney. Examination of the perineum may identify overt structural abnormalities in the urethral opening, sacral spine, genital adhesions, vulvovaginitis, or stigmata of sexually transmitted disease in victims of abuse. Such findings can either produce urinary symptoms or increase risk for eventual bladder colonization by uropathogens from the gastrointestinal tract, genitourinary tract, or skin.

Imaging and Recurrent UTI

Patients with febrile, recurrent UTI often undergo additional imaging beyond the recommended renal and bladder ultrasound. However, there is no consensus on which patient population would benefit from additional imaging studies or what studies are indicated. VCUG in patients with recurrent febrile UTI may identify VUR as well as other anatomic findings that predispose to rUTI such as posterior urethral valves, ureterocele, or urachal cyst. Furthermore, ultrasound and VCUG - together with patient history - may identify findings suggestive of voiding dysfunction. For example, bladder wall thickening, irregularity, and diverticuli suggest high voiding pressures. Alternatively, large bladder volume and post-void residuals after spontaneous voiding suggest impaired bladder emptying. Referral to a Pediatric Urologist for formal urodynamic studies can assist in diagnosing suspected voiding dysfunction, guiding treatment, and assessing response to therapy.

When children suffer rUTI due to the same uropathogen, suspicion should arise that the patient has developed a renal abscess. Clinically, this child may present with persistent fevers despite prolonged administration of parenteral antibiotics. Laboratory studies may demonstrate leukocytosis or elevated inflammatory markers such as serum erythrocyte sedimentation rate (ESR) or C-reactive peptide (CRP). Ultrasound may identify a renal abscess on the basis of its thick wall surrounding a fluid cavity. Computerized tomography (CT) with contrast enhancement remains the best imaging modality for evaluation of renal or perinephric abscess and its extension to adjacent structures [55].

Additional imaging modalities may be employed in certain patients with rUTI. MAG-3 imaging is recommended to evaluate for obstruction and magnetic resonance urography may

help in defining complex urinary tract anatomy. DMSA scan is a sensitive method to detect post-pyelonephritic scarring, which may be distinguished from dysplasia on the basis of focal cortical defects [56].

Recurrent UTI Treatment and Prevention

Treatment of rUTI consists of prompt, empiric institution of antibiotics as described for patients with a first febrile UTI. Antibiotic therapy should be tailored to prior positive urine culture results and local antibiotic resistance patterns. Antibiotic therapy should be adjusted once urine culture results and antibiotic susceptibility are available. Therapy duration should be guided by clinical severity but in general is limited to 14 days unless there is suspicion for a renal abscess, in which case treatment may require 21 days or more of IV antibiotic therapy [57].

Other aspects of rUTI treatment are directed toward the underlying etiologies. All patients and caregivers should be instructed on proper toileting and hygiene. Bowel and bladder dysfunction should be aggressively diagnosed and treated. Additional measures to prevent rUTI are necessary on a case-by-case basis and may require subspecialty consultation with a Pediatric Urologist or Nephrologist. For example, children with urinary retention and rUTI may require regular bladder emptying via clean intermittent catheterization. Breakthrough UTI in patients undergoing regular clean intermittent catheterization may require intravesical antibiotic therapy or even urinary diversion. Efforts should always be made to reduce indwelling catheter usage, given the strong association between duration of catheterization and UTI [58].

The Role of Antibiotic Prophylaxis in Preventing Recurrent UTI

Few topics in academic pediatric circles evoke stronger opinions than the use of prophylactic antibiotics in UTI. Evidence regarding the utility of continuous antibiotic prophylaxis (CAP) in rUTI 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 from CAP in preventing recurrent UTI, while several of the smaller, “traditional” studies show limited benefit. Data from Craig *et al* suggest that CAP with trimethoprim-sulfamethoxazole (TMP-SMX) was associated with a modest reduction in rUTI in patients aged 0–18 years over a one-year period, but VUR status was unknown for 17% of study participants [59]. In contrast, Garin and colleagues noted that CAP and grade I-III VUR did not significantly influence UTI recurrence or renal scarring in children ages 3 months to 18 years over a one year period [60]. In the Swedish Reflux Study, rUTI incidence and renal scarring were reduced in girls with grade III-IV VUR on CAP versus placebo over two years [53, 61].

