Urinary tract infections in children: Epidemiology and risk factors

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INTRODUCTION — Urinary tract infection (UTI) is a common and important clinical problem in childhood. Upper urinary tract infections (ie, acute pyelonephritis) may lead to renal scarring, hypertension, and end-stage renal disease. Although children with pyelonephritis tend to present with fever, it is often difficult on clinical grounds to distinguish cystitis from pyelonephritis, particularly in young children (those younger than two years) [1]. Thus, we have defined UTI broadly here without attempting to distinguish cystitis from pyelonephritis. Acute cystitis in older children is discussed separately. (See "Acute cystitis: Clinical features and diagnosis in children older than two years and adolescents".)

The presence of risk factors for UTI and renal scarring in a child presenting with fever and/or urinary symptoms is helpful in guiding diagnostic testing and management. The epidemiology and risk factors for UTI and renal scarring in children will be reviewed here. Clinical features, diagnosis, and management of UTI, and UTI in newborns (younger than one month of age) are discussed separately. (See "Urinary tract infections in infants and children older than one month: Clinical features and diagnosis" and "Urinary tract infections in infants and children older than one month: Acute management, imaging, and prognosis" and "Urinary tract infections in children: Long-term management and prevention" and "Urinary tract infections in neonates".)

EPIDEMIOLOGY — Knowledge of the epidemiology of urinary tract infection (UTI) is important in the evaluation of a child with suspected UTI. (See "Urinary tract infections in infants and children older than one month: Clinical features and diagnosis", section on 'Laboratory evaluation'.)

Prevalence — Awareness of the prevalence of UTI in various subgroups of children enables the clinician to grossly estimate the probability of infection in the patient (ie, the pretest probability) (table 1).

In young children with fever — The prevalence of UTI in children <2 years presenting with fever has been the subject of several large prospective studies and a meta-analysis [2-4]. Important points that emerged from these studies include:

- The overall prevalence of UTI is approximately 7 percent in febrile infants and young children but varies by age, race/ethnicity, sex, and circumcision status.
- White children have a two- to fourfold higher prevalence of UTI than do black children.
- Girls have a two- to fourfold higher prevalence of UTI than do circumcised boys.
- White girls with a temperature of ≥39ºC have a UTI prevalence of 16 percent.

The approximate probability of having a UTI by demographic group, as determined by the above studies, is summarized in the table (table 1).

In older children — In pooled analysis of four studies that included children <19 years (most of whom were older than two years) and had urinary symptoms and/or fever, the prevalence of UTI was 7.8 percent (95% CI 6.6-8.9) [4].

MICROBIOLOGY — *Escherichia coli* is the most common bacterial cause of UTI; it accounts for approximately 80 percent of UTI in children [5]. Other gram-negative bacterial pathogens include *Klebsiella*, *Proteus*, *Enterobacter*,

and *Citrobacter*. Gram-positive bacterial pathogens include *Staphylococcus saprophyticus*, *Enterococcus*, and, rarely, *Staphylococcus aureus*.

Infection with an organism other than *E. coli* is associated with renal scarring. In a meta-analysis of individual patient data from nine studies including 1280 children (0 to 18 years) who underwent renal scintigraphy at least five months after their first UTI, non-*E. coli* UTI was associated with an increased risk of renal scarring (odds ratio 2.2, 95% CI 1.3-3.6) [6].

Viruses (eg, adenovirus, enteroviruses, Coxsackieviruses, echoviruses) and fungi (eg, *Candida* spp, *Aspergillus* spp, *Cryptococcus neoformans*, endemic mycoses) are uncommon causes of UTI in children [7,8]. Viral UTI are usually limited to the lower urinary tract. Risk factors for fungal UTI include immunosuppression and long-term use of broad-spectrum antibiotic therapy, and indwelling urinary catheter [9]. (See "Acute cystitis: Clinical features and diagnosis in children older than two years and adolescents", section on 'Microbiology'.)

