CHAPTER 69

Urinary Tract Infections in Childhood

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Urinary tract infections (UTIs) are a common and important clinical problem in childhood and may lead to systemic illness and renal injury in the short term; with repeated infections, renal scarring, hypertension, and end-stage renal dysfunction may develop.

The overall prevalence of UTI is estimated at 5% in febrile infants but varies widely by race and gender.[1,2] The highest prevalence rates of childhood UTI occur in uncircumcised male infants under 3 months of age (prevalence ~20%), and among females (prevalence ~8%). Uncircumcised older male children have the lowest prevalence of UTI (~1%).

PATHOGENESIS

Most UTIs beyond the newborn period represent an ascending infection. Colonization of the periurethral area by uropathogenic enteric organisms is the first step. The most common bacterial species is *Escherichia coli*, which accounts for about 80% of UTIs in children. Other bacteria include both gram-negative species *(Klebsiella*, *Proteus*, *Enterobacter*, and *Citrobacter)* and gram-positive species (*Staphylococcus saprophyticus*, *Enterococcus*, and rarely, *Staphylococcus aureus*). The presence of pathogens on the periurethral mucosa is not sufficient to cause UTIs.[3] Attachment of bacteria to uroepithelial cells is an active process mediated by specific bacterial adhesins and specific receptor sites on the epithelial cells. This process allows bacteria to ascend into the kidney, even in children without vesicoureteral reflux (VUR). In the kidney, the bacterial inoculum can produce an infection with an intense inflammatory response that may ultimately lead to renal scarring.

Many host factors influence the predisposition that children may have to UTI, including familial predisposition, genitourinary anatomy and function, instrumentation, and sexual activity, as well as periurethral flora. The determination of risk factors in a child presenting with UTI is important in preventing further recurrences.

First-degree relatives of children with UTIs are more likely to have UTIs,[4] and adherence of bacteria may, at least in part, be genetically determined.

Uncircumcised febrile male infants have a four- to tenfold higher prevalence of UTIs than circumcised males do.[5] Although uncircumcised males are at increased risk for the development of a UTI, it is important to point out that UTIs do not develop in most uncircumcised boys.[6] It is estimated that 195 circumcisions would be needed to prevent one hospital admission for UTI in the first year of life.[5]

Dysfunctional elimination syndrome (DES) refers to a functional disorder of unknown etiology characterized by the features delineated in Table 69-1. DES, also known as voiding dysfunction, usually appears in healthy school-aged children and may persist for months to years. Although DES is a relatively common condition in the pediatric population, with a prevalence estimated at 15%,[7] it is often underdiagnosed and undertreated by primary care physicians.[8] Approximately 40% of toilet-trained children with their first UTI[9-11] and 80% of children with recurrent UTI[12] report symptoms of DES. In a study of 141 girls older than 3 years with recurrent (more than three) UTIs, 108 had DES.[12] This syndrome is also a risk factor for VUR persistence[13-15] and renal scarring.[10,15]

VUR is the most frequently occurring urologic abnormality in children, with an overall prevalence of 1% and a prevalence of 40% in young children with febrile UTIs. A strong genetic predisposition for VUR exists and has been identified in up to 40% of siblings of children with VUR. The incidence of VUR is markedly lower in the African American population. VUR is graded according to the international classification from grade 1 to grade 5 (Fig. 69-1). In children presenting with their first UTI to a primary care physician, 95% of cases of VUR have been found to be grades 1 to 3.[16] Most VUR improves or resolves as the child ages, with resolution occurring more frequently in children with low-grade and unilateral disease.[17,18] The likelihood of resolution of VUR, 5 years after detection, as derived from a large meta-analysis, is summarized in Figure 69-2.[19]

It has been widely believed that VUR is the major risk factor for pyelonephritis and renal scarring in young children. The role of VUR in initiating pyelonephritis and scarring, however, has been poorly documented in the literature, and there is evidence that its importance in the pathophysiology of pyelonephritis and renal scarring may have been overstated.[20] Current evidence implies that VUR is neither necessary nor sufficient to cause renal scarring and that exclusive focus on VUR, without a search for other modifiable risk factors (such as DES), may be inadequate.

Children with obstructive abnormalities, whether anatomic (e.g., posterior urethral valves, ureteropelvic junction obstruction, constipation), neurologic (e.g., myelomeningocele with neurogenic bladder), or functional (e.g., DES), are at increased risk for the development of UTIs. Stagnant urine is an excellent culture medium for most uropathogens. However, obstructive anatomic abnormalities in children presenting with their first UTI are infrequent (1% to 4%) in nonsyndromic children.[16,21-23] Obstruction should be suspected when other family members have had urologic abnormalities, when dysmorphic features are detected on physical examination, or when symptoms do not respond to appropriate therapy.

