Published in final edited form as:

Curr Opin Pediatr. 2013 February ; 25(1): 88–94. doi:10.1097/MOP.0b013e32835c14cc.

Update on recent guidelines for the management of urinary tract infections in children: the shifting paradigm

Elijah Paintsil

Departments of Pediatrics and Pharmacology, Yale School of Medicine, New Haven, Connecticut, USA

Abstract

Purpose of review—Recent guidelines on the management of urinary tract infections (UTIs) in children have seen a shift from aggressive imaging studies and the use of prophylactic antibiotics to a more restrictive and targeted approach. This review focuses on new additions to the literature on management of UTI from January 2011 to September 2012.

Recent findings—The causal relationship between UTI–vesicoureteral reflux (VUR) and renal scarring has been challenged by several studies. Concerns about unnecessary exposure to ionizing radiation, invasiveness of some of the procedures, and risk of infection have also been raised. With improved prenatal ultrasound, a ‘top-down’ approach to investigating febrile UTI in children using renal bladder ultrasound alone as an initial study has become popular. Several studies have reported that prophylactic antibiotics and imaging studies after first UTI can be reduced substantially without affecting the risk of recurrent UTI or renal scarring.

Summary—The use of targeted imaging approach in evaluating febrile UTI in children may lead to improved resource use and reduction of potential harmful procedures and interventions, without affecting outcomes of UTI in children. Providers using current guidelines should endeavor to collect practice-based evidence to validate and inform future guidelines.

Keywords

antibiotic prophylaxis; renal scars; renal ultrasound; urinary tract infection; vesicoureteral reflux

INTRODUCTION

Approximately 1% of boys and 3–5% of girls have at least one episode of urinary tract infection (UTI) during childhood and 30–50% of these children will have at least one recurrence. There are about 1.5 million ambulatory visits for UTIs in children in the United States annually [1]. Since the 1950s, the management of UTI in children has been predicated on the conception that recurrent UTIs, particularly with vesicoureteral reflux (VUR), increase the risk of chronic kidney disease (CKD), hypertension, and ultimately end-

Correspondence to Elijah Paintsil, Departments of Pediatrics and Pharmacology, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06520-8064, USA. Tel: +1 203 785 6101; fax: +1 203 785 6961; ; Email: Elijah.paintsil@yale.edu

Conflicts of interest

There are no conflicts of interest.

stage renal disease. Renal scarring after UTI is implicated in these long-term sequelae [2]. Therefore, guidelines for the management of UTI have advocated aggressive treatment and extensive imaging studies to detect VUR and renal scarring [3,4]. Concerns about unnecessary exposure to ionizing radiation, invasiveness of some of the procedures, and risk of infection have been raised [5]. Furthermore, recent studies have questioned the causal relationship between UTI–VUR and renal scarring and the value of the historic approach to managing UTI.

In this review, the management of UTI following the UTI clinical practice guidelines of the National Institute for Health and Clinical Excellence (NICE–2007, United Kingdom) [6] and the American Academy of Pediatrics (AAP–2011, USA) [7^{••}] is discussed. The review excludes management of UTI in neonates, which was recently featured in this journal [8[•]].

KEY POINTS

- The key to the prevention of UTI complications in children is early diagnosis and initiation of appropriate antibiotic treatment.
- There is a paradigm shift in the understanding of the causal association between recurrent UTI and renal scarring.
- Ongoing research and practices support restrictive and targeted imaging studies as recommended by recent guidelines.
- There is a need for further research in host risk factors and genetic susceptibility to renal scarring after UTI.