The recently completed Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial established that prophylactic TMP-SMX significantly reduces rUTI risk in patients aged 2–71 months with grade I-IV VUR. The benefit of antibiotic prophylaxis was particularly evident in patients with female gender, febrile index UTI, and those with bladder and bowel dysfunction. The use of prophylactic TMP-SMX was associated with increased rates of antibiotic resistance in children with breakthrough UTI in the RIVUR

study [62]. The RIVUR study was not adequately powered to establish the role of CAP in prevention of post-pyelonephritis scarring. Meta-analysis of all randomized controlled trials of CAP versus placebo may provide some guidance regarding the net value of CAP in subgroups of patients. Unresolved questions in the field include the choice of antibiotic, duration of prophylaxis, and role of CAP in prevention of post-pyelonephritic scarring.

Recurrent UTI Sequelae

Children who experience rUTI suffer significant morbidity including chronic urinary symptoms, abdominal pain, nausea, vomiting, and malaise. These experiences have a significant negative impact on their well-being. Moreover, rUTI can lead to renal scarring which ultimately may lead to hypertension, proteinuria, and chronic renal insufficiency [63, 64]. The incidence of post-pyelonephritis renal scarring is dependent on many patient factors (Table 3). The incidence of scarring varies according to method of detection (e.g., renal ultrasound versus DMSA scan) and can be confounded by lack of baseline renal imaging – making it difficult to distinguish pyelonephritis-acquired scarring from congenital scarring secondary to renal dysplasia [65–67].

Expert commentary and five-year view

Diagnostic Perspectives

To date, most UTI are unable to be appropriately treated with targeted antibiotics until the uropathogen is cultured, identified, and subjected to antibiotic susceptibility testing. This standard culture-based technique has a typical delay of two to three days. In the absence of definitive microbiological diagnosis at the point-of-care, physicians frequently initiate broad-spectrum antibiotic treatment. Antibiotic misuse and overuse has contributed to the emergence of multi-drug resistant uropathogens. The rate of UTI caused by UPEC resistant to TMP-SMX is typically greater than 30% [68]. Novel advances are needed to improve the efficiency and accuracy of UTI diagnosis through improved urine collection devices, screening technologies, and point-of-care culture techniques. Currently, there are ongoing efforts to develop (A) alternative, non-invasive urine collection methods in non-toilette trained children and adults that will improve UTI diagnosis and (B) and create urine collection devices that limit contamination. Alternatively, the identification of new UTI biomarkers (in addition to urinary nitrite and leukocyte esterase) may have the potential to improve the accuracy of UTI diagnosis, determine infection severity, and identify renal scarring risk [69, 70]. Finally, there is a growing clinical use of microbiological point-of-care diagnostics. For many infectious diseases, molecular techniques such as real-time PCR are used to complement conventional culture methods. Ongoing research efforts are being made to utilize these techniques as UTI diagnostics, which will shorten the time to pathogen identification. Finally, rapid antibiotic susceptibility testing will help guide early UTI treatment with the most cost-effective and targeted therapy.

UTI Sequelae and Renal Injury—The belief that UTI is responsible for scarring with long-term consequences has been challenged over the last several years [60, 71, 72]. Since the new UTI guidelines center upon acute UTI diagnosis and management, there has been little focus on long-term UTI complications [18]. Pyelonephritis has been associated with

glomerular hyperfiltration, proteinuria, renin-mediated hypertension, and deterioration of glomerular filtration rate in children [63, 64, 73, 74]. However, the incidence of UTI sequelae in children with pyelonephritis with and without radiologic evidence of scarring has not been systematically evaluated in a longitudinal, multicenter fashion. Although recent, large national studies have demonstrated that the risk of renal injury after pyelonephritis is low, the evaluation of renal scarring was not the primary objective of these studies and longitudinal follow-up is lacking. Thus, long-term renal scarring risk is unknown [61, 71]. In addition, the clinical significance of renal scarring in affected individuals has not been adequately evaluated. Thus, future studies and guidelines are needed to clarify the best practices for recurrent UTI, long-term UTI management, and the prevention of UTI sequelae.