There is indirect evidence that alteration of the normal periurethral flora in females (*Lactobacillus* and *Corynebacterium* spp.) promotes attachment of pathogenic bacteria.

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Table 69-1 Dysfunctional Elimination Syndrome

Clinical Triad	Symptoms
Abnormal elimination pattern	Frequent voiding (>10 times/day) Infrequent voiding (≤3 times/day) Urgency (often runs to the bathroom) Infrequent hard painful stools (ask the child, not the parent)
Incontinence	Bladder (ask about damp underwear) Bowel (ask about streaks of stool in underwear)
Withholding maneuvers	Pee dance Kneeling with the perineum on the heel (Vincent's curtsey)

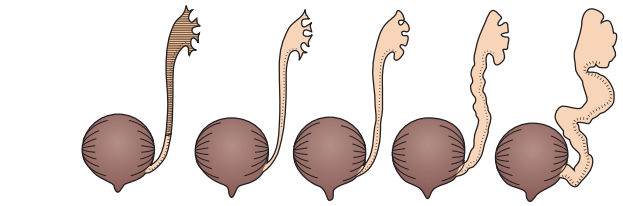

Figure 69-1 Grading of vesicoureteral reflux.

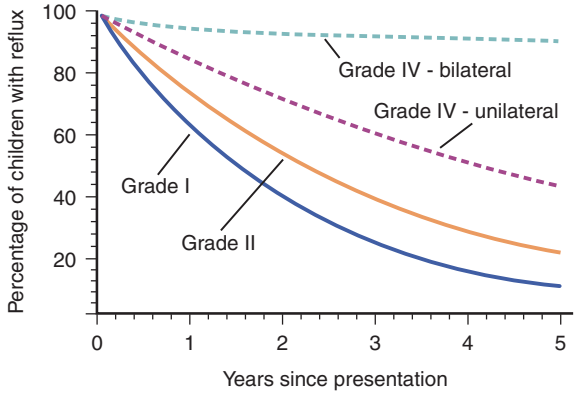

Figure 69-2 Persistence of vesicoureteral reflux in young children.

Sexual activity is also associated with UTI in women. In a prospective study of young sexually active women, recent intercourse was independently associated with the development of UTIs.[24] The use of spermicidal condoms and spermicidal jelly with diaphragms has been independently associated with *E. coli* bacteriuria, thus suggesting that these agents predispose to UTI by altering the vaginal flora.[24]

The risk for UTI increases with increasing duration of catheterization. In a 7-year retrospective study, nosocomial UTIs were found to be the fifth most common infection in hospitalized children. However, only 50% of children with nosocomial UTIs were catheterized, and nosocomial UTIs occurred with a disproportionately high rate in newborns.[25]

CLINICAL PRESENTATION

In general, the younger the child, the less specific the presenting signs and symptoms of UTI. Many infants with UTI are described as "well appearing."

Several prospective studies have shown that infants and young children can present with fever as the sole manifestation of UTI.[1,2] Furthermore, the presence of another potential source for fever (upper respiratory tract infection, acute otitis media, acute gastroenteritis, etc.) does not rule out the possibility of UTI. In one study, the prevalence of UTI in infants and young girls with fever was 6% if no other potential source of fever was identified, but the prevalence was 3% even if another potential source of fever was identified.[2] This finding highlights the importance of considering urine cultures in all febrile infants without a definite source for fever. Parental reporting of foul-smelling urine[26] or the presence of gastrointestinal symptoms (vomiting, diarrhea, and poor feeding[1,2]) does not correlate with the presence of UTIs. Other less common symptoms of UTI in infants include conjugated hyperbilirubinemia and failure to thrive.

Symptoms of UTI in older children may include fever, urinary symptoms (dysuria, urgency, frequency, incontinence, macroscopic hematuria), and abdominal pain.[27,28] Suprapubic tenderness and costovertebral angle tenderness may be present on examination. Occasionally, older children may present with failure to thrive, nephropathy, or hypertension secondary to unrecognized UTIs earlier in childhood.[29]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a well-appearing infant or young child with "fever without a definite source" is extensive but most commonly includes UTI, occult bacteremia, and viral infections. In children vaccinated against *Haemophilus influenzae* and *Streptococcus pneumoniae*, the odds of UTI are much higher than the odds of occult bacteremia. The differential diagnosis of an older child presenting with urinary symptoms and bacteriuria includes nonspecific vulvovaginitis, an abdominal process such as appendicitis, urinary calculi, urethritis secondary to sexually transmitted disease, and a vaginal foreign body. Patients with group A streptococcal infection, appendicitis, and Kawasaki disease may present with fever, abdominal pain, and pyuria.

