Issues in Febrile Urinary Tract Infection Management

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INTRODUCTION

Urinary tract infection (UTI) affects approximately 7% to 8% of girls and 2% of boys during the first 8 years of life.1,2 Febrile UTI (fUTI) is most common in infants and children less than 1 year old, whereas nonfebrile UTI predominates in girls more than 3 years old.2 It is now the most common serious bacterial infection of childhood. Vesicoureteral reflux (VUR), the abnormal retrograde flow of urine from the bladder to the upper urinary tract, is present in 30% to 40% of symptomatic documented UTIs.3,4 This association of VUR with fUTI diminishes with increasing age, because lower grades of VUR, in particular, are most likely to resolve spontaneously over time.

An editorial commentary by Dr Thomas Newman, entitled, “Evidence Basis for Individualized Evaluation and Less Imaging in Febrile Urinary Tract Infection: An Editorial Commentary” is based on this article and can be found in Pediatric Clinics of North America (59:4), August 2012.

KEY POINTS

• Urinary tract infections are common occurrences in the pediatric age group and are a cause of significant morbidity and expense. The understanding of the consequences and sequelae of febrile urinary tract infections, and especially recent analysis of the risk versus benefit of radiologic evaluation of this population, has led to revision of standard protocols initiated by the American Academy of Pediatrics (AAP) in 1999.
• Proper diagnosis of urinary tract infection is considered essential before a child is improperly labeled as having suffered a urinary tract infection.
• A less invasive protocol of radiologic evaluation, with an emphasis on reducing the number of voiding cystourethograms, has been the major outcome of the revised AAP guidelines.
• Emphasis on prevention of recurrent febrile urinary tract infections by understanding the importance of bowel-bladder dysfunction/dysfunctional elimination-voiding syndromes as a major cause, has also led to therapeutic programs that are centered less around the use of prophylactic antibiotics than has previously been the practice.

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The most important clinical sequelae of VUR include fUTI/acute pyelonephritis (APN) and, potentially, renal scarring. The severity (higher grades) of VUR and increased frequency of fUTI are directly related to the risk of scarring.4 APN, defined as inflammation or infection of the kidneys, affects an estimated 60% of children with fUTI. High fever with temperature of 39.5°C or more is the single best predictive parameter.5,6 The risk of APN increases when bladder infection occurs in patients with VUR, because colonized lower tract urine then has direct retrograde access to the upper tracts.7 Furthermore, results of the International Reflux Study Committee (IRSC) have shown that successful antireflux surgery reduces the risk of fUTI by a factor of 3.8 Additional risk factors for APN include other anatomic urologic and neurologic disorders, bowel-bladder dysfunction (BBD), recurrent UTIs, female gender for children more than 1 year old, and certain social situations, especially those that lead to delayed treatment. It is estimated that 15% of all children develop renal scarring after a first UTI, with VUR itself a risk factor for renal scarring.6,9,10 However, patients with fUTI may also develop scarring in the absence of VUR. Moreover, most children with VUR and fUTI do not develop acquired (secondary) scars. Despite the finding of chronic photopenic areas on dimercaptosuccinic acid (DMSA) scans that are thought to represent scars, there is controversy as to their ultimate physiologic and clinical significance. A better understanding of which patients are most likely to develop renal scarring, and, of paramount importance, identifying the significance of such scarring in a given individual patient, is essential to enable better management selection.

ISSUES IN PEDIATRIC UTI: DEVELOPMENT OF GUIDELINES

Clinical practice guidelines are developed to help physicians, patients, and their families make sound decisions about specific clinical situations. However, guidelines reflect interpretations of available data, and are thus subjective and tend to differ between different groups of experts. Furthermore, guidelines are most applicable to a large group of patients who fulfill specific clinical criteria rather than to the individual patient; this is particularly problematic in pediatric medicine, in which parents may be more prone to make treatment decisions for their children based on present symptoms and family history rather than what is published in academic journals. It is even more difficult in a tertiary referral practice to follow algorithmic protocols, rather than to individualize care to a patient who is being evaluated for expert care.