Antibiotics and Recurrent UTI Prophylaxis—Antibiotics are the foundation for acute UTI treatment. In contrast, the role of prophylactic antibiotics for rUTI management remains unclear and has been traditionally been used in young children with VUR. The results for the studies mentioned above suggest that the benefit of antibiotic prophylaxis is modest and is associated with the development of multidrug resistant uropathogens [59, 71]. To date, the AAP does not have specific recommendations for the role of prophylactic antibiotics in rUTI. In contrast, the European urology guidelines recommend managing rUTI using antibiotics in two different regimens. The first is low-dose prophylaxis and the other is self-start treatment [75]. Since prevention of renal scars following UTI remains the most important clinical outcome, it is advisable that UTI be considered a risk factor for renal scarring and each child needs to be treated with discretion. Rapid diagnosis and prompt therapy are critical in the prevention of long-term UTI sequelae.

Therapeutic Perspectives—Despite our many advances in understanding of the interaction between uropathogenic bacteria and the host urinary tract, UTI pathogenesis is not clearly understood. Current evidence suggests that local molecular events that are activated by the interaction between the uroepithelium and uropathogenic bacteria appear to be an important determinant of overall clinical outcome [16]. Inter-individual variability in these cellular responses may explain the spectrum of clinical outcomes and may help explain why certain individuals are susceptible to recurrent infections and why some patients develop progressive renal scarring. Polymorphisms in a number of candidate genes responsible for host defense, such as toll-like receptors, cytokines, chemokines, and antimicrobial peptides, may be involved in identifying UTI risk and renal scarring [12, 76, 77].

Moreover, as we further understand UTI pathogenesis, we may be able to develop treatments or preventative strategies that do not depend on conventional antibiotics. Novel treatments may be more cost effective and may circumvent the issues associated with antibiotic resistance. Novel treatment avenues may include: (A) Systemic vaccination protocols against bacterial virulence factors as a prevention therapy in individuals with an increased UTI risk like transplant recipients, young women, patients with spinal cord injuries, and diabetics. (B) Suppressing the inflammatory immune response to minimize irreversible tissue damage. (C) Altering neutrophil migration, macrophage activation, or the

complement cascade to identify potential therapeutic targets. (D) Boosting the innate immune response and enhancing antimicrobial peptide production to combat acute infection or prevent recurrent infection.

Complementary Therapy—Although the evidence is inconsistent, alternative medicinal therapy for UTI is popular. The use of cranberry juice for UTI treatment and prevention is often questioned. The Cochrane review on the use of cranberry juice in UTI prevention suggest there is some evidence that it may reduce the number of symptomatic UTI over a one-year period in women. It has been suggested that cranberries prevent *E. coli* from adhering to bladder uroepithelial cells [78].

Probiotics are another alternative therapy that is commonly used for UTI treatment. Although initial trials with oral probiotics did not demonstrate a defined benefit, recent studies have shown a 43% reduction in the incidence of UTI in women with a history of rUTI using *L. acidophilus* [79]. In Iranian children, the combination of a probiotic (*L. acidophilus* and *Bifidobacterium lactis*) with prophylactic nitrofurantoin was superior to nitrofurantoin alone in reducing the incidence of febrile UTI [80]. In Korean children with primary VUR, *L. acidophilus* was noninferior to TMP-SMX in preventing rUTI [81]. Although these findings are encouraging, additional confirmatory research - including placebo-controlled randomized trials – is required before probiotics can be adopted as a front-line choice for UTI prophylaxis [77].