DIAGNOSIS AND EVALUATION

Particular elements of the history of the acute illness should include the height and duration of fever and the presence of urinary symptoms, hematuria, vomiting, nonurinary symptoms (rash, rhinorrhea, cough, etc.), genitourinary instrumentation, sexual activity, and method of contraception. The past history should include any history of chronic constipation, chronic urinary symptoms (incontinence, lack of proper stream, frequency, urgency, withholding maneuvers), previous UTIs, VUR, and previous undiagnosed febrile illnesses. Relevant family history would include frequent UTIs, VUR, and other genitourinary abnormalities in close relatives.

Key elements of the physical examination include blood pressure and temperature, assessment of suprapubic and

costovertebral tenderness, and if febrile, a search for signs of other sources of fever. The external genitalia should be examined for signs of vulvovaginitis, vaginal foreign body, sexually transmitted diseases, and anatomic abnormalities.

Given that the signs and symptoms of UTI in children are nonspecific, diagnosis of UTI requires laboratory confirmation. A clean-catch specimen and a catheterized specimen are the preferred methods of urine collection in a toilet-trained and a diapered child, respectively. Suprapubic aspiration may also be used to collect a specimen in young children. The use of a sterile bag is not generally recommended because up to 85% of positive cultures from bag urine specimens will represent false-positive results[30]; therefore, results are useful only if negative. The high false-positive rate of bag specimens can lead to unnecessary and even harmful interventions.[31] Specimens should be examined soon after collection inasmuch as delay of even a few hours increases both false-positive and false-negative rates substantially.[30]

The accuracy of the various diagnostic tests for UTI has been the subject of two meta-analyses.[32,33] The sensitivity, specificity, and likelihood ratios of bedside tests available to diagnose UTIs in children are summarized in Table 69-2.

Dipstick tests are convenient and inexpensive and require little training for proper use, but they may miss some children with UTI (88% sensitivity at best).[33] Furthermore, a positive leukocyte esterase test does not always confirm the diagnosis of UTI.

Microscopic examination requires more equipment and training than dipstick tests do. Traditionally, a centrifuged sample of unstained urine is examined for the presence of bacteria and white cells. The accuracy of microscopic analysis is improved by using (1) an uncentrifuged specimen,[32] (2) a Gram-stained specimen,[33] and (3) a hemocytometer (results reported as white blood cells/mm^3).[34] Examination of urine with these three techniques has been termed "enhanced urinalysis."[34] In young children, in whom prompt diagnosis and treatment are paramount, enhanced urinalysis offers the best combination of sensitivity and specificity. A child with neither pyuria nor bacteriuria on enhanced urinalysis is very unlikely to have a UTI, whereas a child with both pyuria and bacteriuria is very likely to have a UTI.

UTI is best defined as significant bacteriuria on urine culture in a patient with abnormal urinalysis findings (leukocyturia or bacteriuria). Determination of "significant" bacteriuria by culture depends on the method of collection. Guidelines are provided in Table 69-3.

A high white blood cell count or elevated C-reactive protein does not reliably differentiate between children with cystitis and pyelonephritis. Accordingly, these tests are not necessary in the initial evaluation of children with suspected UTIs. Determination of serum creatinine is appropriate in a child with multiple UTIs and suspected renal involvement. Although 4% to 9%[35,36] of infants with UTI are bacteremic and although fever in bacteremic infants with UTI may persist on average 1 day longer than in nonbacteremic children,[37] the organisms isolated from blood and urine are identical, as is the prognosis. For this reason, routine performance of a blood culture in children older than 2 months with a UTI is not necessary because it does not alter management in the vast majority of children. Children younger than 1 month with high fever and abnormal urinalysis results should undergo lumbar puncture as part of the initial evaluation inasmuch as some neonates (≈1%) with UTI may also have bacterial meningitis.[38]