The management landscape of fUTI is constantly evolving as past tradition and dogma are questioned, and more is learnt about the pathophysiology and treatment outcomes. As a result, pediatric UTI guidelines are appropriately updated with expanding data and knowledge. In recent years, the UK National Institute for Health and Clinical Excellence (NICE), the American Urological Association (AUA), and the American Academy of Pediatrics (AAP) have updated their pediatric UTI and VUR guidelines. The NICE guidelines, which were published in 2007, were developed to achieve more consistent clinical practice based on accurate diagnosis and effective management.11 With respect to diagnosis, the NICE guidelines underscore the importance of urine culture in patients with fever without a source (FWS), and they distinguish between upper and lower UTI. The AUA guidelines published in 2010 are specific to VUR, and reflect the limited amount of evidence-based knowledge about this condition.10 However, these guidelines contribute to the understanding of several issues specifically in patients with UTI and VUR, including the relevance of renal scarring, usefulness of continuous antibiotic prophylaxis (CAP), appropriate use of imaging, and consideration of BBD. The AAP guidelines, which were published in
August 2011, have been long awaited and have led to confusion among practitioners because of major investigational protocol changes that have been made compared with the 1999 guidelines. In particular, the AAP guidelines have been cited for stating that CAP is not useful in preventing recurrent fUTI and that routine voiding cystourethrogram (VCUG) is not indicated after first fUTI if ultrasonography results are normal. However, these guidelines were developed for a specific age group (pre–potty-trained infants and children age 2 to 24 months) and they should not be extrapolated to older or younger patients, or to those with complex situations. Key issues in pediatric UTI management are discussed later; where pertinent, a discussion of the guidelines regarding these issues is also presented.

ISSUES IN PEDIATRIC UTI: DIAGNOSIS

Fever in children, especially in young children, is a cause of concern for parents and caregivers and is the most common reason for children to be taken to the doctor or hospital. Of 5.4 million emergency department (ED) visits per year with fever, an estimated 6% to 14% have an FWS; UTIs occur in approximately 7% of boys 6 months old or younger and 8% of girls 1 year old or younger with an FWS. Thus, testing for the presence of UTI seems to be warranted in this patient population, in particular if certain risk criteria are met. The AAP guideline analyzes risk factors that can be addressed to define the at-risk populations: sex, age, fever greater than 39°C, sustained fever of more than 2 days, white more than black race, and uncircumcised status. This analysis is reflected in recent guidelines from major organizations, as summarized in Box 1. An important component of diagnosis is proper collection of

<table>
<thead>
<tr>
<th>Box 1</th>
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<tr>
<td><strong>Guidelines on diagnosis of UTI in children</strong></td>
</tr>
</tbody>
</table>

**NICE guidelines**
- Infants and children presenting with unexplained fever of 38°C or higher should have a urine sample tested after 24 hours at the latest.
- Infants and children with symptoms and signs of UTI should have a urine sample tested for infection.

**AAP guidelines**
- If a clinician decides that a febrile infant with no apparent source of the fever requires antimicrobial therapy to be administered because of ill appearances or another pressing reason, the clinician should ensure that a urine specimen is obtained for both culture and urinalysis before an antimicrobial agent is administered.
- The first option is for the urine specimen to be obtained through catheterization or suprapubic aspiration, because the diagnosis of UTI cannot be established reliably through culture of urine collected in a bag. The second option is to obtain the urine specimen through the most convenient means and to perform a urinalysis. If the urinalysis suggests a UTI, then a urine specimen should be obtained through catheterization or suprapubic aspiration.


urine. A clean-catch urine specimen is preferred, when possible, in older, potty-trained patients, although catheterization or suprapubic aspiration (SPA) must be performed in younger patients, especially if a urine sample collected by other means (such as bag collection) is suspicious for the diagnosis of UTI. If the treating physician decides that a febrile infant requires antimicrobial therapy, and the urinary tract is considered a most likely source, then collection bag specimens, by themselves, are not generally considered to be acceptable to support the diagnosis.\textsuperscript{4,11,12} The 2011 AAP guidelines recommend that in patients 2 to 24 months old, both a urinalysis with pyuria and/or bacteriuria and a culture with at least 50,000 colony-forming units of a uropathogen per milliliter, are essential to establish a diagnosis of UTI.\textsuperscript{12}

**ISSUES IN PEDIATRIC UTI: TREATMENT**

Once the diagnosis and decision to treat have been made, oral antimicrobial or parenteral treatment may be administered, because they are equally effective. The 2011 AAP guideline states that the route of administration should be based on practical considerations, such as whether the child can retain orally administered fluids and medications.\textsuperscript{12} Choice of agent should be based on antimicrobial susceptibility of the isolated uropathogen and may include ceftriaxone, cefotaxime, ceftazidime, gentamicin, tobramycin, or piperacillin for parenteral treatment and amoxicillin plus clavulanic acid, trimethoprim-sulfamethoxazole, sulfisoxazole, or a cephalosporin for oral treatment. The duration of antimicrobial therapy should be 7 to 14 days. The AAP guideline recommends against agents such as nitrofurantoin and others that predominantly are excreted in urine to treat fUTI in infants, because the serum antimicrobial concentration attained is not sufficient to treat pyelonephritis or urosepsis.\textsuperscript{12}