PATHOGENESIS — The bacteriology of urinary tract infection (UTI), along with the observation that a minority (4 to 9 percent) of children with UTI are bacteremic [10,11], is consistent with the hypothesis that most UTI beyond the newborn period are the result of ascending infection.

Colonization of the periurethral area by uropathogenic enteric pathogens is the first step in the development of a UTI. The presence of pathogens on the periurethral mucosa, however, is not sufficient to cause UTI [12]. Pathogens attach to the uroepithelial cells via an active process mediated by glycosphingolipid receptors on the surface of epithelial cells [13-15]. Bacterial attachment recruits toll-like receptors (TLR), a family of transmembrane coreceptors involved in the recognition of pathogen-associated protein patterns [15]. TLR binding triggers a cytokine response, which generates a local inflammatory response.

A variety of virulence factors enable bacteria to ascend into the bladder and kidney. The best-studied virulence factors in *E. coli* are pili, hair-like appendages on the cell surface. Bacteria possessing pili can adhere effectively to the uroepithelium and ascend into the kidney, even in children without vesicoureteral reflux (VUR). In the kidney, the bacterial inoculum generates an intense inflammatory response, which may ultimately lead to renal scarring. (See "Bacterial adherence and other virulence factors for urinary tract infection".)

HOST FACTORS — A variety of host factors influence the predisposition to urinary tract infection (UTI) in children.

Age — The prevalence of UTI is highest in boys younger than one year and girls younger than four years [4,16].

Lack of circumcision — Uncircumcised male infants with fever have a four- to eightfold higher prevalence of UTI than circumcised male infants [4,17]. (See 'Prevalence' above.)

Two plausible mechanisms have been proposed to explain this difference:

- The mucosal surface of the uncircumcised foreskin is more likely to bind uropathogenic bacterial species than keratinized skin on a circumcised penis [18]. The keratinization of the mucosa is largely complete by one year of age and temporally coincides with the decreasing prevalence of UTI in boys.
- Partial obstruction of the urethral meatus by a tight foreskin may be the explanation for the higher incidence of UTI in uncircumcised boys [19,20]. In one study of uncircumcised male infants (<7 months of age), inability to retract the foreskin to expose the urethral meatus was more common among boys with febrile UTI than among those without UTI (85 versus 42 percent) [19]. The tightness of the foreskin diminishes with time and is an infrequent finding after one year of age [19].

Despite the increased risk, most uncircumcised boys do not develop UTI [21]. A systematic review of randomized and observational studies of circumcision for the prevention of UTI found that 111 circumcisions would be needed to prevent one UTI [17]. Sensitivity analysis of a decision model for circumcision suggested that the decision to circumcise a boy hinges more heavily on the parents' values regarding pain than on the UTI prevalence or circumcision complication rates [22]. This observation underscores the importance of respecting parental values as they decide whether to circumcise their sons. (See "Neonatal circumcision: Risks and benefits".)

Female infants — Female infants have a two- to fourfold higher prevalence of UTI than male infants [4]. This has been presumed to be the result of the shorter female urethra. Because the incidence of UTI in male neonates is as high, if not higher, than in female neonates, the importance of the length of the urethra in the pathogenesis of UTI has been questioned. Alternatively, the propensity of bacterial attachment to the female periurethral mucosa may account for this difference.

Race/ethnicity — For reasons that are not completely understood, white children have a two- to fourfold higher prevalence of UTI than do black children [2-4].

Genetic factors — First-degree relatives of children with UTI are more likely to have UTI than individuals without such a history [23,24]. Adherence of bacteria may, in part, be genetically determined (eg, by the expression of blood group antigens on the surface of uroepithelial cells) [25,26]. In addition, women with recurrent UTI have a higher density of receptors for *E. coli* in the periurethral area. On the other hand, individuals with mutations in the toll-like receptor (TLR) signaling pathway do not mount a significant inflammatory response, even when virulent bacteria are present [27,28]. (See "Recurrent urinary tract infection in women", section on 'Biologic or genetic factors'.)