COURSE OF ILLNESS

In two large studies, details of the hospital course were documented. Mean time to defervescence was approximately 24 hours.[39] Approximately 90% of children were afebrile by 48 hours, and only 5% of children remained febrile for longer than 72 hours.[40] None of the follow-up urine cultures, including cultures from children with fever that lasted longer than 48 hours, were positive. No renal abscesses were found. Since the incidence of renal abscess formation is very low,

Table 69-2 Diagnostic Indicators of Urinary Tract Infection

	Sensitivity	Specificity	Positive Likelihood Ratio	1/Negative Likelihood Ratio	Reference
Dipstick					
Leukocyte esterase (LE)	84%	78%	4	5	33
Nitrite	50%	98%	25	2	33
Nitrite or LE	88%	93%	13	8	33
Nitrite and LE	72%	96%	18	3	33
Microscopy					
Uncentrifuged					
Pyuria (<10/mm^3) (all ages)	77%	89%	7	4	33
Pyuria (<10/mm^3) (>2 yr)	90%	95%	18	10	33, 34
Bacteriuria (by Gram stain)	93%	95%	19	14	33
Overall (P and B)*	85%	99.9%	85	7	33
Overall (P or B)	95%	89%	9	17	33
Centrifuged					
Pyuria (<5/hpf)	67%	79%	3	2	33
Bacteriuria	81%	83%	5	5	30
Overall (P and B)	66%	99%	7	2	34

*Represents enhanced urinalysis.
B, bacteriuria; hpf, high-power field; P, pyuria.

Table 69-3 Guidelines for Determining Urinary Tract Infection from Quantitative Urine Cultures

Method of Collection	Colony-Forming Units per Milliliter		
	*Definite**	*Indeterminant*†	*Contaminant*
Suprapubic	Any growth		Growth of nonpathogens Mixed culture‡
Catheterization	>50,000	10,000-50,000, single pathogen	Growth of nonpathogens Mixed culture‡ <10,000
Clean catch	>100,000	50,000-100,000, single pathogen	Growth of nonpathogens Mixed culture‡ <10,000

*If accompanied by abnormal urinalysis findings (leukocyturia or bacteriuria).
†Need to obtain a repeat specimen.
‡Mixed culture = uropathogen + nonpathogen *or* two uropathogens.

Table 69-4 Imaging Studies in Children

Diagnostic Study	Purpose/Indications	Comments
Renal ultrasound	To determine the presence of anatomic abnormalities or complications of UTI such as renal abscess	Currently not recommended with a 1st UTI if normal prenatal ultrasound results (beyond 30 weeks' gestation)*
Voiding cystourethrogram Radiographic Nuclear	To determine the presence of VUR or urinary outflow obstruction	Currently recommended with/after a 1st UTI to determine the presence of VUR
Renal scintigraphy (DMSA scan)	To determine the presence of pyelonephritis or extent of renal scarring	Not routinely performed; may be useful in the diagnosis and management of certain children
Intravenous pyelogram	To determine the ability of the kidneys to filter and excrete radiopaque material and to delineate the anatomy of the urinary system	Rarely used in children Adequate hydration and good renal function must be ensured before conducting this study

*See text regarding clarification of this recommendation.
DMSA, ^{99m}Tc-labeled dimercaptosuccinic acid; UTI, urinary tract infection; VUR, vesicoureteral reflux.

children who are clinically improving do not routinely need a repeat urine culture or a renal ultrasound despite persistent fever. A renal ultrasound is indicated in children who are clinically deteriorating.

TREATMENT

Treatment of children with presumed UTI depends on a number of factors, including age, degree of toxicity, presence of vomiting, duration of fever, underlying disorders, availability of outpatient follow-up, and antimicrobial resistance patterns in the community.

The probable organisms and local resistance patterns should guide the practitioner in the choice of initial antimicrobial agent. Gram staining of urine, if readily available, provides additional guidance for this choice. Given that *E. coli* is the most common pathogen causing UTI and that many *E. coli* strains are resistant to amoxicillin or ampicillin (≈50%),[38,41] these agents cannot be recommended routinely for the empirical treatment of a young child with UTI. First-generation cephalosporins,[38] amoxicillin-clavulanate or ampicillin-sulbactam,[40] and trimethoprim-sulfamethoxazole[38,42] should be used with caution because increasing rates of resistance to these antibiotics have been reported in some communities. Alternatives include second- and third-generation cephalosporins and gentamicin, although they would not be good choices if enterococcus is a probable pathogen. Quinolones are effective and resistance is rare, but safety of these antimicrobials in children is still under study, so quinolones are not appropriate choices for first-line therapy at this time. The ultimate choice of antimicrobial therapy should be based on the resistance pattern of the organism or organisms cultured from the patient's urine.