PATHOGENESIS OF URINARY TRACT INFECTION

Escherichia coli is the prototypic and most predominant uropathogen. Pathogenesis of UTI is mainly based on *E. coli* models. UTI results from bacterial colonization of the urinary tract mucosa, evasion of host defenses, bacterial multiplication, and damage to host cells [9,10^{••}]. The perturbation of host cell receptors by pathogens activates different signal pathways leading to a cascade of innate immune response effectors such as defensins, cytokines, inflammatory cells, and specific immunity [10^{••}]. The localization and severity of UTIs depend on the magnitude of the immune response resulting from bacteria–host interaction [11]. Using an in-vitro cytokine [interleukin (IL)-6] assay, Storm *et al.* [12[•]] demonstrated that *E. coli* producing high levels of cytokine were more likely to cause cystitis compared with pyelonephritis. Infection with bacteria that elicit high cytokine levels results in high bladder inflammation, which sequesters the bacteria within the bladder and reduces ascent to the kidneys (upper tract) [13]. Uropathogens causing upper tract infections produced more virulence genotypes (e.g., adhesion, toxin production, siderophores, capsule synthesis, and invasion) compared with those causing lower tract infections [14].

Individual differences in clinical presentation and severity of UTI underscore the importance of host factors and genetic variation in susceptibility to bacterial invasion and infection. Several studies have linked individual susceptibility to uropathogens to defects in the genes

that modulate innate immune responses to bacterial clearance and elimination. Genotyping of the promoter regions and genes encoding Toll-like receptor-4 (TLR-4), IL-8, and IL-8 receptors CXCR1 and CXCR2 in children with UTI found that the AA genotype and A allele of the IL-8 single-nucleotide polymorphism (SNP) was related to susceptibility to and severity of upper UTI [15[•]].

LONG-TERM SEQUELAE OF URINARY TRACT INFECTION

Renal scarring is the main culprit for the long-term clinical sequelae of UTI such as hypertension, preeclampsia during pregnancy, proteinuria, and chronic renal insufficiency [10^{••}]. The prevalence of permanent scarring after UTI ranges from 15 to 60% of affected children. This wide range has been attributed to heterogeneity of studies. Recent studies have reported prevalence rates less than or close to the lower limit of the range. It is becoming evident that UTI has been overcredited for renal scarring, thus underestimating the contribution of congenital renal and urinary tract abnormalities.

Salo *et al.* [16^{••}] assessed the causal relationship between childhood UTIs and chronic kidney disease by reviewing literature and medical records of patients with chronic kidney diseases at Oulu University Hospital, Oulu, Finland. Of 366 living patients with CKD who were monitored at Oulu University Hospital, only three had recurrent UTIs in childhood. The authors concluded that the etiologic fraction of recurrent childhood UTIs as a main cause of CKD was less than 1%, and that a child with normal kidneys is not at significant risk of developing CKD with recurrent UTIs [16^{••}]. Clearly, the management of UTI has focused on the care of individual children in preventing CKD without considering the fact that hundreds of children who had UTI have not developed CKD [17].

Reported risk factors for renal scarring in children with UTI include age at diagnosis, sex, race/ ethnicity, delayed treatment, recurrent infections, peak of fever, laboratory indices of inflammation such as total white blood cell count and C-reactive protein (CRP) concentration, presence of VUR, and extent of renal parenchymal lesions. In a retrospective study of 545 children with first episode of UTI, Cheng *et al.* [18[•]] found that the incidence of renal scarring was significantly higher in patients with nephromegaly than in those without (90 vs. 32%, $P < 0.001$). In a prospective study, Lee *et al.* [19[•]] found that 6 months after therapy 17.4% (37 of 213) of children had renal scars. The presence of VUR was the only independent risk factor for renal scarring after acute UTI in this study. A meta-analysis of recent studies on genetic susceptibility to renal scar formation after UTI showed a moderate association between scarring and inflammation and vasomotor genes [20[•]]. In a study by Akil *et al.* [21], the frequency of polymorphism of TLR-4 gene in the patients with scar was two times higher than in those without scars.

DIAGNOSIS OF URINARY TRACT INFECTION

The diagnosis of UTI may be suggested by certain signs and symptoms depending on the age of the child. However, a definitive diagnosis is made on the basis of positive urinalysis and quantitative urine culture results from samples obtained appropriately according to age [7^{••}]. The results of urinalysis can be influenced by the transit time of urine in the bladder

and how long it takes to process the sample after collection (ideally within 1 h of collection) [22]. In the new AAP guidelines, physicians are encouraged to evaluate the likelihood of a child having UTI before proceeding to the work up. This approach is based on the fact that certain host risk factors increase the likelihood of UTI [7^{***}].