Urinary obstruction — Children with obstructive urologic abnormalities are at increased risk of developing UTI; stagnant urine is an excellent culture medium for most uropathogens. Predisposing obstructive abnormalities may be anatomic (posterior urethral valves, ureteropelvic junction obstruction), neurologic (eg, myelomeningocele with neurogenic bladder), or functional (eg, bowel and bladder dysfunction). (See appropriate topic reviews).

Despite the increased risk of UTI in children with obstructive abnormalities, obstructive anatomic abnormalities are infrequent in children presenting with a first UTI (1 to 4 percent) [1,29-32]. Urinary obstruction should be suspected when the patient has voiding problems (eg, daytime enuresis, dribbling of urine), other family members have had urologic abnormalities, when genitourinary abnormalities are detected on physical examination, or when symptoms do not respond to appropriate therapy.

Bowel and bladder dysfunction — Bowel and bladder dysfunction, of which bladder dysfunction is a subset, is characterized by:

- An abnormal elimination pattern (frequent or infrequent voids, urgency, infrequent stools [constipation])
- Bladder and/or bowel incontinence
- Withholding maneuvers

Bowel and bladder dysfunction usually presents in otherwise-healthy school-age children and may persist for months to years. The pathophysiology is varied but basically involves a behavioral or learned abnormality of function of the muscles of the pelvis, bladder, and/or sphincter. Although this condition is relatively common in children (its prevalence is approximately 15 percent), it is often underdiagnosed and undertreated by primary care clinicians [33,34]. Presenting manifestations include urgency, frequency, nocturnal enuresis, retention, incontinence, and urinary infection [35].

Bowel and bladder dysfunction is an important and often overlooked factor in the pathophysiology of UTI in children. Up to 40 percent of toilet-trained children with their first UTI and 80 percent of children with recurrent (three or more) UTI report symptoms of bowel and bladder dysfunction [29,36-39]. Bowel and bladder dysfunction is also a risk factor for persistent vesicoureteral reflux (VUR) and renal scarring [36,37,40-42]. In baseline data, bowel and bladder dysfunction was identified in 56 percent of 126 toiled trained children (<6 years of age) enrolled in the randomized intervention for VUR (RIVUR) trial comparing antibiotic prophylaxis and placebo in children with grades I to IV VUR [43]. (See "Etiology and clinical features of bladder dysfunction in children".)

The diagnosis usually is evident clinically. Initial evaluation and management should be initiated by the primary care clinician. Bowel and bladder dysfunction is a diagnosis of exclusion. Thus, a complete history and physical examination, a urinalysis, and a bladder ultrasound are usually obtained as part of the diagnostic evaluation (to rule out organic causes of incontinence, such as diabetes and neurogenic bladder). Chronic problems with elimination

put these children at risk for significant psychosocial problems both at home and at school.

Bowel and bladder dysfunction is discussed separately. (See "Etiology and clinical features of bladder dysfunction in children" and "Evaluation and diagnosis of bladder dysfunction in children".)

Vesicoureteral reflux — Vesicoureteral reflux (VUR) is the retrograde passage of urine from the bladder into the upper urinary tract. It is the most common urologic anomaly in children. Children with VUR are at increased risk for recurrent UTI. The clinical manifestations, management, and long-term implications of VUR are discussed separately. (See "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux" and "Management of vesicoureteral reflux".)

It has been widely believed that VUR constitutes a major risk factor for pyelonephritis and renal scarring in young children. However, the role of VUR in initiating pyelonephritis and scarring is poorly documented and may have been overstated [44]. An association between VUR and pyelonephritis has been demonstrated in some studies [1,45], but not in others [40,46]. The role of VUR in renal scarring is discussed separately. (See "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux", section on 'Renal scarring and/or dysplasia'.)

Sexual activity — The association between sexual intercourse and UTI in females has been well documented. (See "Acute uncomplicated cystitis and pyelonephritis in women", section on 'Pathogenesis'.)

