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New Developments in the Diagnosis and Management of Pediatric UTIs

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Urinary tract infections (UTIs) in children are common and a major source of morbidity. The incidence of UTIs in childhood is not precisely known because it is not a reportable disease, and in many cases, especially in infants, UTIs are probably underdiagnosed. Furthermore, the definitions and criteria for diagnosis vary considerably; for example, should children with asymptomatic bacteriuria be included, or what criteria should be used to diagnose a UTI when the urine is obtained with a bagged urine specimen [1]. Nonetheless, it has been estimated that 7% of girls and 2% of boys have a UTI prior to age 6 [2]. During the first year of life more boys than girls are diagnosed with a UTI, with uncircumcised boys having a 10-fold greater risk than those circumcised [2]. This trend reverses after the first year of life, with more girls than boys being diagnosed with a UTI.

Pediatric UTIs constitute a significant health burden, although the actual costs are not known [3]. In the United States, overall inpatient hospital costs are estimated to be greater than $180 million alone. This fails to include the costs of follow-up, including imaging, or the costs to society of parents losing productivity for diagnosis, treatment, and follow-up of their child's infection [3–5].

This article reviews the diagnosis and work-up of UTIs in children, and presents current data reviewing the roles of radiologic imaging, surgical correction, and antibiotic prophylaxis in the setting of pediatric UTIs.

Diagnosis of urinary tract infections in children

Early and rapid diagnosis is paramount to initiating prompt antimicrobial therapy and thereby limiting renal damage. In children, however, the diagnosis is in no way straightforward. UTIs are found in more than 5% of infants and young children who have no source of fever from history or physical examination [6], and in another study of febrile infants, 13.6% were found to have infections of the urine. The symptoms of a UTI in young children, however, are very nonspecific. Rarely are symptoms referable to the urinary tract observed. Even in older children UTIs rarely present with dysuria (more likely a sign of introital irritation) or urgency. Instead, frequency and urgency may be manifest as new-onset or increased incontinence. Likely, many UTIs are either not diagnosed or diagnosed late. Because the symptoms can be quite obscure, it is important that primary care providers have a high index of suspicion for UTIs in children [6].

It is well recognized that a well-collected urinary specimen is critical to make the diagnosis of infection; however, a noncontaminated specimen is hard to obtain in children. There are four ways that urine may be obtained: (1) a bagged specimen, where a bag is taped to the perineum and urine obtained after the child voids (obviously useful in infants, but there is a high risk of obtaining a contaminated sample); (2) a midstream collection (unreliable in children, especially young girls and uncircumcised boys in whom contaminated samples are likely) is useful if negative, but if positive, it is hard to tell whether the collection was contaminated; (3) a catheterized specimen (obviously traumatic in children and

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further, in the uncooperative girl it can easily be contaminated); and (4) suprapubic aspiration (clearly the least likely to be contaminated, but again, traumatic in children and rarely practiced in the current, litigious environment).

Four determinants from the urinalysis have been accepted as supporting a UTI: (1) positive urinary leukocyte esterase on dipstick (revealing the presence of white blood cells in the urine), which has a sensitivity and specificity of about 75% [7]; (2) positive urinary nitrite on dipstick (dietary nitrates are reduced to nitrite by many gram-negative urinary bacteria), the sensitivity is low at 60% although the specificity approaches 100% [7]; (3) more than five white blood cells per high-powered field on microscopic examination of the spun urinary sediment; and (4) any bacteria seen on a high-powered examination of the spun urinary sediment. The presence of any bacteria on Gram stain has a sensitivity of 93% and specificity of 95%, better than dipstick evaluation for leukocyte esterase and nitrite [8]. Microscopic examination of the sediment can also reveal epithelial cells (strongly suggestive of contamination) or white blood cell casts (pathognomonic of pyelonephritis) [6].