ANTIBIOTIC THERAPY OF ACUTE URINARY TRACT INFECTION

The key to management of UTI is early diagnosis and timely initiation of appropriate antibiotics (Fig. 1). For presumed UTI, the following factors should be considered in the choice and route of administration of empiric antibiotics: age of patient, severity of clinical presentation, location of infection, presence of complications, and local antibiotic resistance prevalence and pattern [23^{*}]. Table 1 lists antibiotics commonly used for febrile UTIs. Recent guidelines have weighed favorably toward oral therapy for UTI [7^{***}]. In a multicenter randomized trial comparing a 10-day course of oral cefixime with a 4-day course of intravenous ceftriaxone followed by a 6-day course of oral cefixime for the treatment of acute pyelonephritis in children aged 1–36 months, there was no difference between the two groups in the prevalence of renal scarring 6–8 months after UTI [24^{***}]. The total course of antibiotic therapy should be 7–14 days.

A study of antibiotic susceptibility pattern of uropathogens in a tertiary care hospital in Greece showed that *E. coli* was responsible for about 70% of UTI [25]. The prevalence of *E. coli* isolates resistant to ampicillin was 50%. Marcus *et al.* [26] reviewed the UTI pathogens and their antibiotic susceptibility in Schneider Children's Medical Center of Israel from 2001 to 2005. Of the 355 culture-proven UTI episodes, 26 (6.2%) were due to *Enterococcus* spp., and the remaining 333 (93.8%) to Gram-negative bacteria, mainly *E. coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa*. The Gram-negative isolates showed 24, 7, and 5% resistance to first-generation, second-generation, and third-generation cephalosporins, respectively. There has been no significant difference in the outcome of children with UTI due to extended spectrum β -lactamases (ESBL)-producing uropathogens compared with those with non-ESBL-producing uropathogens [27^{*}].

POST-URINARY TRACT INFECTION IMAGING

When and which imaging studies to obtain for evaluation of a child with UTI still remain controversial. The main question fueling the debate is the relevance of VUR in the causal pathway between UTI and renal scarring. Based on the answer to this question, two approaches have evolved: 'top-down' and 'bottom-up' [5]. The 'top-down' approach focuses on kidney involvement during UTI with a goal of ruling in or out acute pyelonephritis, renal dysplasia, or acquired renal scarring. Proponents of 'top-down' approach recommend the use of renal bladder ultrasonography (RBUS) and dimercaptosuccinic acid (DMSA) renal scan first. Vesicoureterogram (VCUG) is performed only if renal involvement is observed. The 'bottom-up' approach focuses on bladder involvement during UTI with a goal of diagnosing VUR; therefore, VCUG is obtained first. The NICE guidelines discourage routine imaging of all children after a first UTI [6]. RBUS is reserved for only atypical or recurrent UTI or for children less than 6 months of age. DMSA is recommended only in children less than 3 years of age with atypical or recurrent UTI and it is performed 4–6

months after UTI. The new AAP guidelines also do not recommend routine imaging studies for first UTI in children aged between 2 and 24 months. However, it is recommended that febrile infants with first UTI should have RBUS to detect anatomic abnormalities that may require further evaluation [7¹¹]. Thus, VCUG and DMSA are no longer routine investigations after first febrile UTI, as evidence supports that the yield of actionable findings from imaging is relatively low [7¹¹].

Pennesi *et al.* [28] reported on 11 years of experience in management of children with UTI using a protocol with reduced numbers of invasive studies; consistent with current guidelines. Children with their first UTI between the ages of 1 and 36 months underwent RBUS examination and only children with abnormal RBUS or recurrence were subjected to VCUG and DMSA renal scans. Of the 406 children, only 7.4 and 4.4% had abnormal RBUS with their first UTI and recurrence of UTI, respectively. The authors concluded that the application of selective imaging approach did not result in missing any useful diagnoses or compromising the child's health [28]. Schroeder *et al.* [29¹²] retrospectively compared the outcomes of UTI in children under 2 years of age before and after adopting the NICE restrictive imaging guidelines in their hospital. They found that prophylactic antibiotics and VCUG use were reduced substantially without affecting the risk of UTI recurrence within 6 months.