Currently, routine imaging is recommended for children less than 3 years of age with their first febrile UTI, and boys with an afebrile UTI. Evidence supporting the utility of routine imaging studies in children, however, is limited. The various imaging studies available provide different diagnostic information, as depicted in Table 69-4.

Renal ultrasonography is a noninvasive test that does not expose the patient to ionizing radiation. It can demonstrate the size and shape of the kidneys and the presence of duplication and dilation of the ureters, gross anatomic abnormalities, or renal abscess. However, routine ultrasonography in the setting of a first UTI is being reconsidered. In a prospective study of 306 children younger than 2 years with their first UTI in whom ultrasound and voiding cystourethrography (VCUG) were performed, the results of renal ultrasound did not identify obstruction nor alter patient management in any instance.[16] In addition, most children with obstructive uropathy are now identified through prenatal ultrasonography. Furthermore, renal ultrasound is not reliable in detecting renal scarring or VUR.[16] Therefore, routine performance of renal ultrasonography after the diagnosis of a first UTI in children with normal prenatal ultrasonographic findings (beyond 30 weeks' gestation) is not recommended.

VCUG is an excellent test to establish the presence and degree of VUR. Two types of VCUG are available: fluoroscopic (radiographic) contrast VCUG and radionuclide (nuclear) VCUG. The procedures involve catheterization to fill the bladder with either a radiopaque or radioactive liquid and then imaging to detect VUR during voiding. Radiographic VCUG allows precise determination of the grade of VUR, whereas nuclear VCUG can only grossly categorize the degree of VUR. Either study can identify outflow obstruction. The amount of radiation exposure used to be less with nuclear VCUG, but this largely depends on the technique and equipment used. Although medical management of children with VUR and UTI includes ongoing antibiotic prophylaxis, it is not clearly established that this provides long-term benefit (reduced renal scarring and reduced risk for hypertension, renal dysfunction, or renal failure later in life). Therefore, the utility of routine VCUG in the evaluation of children with UTI has recently been questioned.[16] Until a large randomized placebo-controlled treatment trial of antimicrobial prophylaxis for VUR is conducted, the current recommendation is for children younger than 3 years with a febrile UTI to have VCUG performed.

The timing of VCUG is often questioned regarding the reliability of the results and need for a test of cure before performing the study. In two of the studies, rates of VUR and the severity of VUR were compared in patients who had VCUG performed "early" (<7 days) or "late" (>7 days) from the time of hospitalization for UTI. Neither the incidence nor the severity of VUR varied according to the timing of the test. A key finding in one of these studies was that 100% of children in the "early" group had VCUG performed, whereas in the late group, the "no show" rate was 50%, even though the tests were scheduled for the patient before discharge.[35,43-45] For these reasons, there is an increasing push to perform VCUG before discharge.

Renal scintigraphy with technetium 99m–labeled dimercaptosuccinic acid (DMSA) is used to detect acute pyelonephritis and renal scarring. DMSA is injected intravenously, and uptake by the renal tubules is measured 2 to 4 hours later. An area of decreased uptake represents an area of pyelonephritis or scarring. Scans may be used in the acute setting to determine the degree and site of involvement. Most initial areas of decreased uptake on DMSA resolve on follow-up.[46] DMSA scanning may also be used to determine the presence and extent of scarring on follow-up. DMSA scans have been shown to be several times more sensitive in the detection of renal scarring than intravenous pyelography. Although some experts recommend prophylactic antimicrobial therapy when a DMSA scan shows a pattern consistent with acute pyelonephritis, the benefits of this strategy have not been evaluated. Because the majority of young febrile children with UTI, in whom imaging is recommended, have pyelonephritis, one strategy is for the clinician to assume that all have pyelonephritis and act accordingly. In most cases, the additional information provided by scintigraphy does not lead to a change in the management or follow-up of patients with pyelonephritis, and its routine use may not be justified. Its use may be warranted in the acute setting if urinalysis and culture results are equivocal. Similarly, the use of follow-up scintigraphy to establish the presence of scarring is not routinely necessary.

ADMISSION CRITERIA

Traditionally, young children with pyelonephritis were managed as inpatients. In a double-blind randomized controlled trial of 306 children 1 to 24 months of age with a febrile UTI, rates of symptom resolution, reinfection, and renal scarring were no different in children receiving an oral third-generation cephalosporin or intravenous therapy.[35] This study would indicate that most infants older than 2 months with pyelonephritis may be managed safely as outpatients with close follow-up.