The urine culture is a critical part of the work-up for a presumed UTI. The culture identifies the organism causing the infection and helps guide treatment with the correct antibiotics. The traditional definition for a clinically significant UTI is more than 100,000 cfu/mL [6]. Lower numbers have also been shown to correlate with a UTI, especially when obtained by suprapubic aspirate. Lower numbers can also constitute a UTI because of additional factors (eg, hydrational dilution and frequent voiding) [6].

Distinguishing upper from lower tract urinary tract infections

Traditionally, clinical grounds have been used to distinguish pyelitis and pyelonephritis from cystitis. In particular, when urinary frequency and dysuria are accompanied by flank pain and a high-grade fever ($>38.5^{\circ}C$) and rigors, this suggests the diagnosis of pyelonephritis [9]. These clinical findings are not entirely reliable, however, in identifying that the kidney is involved. Similarly, urinalysis, C-reactive protein, and erythrocyte sedimentation rate have low predictive value. More recently, there has been interest in identifying new markers to help identify acute pyelonephritis.

Cytokines are small proteins that help initiate the inflammatory process and have been identified as markers of infections and inflammation. The most recognized are tumor necrosis factor-α and interleukin-6 [10]. Although initially promising as markers of upper tract infection, they were ultimately shown to have low sensitivity and specificity for upper tract infections.

More promising is procalcitonin (PCT). PCT is a polypeptide identical to the prohormone of calcitonin that has been described as a potential marker for biologic disease [11,12]. PCT is a 116-amino acid propeptide of calcitonin that lacks hormonal activity. Plasma concentrations in healthy subjects, chronic inflammatory states, viral infections, and autoimmune disease are below 0.5 ng/mL. In moderate localized bacterial infection PCT ranges from 0.5 to 2, and in severe gram-negative bacterial infections with sepsis and multiorgan failure the level is found to be above 2 ng/mL [13].

Bacterial cells produce a cell wall, and all bacterial cell walls contain peptidoglycan. Gram-negative bacteria contain an extra layer in the cell wall structure called the outer membrane, which is outside the peptidoglycan layer. Endotoxin is a component of this outer membrane and is released in gram-negative infections. The most common organisms associated with UTI and pyelonephritis are the gram-negative bacteria *Escherichia coli*, *Proteus* sp, and *Pseudomonas* sp, which all produce endotoxin. Gram-positive organisms including *Staphylococcus aureus* and *Enterococcus faecalis* are also known to cause pyelonephritis but do not form or release endotoxin [6]. It has been shown that PCT is present in the serum 2 to 6 hours after the release of bacterial endotoxin into the bloodstream and its half-life in serum ranges from 24 to 30 hours [14]. The plasma concentration of PCT reaches a peak in 6 hours and stays high as long as the infectious stimulus is present. Because of its relatively short half-life, a rapid downfall is apparent by 48 hours after successful antibiotic treatment [13].

Correlations between PCT and pyelonephritis have now been well demonstrated. PCT levels have been found to be increased significantly in children with febrile UTI, and levels greater than 0.5 ng/mL were found when renal parenchyma involvement was present [15]. PCT has also been evaluated to distinguish risk of scarring in the setting of UTI. In those with UTI and no scarring, PCT levels remained low. In contrast, those with renal scarring had elevated initial PCT levels

that remained elevated for at least 24 hours [16]. Further large multicenter studies are needed to validate the previous studies, determine its use in gram-positive infections, and better delineate sensitivity and specificity rates, but PCT is promising as a useful tool in differentiating pyelonephritis from cystitis in children.

Renal imaging

It has long been recognized that UTIs in the pediatric population may serve as a marker for anatomic abnormalities. Obstructive lesions are found in 5% to 10% of children with reflux and in 21% to 57% of children with UTIs [6]. Hence, imaging has been thought to be appropriate after the diagnosis of a UTI in a young child. There has been considerable controversy, however, over which children to image. A consensus published in the *Journal of Pediatrics* in 1999 provided practice parameters for infants and young children 2 months to 2 years of age with UTIs. These guidelines stated that infants and young children 2 months to 2 years of age with UTIs who do not demonstrate the expected clinical response within 2 days of antimicrobial therapy should undergo ultrasonography promptly, and either voiding cystourethrography (VCUG) or radionuclide cystography should be performed at the earliest convenient time, and young children 2 months to 2 years of age with UTIs who have the expected response to antimicrobials should have a sonogram and either VCUG or radionuclide cystography performed at the earliest convenient time [17].