**ISSUES IN PEDIATRIC UTI FOLLOW-UP: CAP**

The goals of follow-up after initial treatment of fUTI are to reduce the risk of developing another fUTI, to prevent renal injury, and to minimize the morbidity of being recurrently ill. The use of CAP to prevent recurrent UTI has been a contentious issue, although it has been a gold standard for 5 decades. The benefit of CAP must be weighed against the risks (eg, development of antibiotic resistance), cost, and inconvenience of therapy.

Several risk factors for recurrent UTI have been proposed in the literature. The risk of experiencing a UTI recurrence seems to depend on general patient characteristics, such as age and gender, as well as certain patient-specific characteristics. One proposed risk factor is high-grade VUR. VUR is commonly classified into 5 grades according to the International Classification of Vesicoureteral Reflux, with grade V being the most severe (Table 1).\textsuperscript{15} Although higher grade VUR is associated with an increased risk of UTI recurrence, no clear cutoff VUR grade for which CAP is or is not indicated has been established.\textsuperscript{16}

BBD can influence VUR outcomes; the AUA guidelines recommend that the presence of BBD should be determined in patients with VUR. Furthermore, these guidelines state that in children older than 1 year with grades I to IV VUR and BBD, and/or in patients with renal cortical abnormalities, CAP is recommended.\textsuperscript{10} Even the NICE guidelines suggest that CAP might be appropriate in those with recurrent fUTI rather than after a first episode. In contrast, although the AAP guidelines define some similar risk criteria for determining whether or not to use CAP, they, like the NICE guidelines, do not comment on the importance of BBD.\textsuperscript{12} In addition to a lack of anatomic abnormalities such as BBD, factors associated with a low risk of recurrent UTI are listed in Box 2. Children possessing these characteristics may be considered to be low-risk patients who are not expected to have another UTI that could lead to
scarring\textsuperscript{10}; such patients would accordingly derive less benefit from CAP compared with high-risk patients.

Six important clinical studies have addressed the usefulness of CAP in preventing fUTI recurrence. The results of 4 of these studies indicated no benefit of CAP versus observation\textsuperscript{17–20}; however, few of the patients in these studies had grade IV or V VUR. Thus, because high-grade VUR has been shown to be associated with an increased risk of UTI recurrence, the results of these studies are not considered to be definitive. Moreover, and given that these studies were not North American, circumcision status in boys was not reported. The Australian Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts (PRIVENT) study was designed to test the efficacy of CAP in preventing recurrence in children who had had 1 or more fUTIs.\textsuperscript{21} A total of 576 children were randomly assigned to receive CAP versus placebo for 12 months. Although the results of this study suggested a benefit of CAP in reducing the incidence of UTI recurrence, this benefit was not convincing: 15 children had to be treated for 12 months to prevent a single UTI. This study also did not have sufficient statistical power to assess risk according to VUR grade.\textsuperscript{21} Renal scarring was not studied and it is likely that many more children would have required treatment to prevent a single significant renal scar.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Reflux into a nondilated ureter only</td>
</tr>
<tr>
<td>II</td>
<td>Reflux into the renal pelvis and calyces without dilatation</td>
</tr>
<tr>
<td>III</td>
<td>Reflux into a mildly to moderately dilated ureter and renal pelvis with no or only slight blunting of fornices</td>
</tr>
<tr>
<td>IV</td>
<td>Moderate dilatation and tortuosity of the ureter and renal pelvis, with obliteration of the sharp angle of the fornices but maintenance of papillary impressions in most calyces</td>
</tr>
<tr>
<td>V</td>
<td>Gross dilatation and tortuosity of the ureter, renal pelvis, and calyces with loss of papillary impressions</td>
</tr>
</tbody>
</table>


Box 2: Factors associated with a low risk of recurrent UTI

- Lack of anatomic abnormalities (eg, BBD)
- No recent history of prior UTIs
- Circumcised boys
- Absence of scarring
- Completion of toilet training/normal voiding habits
- Older children who can verbalize symptoms well
- Lower grades of VUR
- Normal renal ultrasound or DMSA scan

The Swedish Reflux Trial is the only clinical trial to specifically evaluate children with higher grade (grade III–V) VUR. This study enrolled 203 children (128 girls, 75 boys) aged 1 to 2 years with VUR. The results indicated that CAP and endoscopic injection (EI) were comparable in reducing fUTI recurrences compared with cohorts who were only observed. Although they were unable to recruit their desired number of patients into the study, they showed, that girls were at risk of developing new scars, with boys seemingly having resilient kidneys to new scars. Thus, the body of literature regarding the usefulness of CAP in preventing UTI recurrence remains unsatisfactory.