Tsai *et al.* [30¹³] recently assessed four imaging approaches: RBUS alone, DMSA scan alone, RBUS or DMSA scan (abnormality on either study or on both was an indication for VCUG), and RBUS and DMSA (abnormality on both studies was required for performance of VCUG). They found that 136 of 220 (61.8%) and 111 of 220 (50.5%) had abnormal RBUS and DMSA scans, respectively. The sensitivities for high-grade VUR on RBUS alone and DMSA alone were 76.9 and 82.1%, respectively. With RBUS or DMSA strategy, the sensitivity increased to 92.3% with negative predictive value of 94.3%. Their study validated the current recommendation of 'top-down' approach to imaging. Other studies have concluded that RBUS could be used alone in the initial evaluation of children with UTI [31,32].

PREVENTION OF URINARY TRACT INFECTION

Ultimately, 'an ounce of prevention is better than a pound of cure.' The role of prophylactic antibiotics, cranberry juice, management of dysfunctional elimination syndrome, probiotics, and circumcision in preventing UTI is discussed below.

Prophylactic antibiotics have been used on the assumption that they prevent recurrent UTI, renal damage, or both in young children with UTI with or without VUR. Several studies have discredited this assumption. Moreover, chronic antibiotic use has a number of disadvantages for the individual as well as the population as a whole. The NICE guidelines do not recommend routine antibiotic prophylaxis in infants and children after first UTI. The recent AAP guidelines also do not recommend prophylactic antibiotics after first UTI in children aged 2–24 months [7¹¹]. Islek *et al.* [33] followed infants ($n = 84$) with prenatal ureteropelvic junction obstruction without antibiotic prophylaxis for 12–24 months and none of the patients had UTI or renal scar during the follow-up period.

There is resurgence in the use of cranberry products to prevent recurrence of UTI. The proposed mechanism of action is inhibition of uropathogenic *E. coli* at the uroepithelium. In a recent systematic review of published randomized clinical trials, Wang *et al.* [34] found that consumption of cranberry products may protect against UTIs in certain populations. However, they concluded on a cautious note, based on the substantial heterogeneity across trials. Stapleton *et al.* [35] randomized 176 women to two arms (120 to cranberry juice and 56 to placebo) and followed them for a median of 168 days. The cumulative rate of UTI was 0.29 in the cranberry juice group and 0.37 in the placebo group ($P = 0.82$). The adjusted hazard ratio for UTI in the cranberry juice group vs. the placebo group was 0.68 (95% confidence interval 0.33–1.39; $P = 0.29$). They concluded that, though cranberry juice did not significantly reduce UTI risk compared with placebo, the potential protective effect observed warrants confirmation in larger, well-powered studies. Salo *et al.* [36] randomized 263 children with UTI to receive either cranberry juice ($n = 129$) or placebo ($n = 134$) for 6 months and followed them for a year in seven Finnish hospitals. The intervention did not significantly reduce the number of children who experienced a recurrence of UTI.

Dysfunctional elimination syndrome is a known cause of UTI. The syndrome comprises of inability to effectively empty the bladder, incontinence, constipation, and other voiding symptoms. Biofeedback therapy has been helpful in improving voiding symptoms in children with dysfunctional voiding. The pooled estimate from 27 studies reviewed by Desantis *et al.* [37] showed 83% (95% confidence interval 76–86%) improvement in UTI with biofeedback therapy in children less than 18 years of age. The authors concluded that well-designed trials are needed to evaluate the effectiveness of biofeedback in prevention of UTI in children.