Ultrasound

Ultrasonography can be used to identify many renal abnormalities, such as abnormalities of renal size and shape, duplication anomalies, hydronephrosis, or hydroureters. The bladder is also evaluable with ultrasound and may show thickening or the presence of other abnormalities like bladder diverticula or ureteroceles [17]. These findings may diagnose an abnormality or may suggest a problem like vesicoureteral reflux (VUR). Further, Doppler ultrasonography (and so-called power Doppler ultrasonography) can also be used to detect small areas of inflammation within the kidney, essentially diagnosing acute pyelonephritis. Unfortunately, the sensitivity and specificity of ultrasound for acute pyelonephritis is not very good [18]. An important caveat of renal-bladder ultrasound is that it is dependent on the skill of the operator, so it is important to have technicians and radiologists who have experience with both ultrasound and pediatric patients [6].

Even so, it has been argued that ultrasound may not be needed after UTIs in young children, perhaps because many have had prenatal ultrasounds that have demonstrated normal kidneys [19,20]. The authors' study of their population has confirmed that ultrasound remains a highly useful study. In their experience, it altered the diagnosis and treatment in at least 4.4% of patients [21]. Because it is noninvasive and radiation free, it is an excellent study in young children with UTIs.

Voiding cystourethrogram

Because VUR is seen in up to 50% of children with pyelonephritis, a VCUG has been thought to be a most important examination for children with clinical pyelonephritis. It has been shown that normal children have a very low rate of VUR ($<1\%$), whereas those with pyelonephritis have a much higher rate [22]. The test is considered invasive because it requires urethral catheterization. Because of this, parents and pediatricians have for many years questioned its necessity. Many techniques have been tested for reducing the trauma of the test, including hypnosis and sedation with midazolam [23,24]. Because these techniques greatly increase the time, cost, and risk of the test, they have not been widely adopted.

Radiation exposure has also been an issue. The test may be done with either traditional fluoroscopic techniques or with a radioisotope [6]. The radionuclide cystogram has traditionally had approximately 1/100th of the radiation exposure. Further, because imaging is continuous with a radionuclide cystogram (versus intermittent with fluoroscopy), it seems to be more sensitive in determining reflux than a traditional contrast VCUG [25,26]. Fluoroscopic VCUG is more accurate at grading reflux, however, and can show spinal abnormalities, bladder and urethral anatomy, periureteral diverticula, and other upper tract detail that cannot be identified with radionuclide cystography [6]. Traditionally, fluoroscopic VCUG has been the choice over radionuclide cystography in boys where urethral abnormalities may be present and for the initial study in girls [17]. More recently, new fluoroscopic equipment and tailored techniques have reduced the difference in radiation exposure and have led to more widespread adoption of the traditional VCUG [27,28]. Ultrasonographic techniques, including

using microbubbles as a contrast agent, have been attempted, but have not been found to be useful [29]. Similarly, techniques that avoid catheterization, including ultrasound and indirect radionuclide methodologies, have not been found to be useful [30]. In the authors' experience, the traditional fluoroscopic VCUG remains an important study for children with febrile UTIs.

Tc 99m dimercaptosuccinic acid renal scanning

A positive urine culture is the gold standard for identifying a UTI. Determining whether the infection affects the kidneys, however, has been difficult. Radionuclide scanning using Tc 99m dimercaptosuccinic (DMSA) has become readily available and is used in many centers to help diagnose acute pyelonephritis [31].