The following children should be hospitalized:

- Those with vomiting who cannot tolerate oral medications or cannot maintain adequate hydration
- Those who have significant underlying medical disorders that may complicate management of the underlying illness or the UTI
- Those with inadequate outpatient support or follow-up
- Those who have responded inadequately to outpatient therapy

DISCHARGE CRITERIA

Children who are clinically improving and who are tolerating oral feeding may be discharged from the hospital on a regimen of oral antibiotics. Follow-up studies (e.g., VCUG) may be completed before discharge or scheduled on an outpatient basis.

POSTDISCHARGE CONSIDERATIONS

Children with Recurrent Urinary Tract Symptoms

Approximately 8% to 30% of children with UTI experience one or more symptomatic reinfections,[35,45,47] usually within the first 6 months after the initial UTI, and require prompt reevaluation. Prompt recognition and treatment of UTIs may be the most important factor in the prevention of renal scarring. Routine surveillance of asymptomatic children with monthly urine studies has not been shown to be associated with a better prognosis and is therefore not recommended. Children with recurrent febrile UTIs may be candidates for low-dose long-term antimicrobial therapy, although there is no evidence demonstrating the efficacy of

this approach. When these children present with fever without a clear focus of infection, evaluation for possible UTI is strongly recommended.

Children with Vesicoureteral Reflux

The goal of treating VUR is to prevent progressive renal damage. The majority of young children with VUR will have low-grade VUR (grades 1 to 3), which will often resolve spontaneously as the child ages. Children with grades 4 and 5 VUR and older children are less likely to experience spontaneous resolution. Children with VUR have traditionally been treated either medically, with low-dose long-term antimicrobials, or surgically. Surgical treatment involves reimplantation of the ureter or ureters into the bladder and creation of a longer mucosal tunnel. Several large prospective studies[18,48] have demonstrated that the incidence of renal scarring in children with persistent grade 3 and 4 VUR is equivalent in medically and surgically treated children. Therefore, it has been recommended[19] that young children with mild to moderate VUR receive treatment with low-dose long-term antimicrobials until resolution of VUR. Antimicrobial agents most appropriate for prophylaxis include trimethoprim-sulfamethoxazole and nitrofurantoin in half the usual therapeutic doses given once daily.[49]

The routine use of long-term antimicrobial therapy in children with mild or moderate VUR has recently been questioned. A significant proportion of children receiving antimicrobial prophylaxis continue to have breakthrough febrile UTIs (30%)[18,48] and scarring (6% to 32% by intravenous pyelography). Furthermore, approximately 10% of children treated with long-term antimicrobials experienced adverse reactions, mostly gastrointestinal and dermatologic, and most adverse events occurred in the first 6 months of therapy.[49,50] No experimental trial to date has satisfactorily compared long-term antimicrobial prophylaxis with placebo in children with VUR. Perhaps prompt treatment of intercurrent episodes of UTI and treatment of underlying dysfunctional elimination, if present, will prove to be as effective as antimicrobial prophylaxis in the care of children with UTI and VUR. Until more research occurs in this area, we recommend antimicrobial prophylaxis for children with VUR until repeat VCUG demonstrates resolution of VUR.

Older children with persistent severe VUR (grades 4 or 5) and those with lesser degrees of VUR but with progressive scarring while receiving prophylaxis may benefit from ureteral reimplantation. The efficacy of endoscopic therapy, a newer, less invasive modality, is currently under investigation. This procedure involves the use of an endoscope introduced via the urethra to implant dextranomer/hyaluronic acid (Deflux) underneath the refluxing ureter.

Determination of children at risk for renal damage from childhood UTI remains difficult. Renal scarring is currently the best indicator of renal damage in children. The long-term significance of scarring identified by DMSA remains to be determined. Modifiable risk factors for renal scarring include pyelonephritis, VUR, and DES. Close attention to these three factors in children with a history of UTI may help prevent further renal compromise.

IN A NUTSHELL

- UTI is the most frequent serious bacterial infection in childhood.
- UTI should be suspected in young children presenting with fever.
- Collection of urine with a bag should be discouraged.
- Enhanced urinalysis is the most accurate bedside test for UTI.
- Dysfunctional elimination is an underrecognized risk factor for UTI.

ON THE HORIZON

- Efficacy and safety of endoscopic subureteral injection in the treatment of VUR.
- Multicenter VUR study to determine the utility of antibiotic prophylaxis.

SUGGESTED READING

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