Microbiota Relevance—Communities of microorganisms are being characterized in several body systems, including the gastrointestinal tract, vagina, and urethra [82]. The Human Microbiome Project aims to discover the diversity of the microbiota associated with humans and to determine if there is a common microbiota profile, termed a “core” microbiota, that is prolific and indicative of health. There is emerging evidence that such a core microbiota may exist in the urinary tract [82–84]. Additional knowledge about this community may provide considerable insight into a potentially symbiotic relationship between the host urothelium and the resident microbiota.

For example, the presence of particular microbes in the urinary tract may impart some protection against uropathogenic bacteria by competitively binding and inhibiting their adherence, competing for nutrients, or by inhibiting the proliferation of the pathogen through the production of antimicrobial compounds [85, 86]. Moreover, an imbalance in the dynamic equilibrium between the host and microbiota may lead to disease. It is conceivable that urinary tract diseases with previously unknown etiologies may be caused by disruptions in the balance between the normal microbiota and the host’s defenses. Moreover, it may be possible that disruption in the vaginal or gastrointestinal microbiota could impact the health of the urinary tract.

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Reference annotations

* Of interest

** Of considerable interest

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Key issues

- Urinary tract infection is one of the most common bacterial infections in children.
- Rapid diagnosis and prompt therapy are critical in the prevention of long-term UTI sequelae.
- Because UTI can present with vague clinical complaints, UTI should be considered in any infant or child presenting with fever without an identifiable source of infection.
- UTI diagnosis requires both a urinalysis demonstrating evidence of pyuria and the presence of >50,000 colony forming units/mL of a single uropathogen in an appropriately collected urine specimen.
- The American Academy of Pediatrics suggests that a 7–14 day course of antibiotic therapy is sufficient UTI treamtment.
- Although VCUG is no longer recommended after the first febrile UTI, renal and bladder ultrasound is recommended.
- Evidence regarding the utility of continuous antibiotic prophylaxis in recurrent UTI prevention has been obtained almost exclusively in the setting of VUR and remains largely inconclusive.
- UTI pathogenesis is not clearly defined. As we further understand UTI pathogenesis, we may be able to develop treatments or preventative strategies that do not depend on conventional antibiotics.

Table 1

Classification of Urinary Tract Infection

Parameter	Subgroup	Definition(s)
Location	Cystitis/Pyelonephritis	• Pyelonephritis is infection of the kidney or upper urinary tract. • Cystitis is infection of the bladder or lower urinary tract.
History	Initial/Recurrent	Recurrent UTI are symptomatic UTI that follow resolution of an earlier UTI episode and may result from: • Unresolved bacteriuria: incomplete bacterial clearance (inadequate treatment, antibiotic resistance). • Reinfection: a new infection occurs with a different uropathogen or with a previous bacterial isolate after treatment with a negative intervening urine culture.
Symptoms	Symptomatic/Asymptomatic	Symptomatic UTI can present with different symptoms including dysuria, foul smelling urine, urinary incontinence, urinary urgency, hematuria, chills, abdominal pain, or vomiting
Vital Signs	Afebrile/Febrile	UTI is considered febrile when the temperature is > 38.3°C.

Table 2

Anatomic and Functional Anomalies Associated with Increased UTI Risk

Lower Urinary Tract Anomalies	Upper Urinary Tract Anomalies
Urachal Reminant	Ureteropelvic Junction Obstruction
Posterior Urethral Valves	Cystic Kidney Disease
Ureterocele	Nephrolithiasis
Vesicoureteral Reflux	Medullary Sponge Kidney
Ectopic Ureter	Duplicated Collecting System (with/without ureterocele)
Megaureter	
Prune Belly Syndrome	
Neurogenic Bladder	

Table 3

Risk Factors Associated with Pyelonephritis Related Renal Damage

Young age and Female gender
Urinary Tract Anomalies
Delay of Treatment
Number of Pyelonephritis Episodes
Uncommon Uropathogens (non-E. coli)