Renal scintigraphy using DMSA has been shown to be accurate in detecting acute pyelonephritis and renal scarring in both animal models of acute pyelonephritis and in humans [32,33]. DMSA when injected intravenously binds to renal proximal tubular cells, and when radiolabeled, renal cortical images can be obtained 2 to 4 hours later. An area of decreased uptake in the kidney represents an area of abnormal or damaged renal tubular cells. These radionuclide scans have been compared with histopathology specimens, have an overall sensitivity and specificity of 86% and 91% for diagnosing acute pyelonephritis in animal studies, and have theoretical benefits over other types of studies for this purpose [34,35].

Scans may be used in the acute setting to determine the degree and site of involvement of a UTI. Many initial DMSA defects, however, resolve on follow-up. DMSA scans also may be used to determine the presence and extent of permanent damage (scarring) after an episode of pyelonephritis by imaging several months after the infection. DMSA scans have been shown to be several times more sensitive in the detection of renal scarring than the intravenous pyelogram or ultrasound [36]. Although the study is associated with relatively high doses of radiation to the kidneys, the radiation exposure to the ovaries and bone marrow is minimal [37]. CT has been proposed as an alternative, but is thought to have higher radiation exposure overall [38].

Although clearly the best study for determining the presence of renal scarring, the role of DMSA scanning has come into question. In an era of cost-benefit analysis, the question is whether the results of the study alter management. In most cases the answer is no, hence the study may not be needed. The presence of scarring, however, may be an indication that reflux is more likely to persist and the study may be beneficial for this purpose. A study supporting the use of DMSA scanning revealed abnormal scans in 42% of patients with first-time UTIs and in 55% of patients with recurrent UTIs [39]. Three categories of abnormalities were noted: (1) renal cortical defects, (2) dilated pelvicalyceal system, and (3) renal swelling showing disproportionate function compared with size. The study concluded that the high yield of renal abnormalities by Tc 99m DMSA scanning emphasizes the importance of scanning all cases of UTIs, including patients with a first-time infection. The authors concluded that the pattern of abnormalities in the scan may help in planning for subsequent management of UTIs in these patients [39].

In further support of DMSA scanning, Nguyen and coworkers [40] compared renal ultrasound results with DMSA results in 34 patients with known sterile reflux. The study found most infants with high-grade reflux had decreased differential function or cortical defects on DMSA. Parenchymal defects detected by Tc 99m DMSA renal scintigraphy were often not identified by renal ultrasound. The study concluded that Tc 99m DMSA renal scintigraphy is especially useful for initially evaluating infants with high-grade, sterile VUR. Further, several studies have demonstrated that renal status, as documented by radionuclide scanning, is predictive of reflux resolution, with normal kidneys being associated with a higher rate of reflux resolution [41,42].

In Wales, a DMSA scan is a mandatory part of the work-up for a UTI in those children less than 7 years of age. A study out of Wales, however, questioned the validity of DMSA scanning in children greater than 1 year old because only 2% of those children were found to have renal scarring. Their final conclusion was that only those children with signs of pyelonephritis should undergo a DMSA scan [43].

Recommendations for imaging

At this time, guidelines at Albany Medical Center for imaging in the pediatric community following UTI are as follows:

Routine tailored VCUG for

- Children younger than 5 years of age with a febrile UTI

- Males of any age with a first UTI
- Girls younger than the age of 2 years with a first UTI
- Children with recurrent UTI

Renal ultrasonography for

- Children younger than 5 years old with a febrile UTI
- Males of any age with a first UTI
- Girls younger than the age of 3 years with a first UTI
- Children with recurrent UTI
- Children with a UTI who do not respond promptly to therapy to determine whether a renal abscess or obstruction is present

Routine DMSA scanning

- DMSA scanning is warranted in selected cases in which the diagnosis of UTI is uncertain on account of equivocal urinalysis or culture results (eg, in patients receiving antimicrobial therapy at the time the urine culture is obtained) and in newborns with reflux
- Follow-up scintigraphy to establish the presence of scarring is not routinely necessary, because the significance and management of scarring seen only on a DMSA scan has not been studied adequately; however, in high-risk populations, such as infants with febrile UTIs or those children with high-grade reflux, this study may well have prognostic significance