The use of probiotics to prevent UTI is being explored. Probiotics contain a live microorganism given to confer health benefit to the host without causing infection or untoward effects. The use of probiotics in prevention of bacterial infections has received mixed reviews. Probiotics work by displacing pathogenic bacteria from the gut as well as boosting the innate immunity of the gut. In a prospective randomized study comparing conventional antibiotics and probiotics in treating children with primary VUR, the incidence of recurrent UTI was comparable in both groups of children [38,39]. In an in-vitro study, Storm *et al.* [40] found that 'Mutaflor' (a probiotic containing *E. coli* Nissle 1917) had bactericidal effect against a wide range of uropathogens. They concluded that probiotics may be effective in preventing and eliminating the colonization of pathogenic bacteria in the gut and that such a reduction in the fecal load of uropathogens will translate to a reduction in the incidence of recurrence of UTI.

Will the cutting of the foreskin become the cutting-edge of prevention of UTI in boys? Previous studies have established an association between circumcision and reduced risk of UTI in boys. However, the number of circumcisions needed to prevent one UTI is reported to be about 111 in the general population [10]. Is this a cost-effective strategy for the general population or should it be reserved for boys at high risk of UTI? The AAP recently highlighted the benefits of male circumcision and concluded that the health benefits of newborn male circumcision outweigh the risks [41]. They encouraged providers to explain

the benefits and risks of circumcision to parents and to leave the final decision for or against circumcision to the parents.

CONCLUSION

With high suspicion for UTI and early treatment, UTI complications including renal scarring could be avoided. Patients and their families should be given the message that UTI is an acute infection and, with appropriate and timely treatment, UTI usually resolves with no untoward consequences. However, certain individuals may have a predilection for recurrences and occasionally this is a marker of congenital renal abnormalities or urinary tract obstruction. These conditions may be screened for with RBUS [17]. Further research is needed to elucidate and validate host factors and genetic variations predisposing to renal scarring. These factors should be considered in future clinical practice guidelines for UTI in order to further avoid unnecessary invasive procedures. Providers using current guidelines should endeavor to collect practice-based evidence to validate and inform future guidelines.

Acknowledgments

Thanks to Dr Allison Langs-Barlow for her critical reading of the manuscript.

E.P. is supported by a grant from the National Institute of Health (K08AI074404).

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 155–156).

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FIGURE 1.

Management of urinary tract infection in children at a glance. Data from the AAP Clinical Practice Guideline Algorithm [7¹¹]. This is a simplified overview of the management of UTI in children of all ages. ^aThe evaluation of UTI depends on the age of the child. The clinical presentations generally shift from nonspecific to more specific complaints with age. The provider should use clinical judgment. ^bThe source of urine for urinalysis and particularly for culture depends on age. For children up to 24 months of age, bladder catheterization or suprapubic aspiration is required. For children who are toilet trained or older, midstream clean catch may suffice. All samples should be processed within 1 h of collection. If for any

reason this is not possible, samples should be refrigerated at 4–8°C pending processing.
AAP, American Academy of Pediatrics; UTI, urinary tract infection.

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Table 1

Antimicrobial agents for treatment of urinary tract infections

Antimicrobial agent	Dosage
Parenteral	
Ceftriaxone	75 mg/kg, every 24 h
Cefotaxime	150 mg/kg per day, divided every 6–8 h
Ceftazidime	100–150 mg/kg per day, divided every 8 h
Gentamicin	7.5 mg/kg per day, divided every 8 h
Tobramycin	5 mg/kg per day, divided every 8 h
Piperacillin	300 mg/kg per day, divided every 6–8 h
Oral	
Amoxicillin clavulanate	20–40 mg/kg per day in three doses
Trimethoprim sulfamethoxazole	6–12 mg/kg trimethoprim and 30–60 mg/kg sulfamethoxazole per day in two doses
Sulfisoxazole	120–150 mg/kg per day in four doses
Cefixime	8 mg/kg per day in one dose
Cefpodoxime	10 mg/kg per day in two doses
Cefprozil	30 mg/kg per day in two doses
Cefuroxime axetil	20–30 mg/kg per day in two doses
Cephalexin	50–100 mg/kg per day in four doses

Adapted with permission from the AAP Clinical Practice Guidelines [7[■]].