Bladder catheterization — The risk of UTI increases with increasing duration of bladder catheterization. (See "Catheter-associated urinary tract infection in adults".)

BACTERIAL-HOST INTERACTIONS — There is indirect evidence that alteration of the normal periurethral flora promotes attachment of pathogenic bacteria as illustrated by the following observations:

- In one study, *E. coli* and other gram-negative uropathogenic organisms were cultured more frequently from the urethras of uncircumcised boys than from those of circumcised boys, and bacterial colony counts were higher [47].
- In a prospective study of preschool children with bacteriuria, recent treatment with antibiotics for upper respiratory infections was associated with an increased risk of febrile urinary tract infection [23].
- The use of spermicidal condoms and spermicidal jelly with diaphragms has been independently associated with *E. coli* bacteriuria, suggesting that these agents predispose to urinary tract infection by altering the normal vaginal flora (Lactobacillus and *Corynebacterium* spp) [48].
- In experimental studies in monkeys, the use of beta-lactam antibiotics (eg, penicillins and cephalosporins) disturbed the normal vaginal flora and promoted *E. coli* colonization [49].

RISK FACTORS FOR RENAL SCARRING — Renal scarring, the loss of renal parenchyma between the calyces and the renal capsule, is a potential complication of urinary tract infection (UTI). Long-term consequences of renal scarring may include hypertension, decreased renal function, proteinuria, and end-stage renal disease.

General risk factors — The development of renal scarring has been associated with the following factors, which are modifiable to some extent:

- Recurrent febrile UTI (see "Urinary tract infections in children: Long-term management and prevention", section on 'Recurrent symptoms' and "Urinary tract infections in children: Long-term management and prevention", section on 'Prevention of recurrent UTI in children without VUR')
- Delay in treatment of acute infection (see "Urinary tract infections in infants and children older than one month: Acute management, imaging, and prognosis", section on 'Empiric therapy')

  Early initiation of UTI treatment requires that the diagnosis be considered even in the absence of symptoms referable to the urinary tract (eg, in the febrile infant or young child with or without a focus of infection) (see "Urinary tract infections in infants and children older than one month: Clinical features and diagnosis", section

on 'Clinical presentation')

- Bowel and bladder dysfunction (see "Urinary tract infections in children: Long-term management and prevention", section on 'Children with bowel and bladder dysfunction')

  Modification of bowel and bladder dysfunction requires that it be recognized; presenting symptoms include urgency, enuresis, urinary retention, and constipation [35] (see 'Bowel and bladder dysfunction' above)

- Obstructive malformations (see "Clinical presentation and diagnosis of posterior urethral valves", section on 'Chronic kidney disease' and "Congenital ureteropelvic junction obstruction", section on 'Outcome')

  Obstructive malformations generally are treated surgically (see "Management of posterior urethral valves" and "Congenital ureteropelvic junction obstruction", section on 'Management')

- VUR (see "Clinical presentation, diagnosis, and course of primary vesicoureteral reflux", section on 'Renal scarring and/or dysplasia' and "Management of vesicoureteral reflux")

Young age has been shown to be associated with scarring in some studies [50-52], but not in others [6,53-58].

Prediction of renal scarring after first UTI — Predictors of renal scarring after a first UTI were investigated in a meta-analysis of individual patient data from nine studies including 1280 children (0 to 18 years) who underwent renal scintigraphy at least five months after their first UTI [6]. Renal scarring was present in 15.5 percent of children. Predictors of renal scarring included:

- VUR – VUR, especially high-grade VUR, was associated with the development of renal scars [Grade I and II (OR = 1.8, 95% CI 1.2–2.8) and Grade IV and V VUR (OR 22.5, 95% CI 11.3-44.8)]
- Abnormal renal bladder ultrasonography (OR 3.8, 95% CI 2.6-5.5)
- Inflammatory markets including a high C-reactive protein of >40 mg/L (OR 3.0, 95% CI 2.0-4.6), or a polymorphonuclear cell count >60 percent (OR 1.9, 95% CI 1.3-2.8); only children who have pyelonephritis are at risk for the development of renal scarring.
- Temperature ≥39°C (102.2°F) (odds ratio [OR] 2.3, 95% CI 1.6-3.3)
- UTI caused by organism other than *E. coli* (OR 2.2, 95% CI 1.3-3.6)