New and somewhat experimental approaches to imaging

There are some new ideas, primarily as regards the use of VCUGs. There is an effort to avoid or at least limit their use. One approach is to use DMSA scanning and ultrasound acutely. If the DMSA scan shows a renal injury, a VCUG is needed. If the DMSA is negative, even acutely after a clinical episode of pyelonephritis, it suggests that scarring in the future is unlikely [44,45]. Hence, some argue that a VCUG is unnecessary. In theory, if the principal reason for diagnosing and treating reflux is to prevent scarring, then there is no need to diagnose or treat reflux in those cases. If there is a normal DMSA scan, no VCUG is necessary in those cases. Some argue that these patients, even if they do not get scarring, likely will have recurrent pyelonephritis and it is worthwhile to diagnose reflux in these patients, if only to put them on prophylactic antibiotics for a period of time (see later).

Another approach is to increase the time between VCUGs in children with known reflux. Traditionally, studies have been performed annually to evaluate for resolution of reflux. It has been proposed that every 2 years is a more reasonable approach and this limits both catheterization and radiation exposure in the child [46].

Finally, there is limited information on what to expect in a child who has had a complete radiographic work-up that is negative. The authors found that about 20% of these children will have recurrent UTIs despite negative radiologic evaluation. Although not statistically significant, there is a trend for an increased recurrence risk in girls and particularly those with a history of recurrent febrile illnesses [47]. The significance of these recurrent infections has not been determined.

Treatment of reflux

VUR is a common problem, yet its importance and treatment remain confusing after many years of study. The relevance of reflux deals with the question of recurrent pyelonephritis and potentially renal scarring as a result. One of the big challenges faced is the decision to treat or not to treat a particular child. Traditional therapy included long-term prophylactic antibiotic treatment to prevent infections along with observation, in anticipation of the child outgrowing the reflux. As more was learned about voiding and bowel dysfunction, treatment of ''elimination dysfunction'' was emphasized in addition to traditional therapy. High spontaneous resolution rates can be obtained, especially for lower grades of reflux, but admittedly with the cost of long-term use of antimicrobials and repeated imaging with VCUGs. Surgical indications were ''breakthrough'' UTIs or failure of resolution of reflux over years. Surgery was associated with considerable morbidity and some complications, hence in a randomized trial, the International Study of Reflux in Children, there were few differences between the groups. The principal findings were that the rate of scarring and infections was similar in both groups, but the rate of clinical pyelonephritis was lower in the surgical group. The rate of surgical complications was much higher in Europe than in the United States [48]. A recent meta-analysis showed similar results. Ten trials were identified involving 964 children. These

trials compared long-term antibiotics and surgical correction of VUR with antibiotics (seven trials); antibiotics with no treatment (one trial); and different materials for endoscopic correction of VUR (two trials). Risk of UTI by 1 to 2 and 5 years was not significantly different between surgical and medical groups. Surgical treatment did result in a 60% reduction in febrile UTI by 5 years but no concomitant significant reduction in risk of new or progressive renal damage at 5 years.

In 1997 the American Urological Association convened the Pediatric Vesicoureteral Reflux Guidelines Panel to make a set of guidelines to determine when to treat reflux medically versus surgically [49]. Table 1 reviews the guidelines for treatment with no renal scarring present, and Table 2 presents the recommendations when renal scarring is present.

As seen from the recommendations, surgery is recommended for higher grades of reflux. Different surgical treatment options are available to these patients. The standard surgical care has always been open surgical repair (eg, ureteral reimplantation). In the past, the problems with open surgical procedures for reflux were that they required many days of catheterization, required many days of hospitalization, and were associated with severe dysuria postoperatively. Attempts have been made to minimize the morbidity and the extravesical approach has been proposed. The extravesical detrussorhapy is highly successful and reduces the morbidity greatly, but there is a 3% to 4% rate of retention when done for bilateral reflux [50,51]. It is usually reserved for cases of unilateral reflux. Nonetheless, with modern surgical and anesthetic techniques open transvesical reimplantation can be done with 23-hour stays or even as an outpatient [52]. Success rates for either technique are about 98% for curing reflux. These developments, combined with a general tendency to avoid over use of antibiotics, have resulted in a trend toward earlier surgery. This has been accentuated even more by the use of laparoscopic techniques in some centers [53,54].

This trend, although promising, has come into question with the advent of endoscopic treatment of reflux. The STING procedure was introduced years ago and has been used successfully in Europe using polytef paste as a bulking agent [55]. The procedure requires anesthesia, but is minimally invasive, takes only minutes, and has a high rate of curing reflux, particularly because a second and even third injection can be done easily in the case of initial failure. Because of scattered reports of possible complications related to the polytef, that substance has never been approved for use in the United States. After an extensive search for alternative agents, dextranomer/hyaluronic acid (Dx/HA) copolymer was approved by the US Food and Drug Administration in 2001 for use for this purpose [56].

This agent consists of dextranomer microspheres of an average size of 80 to 250 μm in sodium hyaluronic acid solution. Each milliliter of mixture consists of 0.5 mL microspheres and 0.5 mL sodium hyaluronan. This substance is biodegradable, has no immunogenic properties, and seems to have no potential to cause malignant transformation. Results vary with some reporting success rates of 90% for individual ureters, but most studies showing success rates of around 70% for curing reflux. Long-term reflux resolution rates are not known because it is difficult to restudy patients who are doing well, but there does seem to be a small recurrence rate after 1 year [57].

Whether endoscopic Dx/HA copolymer treatment should supplant open surgery remains controversial. The success rate of open surgery is still significantly higher and for many open surgeries, postoperative VCUGs are not needed in routine cases. With success rates of 70% to 90% reported, however, VCUGs remain essential for endoscopic treatment. In some parents' perception, the need for VCUG diminishes the benefits of the endoscopic treatment. At this time, in the authors' practice this decision is a family driven choice.

The advent of endoscopic, minimally invasive treatment, however, may have further shifted reflux care in general. If 70% to 90% of patients can be cured with a low-risk, 15-minute procedure with minimal morbidity, one must question whether it is appropriate to continue patients on the traditional management of long-term antimicrobials and repeated testing over years. Although not accepted broadly, there has been a subtle shift in the paradigm of treatment and early endoscopic treatment may be considered appropriate soon.

Not all VUR needs intervention and treatment does not always prevent complications [58]. In one small study no significant differences in risk for UTI or renal damage were found between antibiotic prophylaxis and no treatment [59]. For now, patients continue to be treated according to the guidelines shown in Tables 1 and 2 [49], but the role of intervention continues to be evaluated and new guidelines are currently under development.

Table 1
Guidelines for treatment with no renal scarring present

Clinical Presentation		Treatment					
		Initial (antibiotic prophylaxis or open surgical repair)			Follow-up (continued antibiotic prophylaxis, cystography, or open surgical repair[a])		
Reflux Grade/ laterality	Pt. age (y)	Guideline	Preferred option	Reasonable alternative	Guideline[b]	Preferred option[b]	No consensus[c]
I–II/Unilat. or bilat.	Younger than 1	Antibiotic prophylaxis					Boys and girls
	1–5	Antibiotic prophylaxis					Boys and girls
	6–10	Antibiotic prophylaxis					Boys and girls
III–IV/Unilat. or bilat.	Younger than 1	Antibiotic prophylaxis			Bilat.: surgery if persistent	Unilat.: surgery if persistent	
	1–5	Unilat.: antibiotic prophylaxis	Bilat.: antibiotic prophylaxis			Surgery if persistent	
	6–10		Unilat.: antibiotic prophylaxis Bilat.: surgery	Bilat.: antibiotic prophylaxis		Surgery if persistent	
V/Unilat. or bilat.	Younger than 1		Antibiotic prophylaxis		Surgery if persistent		
	1–5		Bilat.: surgery Unilat.: antibiotic prophylaxis	Bilat.: antibiotic prophylaxis Unilat.: surgery	Surgery if persistent		
	6–10	Surgery					

[a] For patients with persistent uncomplicated reflux after extended treatment with continuous antibiotic therapy.
[b] See Duration of Reflux regarding the time that clinicians should wait before recommending surgery.
[c] No consensus was reached regarding the role of continued antibiotic prophylaxis, cystography, or surgery.
From Elder JS, Peters CA, Arant B Jr, et al. Pediatric vesicoureteral reflux guidelines panel summary report on the management of primary vesicoureteral reflux in children. J Urol 1997;157:1849; with permission.