The authors attempted to develop a model that would enable clinicians to determine the risk of renal scarring in patients with a first UTI. Although grade IV or V VUR was the strongest predictor of renal scarring, only 4.1 percent of patients had grade IV or V VUR. In addition, determination of VUR requires routine voiding cystourethrogram (VCUG) in all infants. The accuracy of a model including only variables that are routinely collected (ie, temperature, renal bladder ultrasonography [RBUS] findings, etiologic organism) had a sensitivity and specificity of 44.9 and 82.4 percent, respectively. The overall predictive ability of this model with three variables was only 3 to 5 percent less than the predictive ability of models requiring a blood draw and/or a VCUG. Children with an abnormal RBUS finding or with a combination of high fever (≥39°C) and an etiologic organism other than *E. coli* (which constituted 21.7 percent of the sample) represent a particularly high-risk group in whom the risk for renal scarring is 30.7 percent.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on

"patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient information: Urinary tract infections in children (The Basics)")
- Beyond the Basics topic (see "Patient information: Urinary tract infections in children (Beyond the Basics)")

SUMMARY

- The prevalence of urinary tract infection (UTI) in febrile children younger than two years varies from <1 to 16 percent depending upon age, sex, circumcision status in boys, and race/ethnicity (table 1). (See 'In young children with fever' above.)
- The prevalence of UTI in older children with urinary tract symptoms and/or fever is approximately 8 percent. (See 'In older children' above.)
- *Escherichia coli* is the most common bacterial cause of UTI. (See 'Microbiology' above.)
- A variety of host factors influence the predisposition to UTI in children. These include genetic factors, urinary tract anomalies, bowel and bladder dysfunction, vesicoureteral reflux (VUR), sexual activity, and bladder catheterization in addition to those mentioned above for febrile young children (eg, lack of circumcision, female sex). (See 'Host factors' above.)
- Bowel and bladder dysfunction is an important and often overlooked factor in the pathophysiology of UTI in children. It is characterized by an abnormal elimination pattern (frequent or infrequent voids, urgency, infrequent stools), bladder and or bowel incontinence, and withholding maneuvers. (See 'Bowel and bladder dysfunction' above.)
- Children with an abnormal renal ultrasonographic finding or with a combination of high fever (≥39°C) and an etiologic organism other than *E. coli* are have a higher risk of developing renal scarring than children without these characteristics. (See 'Prediction of renal scarring after first UTI' above.)

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GRAPHICS

Prevalence of urinary tract infection in febrile* infants and children by demographic group

Demographic group	Prevalence or pretest probability (95% CI)
0 to 3 months	**7.2 percent (5.8-8.6)**
Girls	7.5 percent (5.1-10)
Circumcised boys	2.4 percent (1.4-3.5)
Uncircumcised boys	20.1 percent (16.8-23.4)
3 to 6 months	**6.6 percent (1.7-11.5)**
Girls	5.7 percent (2.3-9.4)
Boys	3.3 percent (1.3-5.3)
6 to 12 months	**5.4 percent (3.4-7.4)**
Girls	8.3 percent (3.9-12.7)
Boys	1.7 percent (0.5-2.9)
12 to 24 months	**4.5 percent¶**
Girls	2.1 percent (1.2-3.6)
Circumcised boys >1 year	<1 percent¶
<19 years with urinary symptoms and/or fever Δ	**7.8 percent (6.6-8.9)**

* Temperature ≥38°C.

¶ 95% confidence interval not available.

Δ Most of these children were older than two years.

Data from: Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of Urinary Tract Infection in Childhood: A Meta-Analysis. Pediatr Infect Dis J 2008; 27:302.

Graphic 76804 Version 6.0

Disclosures

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