Table 2
Recommendations when renal scarring is present

Clinical Presentation		Treatment					
		Initial (antibiotic prophylaxis or open surgical repair)			Follow-up (continued antibiotic prophylaxis, cystography, or open surgical repair[a])		
Reflux Grade/ laterality	Pt. age (y)	Guideline	Preferred option	Reasonable alternative	Guideline[b]	Preferred option[b]	No consensus[c]
I–II/Unilat. or bilat.	Younger than 1	Antibiotic prophylaxis					Boys and girls
	1–5	Antibiotic prophylaxis					Boys and girls
	6–10	Antibiotic prophylaxis					Boys and girls
III–IV/Unilat.	Younger than 1	Antibiotic prophylaxis			Girls: surgery if persistent	Boys: surgery if persistent	
	1–5	Antibiotic prophylaxis			Girls: surgery if persistent	Boys: surgery if persistent	
	6–10		Antibiotic prophylaxis		Surgery if persistent		
III–IV/Bilat.	Younger than 1	Antibiotic prophylaxis			Surgery if persistent		
	1–5		Antibiotic prophylaxis	Surgery	Surgery if persistent		
	6–10	Surgery					
V/Unilat. or bilat.	Younger than 1		Antibiotic prophylaxis	Surgery	Surgery if persistent		
	1–5	Bilat.: surgery	Unilat.: surgery			Surgery if persistent	
	6–10	Surgery					

[a] For patients with persistent uncomplicated reflux after extended treatment with continuous antibiotic therapy.
[b] See Duration of Reflux regarding the time that clinicians should wait before recommending surgery.
[c] No consensus was reached regarding the role of continued antibiotic prophylaxis, cystography, or surgery.
From Elder JS, Peters CA, Arant B Jr, et al. Pediatric vesicoureteral reflux guidelines panel summary report on the management of primary vesicoureteral reflux in children. J Urol 1997;157:1850; with permission.

Antibiotic prophylaxis

VUR is a very common problem in the pediatric urologic practice, and is usually initially managed with antibiotic prophylaxis with the anticipation of either spontaneous or surgical resolution. Surgical intervention has normally been reserved for those children who have febrile breakthrough UTIs, progression of renal scarring, noncompliance with medical therapy, or nonresolution of VUR after prolonged follow-up. All children with VUR have classically been placed on antibiotic prophylaxis until resolution. There is a group of children with continued reflux who remain clinically stable, have normal elimination habits, and VUR is of low to mid grade. These children may be at low risk of UTI and reflux may not impact on renal outcome. In addition, there exists parental pressure to justify the continued use of antibiotic prophylaxis in stable children with VUR [60].

In a nonrandomized review of 196 patients with VUR treated with and without prophylactic antibiotics, the infection rate on and off of antibiotics was 0.29 and 0.24 UTIs per patient per year, respectively [61]. Similar results were seen out of Canada in 2005 [60] and Children's Hospital of Philadelphia in 1999 [62]. The pediatric urologic community has started to question the need for antibiotic prophylaxis in this population, with the caveat that the long-term outcome of children with persistent reflux off antibiotics remains unknown, especially for females who may well enter their sexually active and reproductive years with reflux. Studies now are investigating the role of antibiotic prophylaxis, even in higher-risk populations. In one multicenter, randomized controlled study, 236 patients aged 3 months to 18 years with acute pyelonephritis were randomly assigned to receive urinary antibiotic prophylaxis or not. Although the study has some flaws, no statistically significant differences were found among the groups with respect to rate of recurrent UTI, type of recurrence, rate of subsequent pyelonephritis, and development of renal parenchymal scars over 1 year of follow-up [22]. With the continued growth of multidrug-resistant bacteria, the role of antibiotic prophylaxis will continue to be questioned and researched in the coming years and as noted, at least one study has questioned the need for antimicrobials, even in very young children [22].

Circumcision

The role of circumcision continues to be debated among physicians and the public. The most recent statement by the American Academy of Pediatrics is as follows: "Circumcision is not essential to a child's well-being at birth, even though it does have some potential medical benefits. These benefits are not compelling enough to warrant the AAP to recommend routine newborn circumcision. Instead, we encourage parents to discuss the benefits and risks of circumcision with their pediatrician, and then make an informed decision about what is in the best interest of their child" [63]. Proponents of circumcision believe in it for religious beliefs, infection reduction, cosmetic effects, and prevention of penile cancer. In contrast, opponents state that it is not beneficial medically and places the patient, most often an infant, under unnecessary pain and suffering [6]. In 1999 in the United States, 65.3% of all male newborns born in hospitals were circumcised [64]. For most of the past 20 years, proportionately more white newborns received circumcisions than did black infants, but this has gradually equalized so that by 1999, the latest year data are available, 65.5% of white newborns and 64.4% of black newborns were circumcised [64]. Newborn circumcision rates continue to vary greatly by geographic region. In the past 20 years, 81% of babies born in the Midwest underwent circumcisions. In contrast, in the West only 37% had a circumcision [64].

In relation to circumcision and UTIs, it is well accepted that circumcision reduces the rate of UTI in the first 6 months by about 10-fold [65–67]. The etiology of this benefit is a little unclear. It has been shown that there is bacterial colonization of the foreskin during the first 6 months of life that may be an important risk factor for the development of UTIs. Colonization decreases after the first 6 months of life, probably because the foreskin often becomes retractable around that age. Further, uropathogens are known to adhere to and readily colonize the mucosal surface of the foreskin but not the keratinized shaft skin [63].

The question of whether circumcision helps to prevent infections later in life also continues to be debated throughout the literature. The most recent data in 2005 reviewed over 400,000 children identified from 12 studies and found that circumcision does reduce the risk of UTI [68]. The degree of risk reduction that is present varies, however, based on the patient. Normal boys have a risk of infection of about 1%, meaning 111 boys need

to be circumcised to prevent one UTI. Boys known to have either recurrent UTI or high-grade VUR have a risk of UTI recurrence of 10% and 30% and the numbers-needed-to-treat are 11 and 4, respectively. Circumcision is not without complications, however, and hemorrhage and infection are most common, occurring at rate of about 2%. Taking into account the benefits and dangers of circumcision, net clinical benefit was found to be likely only in boys at high risk of UTI [68].

The role of circumcision in the prevention of HIV has been described in multiple studies in adult men. Most recently studies from Africa have reported lower rates of HIV infection in those who are circumcised. Three randomized studies of circumcision in young men all had to be stopped early because of an approximately 60% risk reduction in the rate of HIV infection [69]. All these studies were done in adult men in high-risk populations. How well they translate to neonates in the United States is unclear. Consideration of this should be given to future studies of neonates.

At this time, the recommendation for circumcision for boys is as follows:

- Multiple documented UTIs with no other source noted
- Neonates with a documented high risk for pyelonephritis, including those with genitourinary abnormalities and high-grade reflux
- Children who may be at high risk for HIV infection

Summary

UTIs in children are common and cause significant morbidity. They are challenging to diagnose and a high index of suspicion is required. Prompt antimicrobial therapy is uniformly accepted for renal and other symptomatic infections, but the type of imaging to be performed has been getting more controversial over time. Finally, therapy for VUR has undergone considerable modification with some recommending very early endoscopic treatment and others recommending observation without prophylactic antibiotics. Ongoing clinical trials will help decipher the future direction in this area.

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