The practitioner is placed in the position of determining whether to administer CAP to a given patient, or to consider the benefits versus risks of surveillance; that is, of not using CAP. The potential benefits of not using CAP include cost, bacterial resistance, side effects, and the parental inconvenience of administering it on a daily basis (ie, compliance). In a surveillance protocol, each child (and family) becomes his or her own stress test and pits the risk aversion of VUR against treatment-associated morbidity. The AAP reviewed raw data from the 6 randomized clinical trials mentioned earlier and compiled a data set of 1091 infants aged 2 to 24 months. They performed a meta-analysis and found no statistically significant benefit of prophylaxis in preventing recurrent fUTI/pyelonephritis in infants without reflux or in those with grades I to IV VUR.

Especially in the presence of documented VUR, if the child does clinically well and renal units remain stable, further invasive imaging (eg, VCUG) becomes superfluous. Regardless, it is imperative to address other overt and covert factors, in particular BBD. The team from pediatric urologist to primary provider to patient and family must completely accept the concept that surveillance does not mean nontreatment. Its success depends on the patient’s family being educated about vigilantly watching for signs and symptoms of UTI recurrence and the importance of prompt evaluation and treatment.

The ongoing RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux) study may help identify acquired renal changes in patients receiving CAP versus observation. This multicenter trial sponsored by the US National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases was initiated in 2005 and will close in 2013. The intended enrollment is 600 children aged 2 to 72 months (ie, 6 years) with grade I to IV VUR identified after fUTI or symptomatic UTI, who will be randomized to CAP versus placebo. The primary outcome measure is UTI recurrence; secondary end points include time to UTI recurrence, renal scarring, treatment failure, renal function, resource utilization, and development of antimicrobial resistance in stool flora. The results of this trial are expected to further contribute to the body of data regarding the use of CAP in children with fUTI.

ISSUES IN PEDIATRIC UTI FOLLOW-UP: IMAGING

Imaging studies traditionally have been performed to provide information about how to best evaluate and manage children with fUTI. The primary goal of imaging has been to identify the presence of risk factors, such as VUR and preexisting renal damage, and thus to determine whether or not further testing or medical or surgical therapeutic intervention is indicated. Several types of imaging modalities are performed in pediatric urology; each is associated with its own benefits and limitations/risks.

Renal-bladder ultrasonography (RUS) enables assessment of anatomic features, such as the renal architecture, size discrepancy, dilatation, and some scarring. However, it cannot be used to reliably detect low-grade/moderate-grade VUR or APN, and it can miss renal scarring. Compared with other imaging modalities, RUS is noninvasive, with
no radiation risks, although it still is associated with costs. RUS, as recommended in the 2011 AAP guideline, is recommended as the initial screening study after fUTI, particularly in younger patients (Boxes 3 and 4; Table 2). Based on the patient peculiarities and the results of the RUS, further studies might be indicated for that patient.

VCUG enables complete examination of the bladder and urethra and has been the gold standard study to evaluate for VUR and to grade it appropriately. Because VUR is the most commonly associated urologic finding in infants and children, initial VCUG in all patients with fUTI, or what has been termed the bottom-up approach to evaluation, has been traditional in most North American pediatric urologic and primary care practices. The requirement for catheterization and the use of fluoroscopy is associated with the inherent radiation exposure and the inconvenience and discomfort of placing a catheter. Catheterization can even introduce bacteria and lead to iatrogenic UTI. Moreover, most cases of VUR that are uncovered with VCUG are of lower grade and it is known from routine maternal-fetal ultrasonography studies in the past quarter of a century that many cases of renal scarring result from embryogenic mishaps and represent congenital dysplasia. Most significant scars are likely primarily developmental, not secondary or acquired. Thus, routine use of VCUG has been increasingly criticized of late. Although some physicians regularly incorporate VCUG as part of follow-up after a first fUTI, the prevailing opinion is that this is not appropriate.

The UK National Institute for Health and Clinical Excellence (NICE) guidelines recommend that VCUG only be performed after the second fUTI or after the first fUTI if 1 or more of the following conditions is present: abnormal sonogram, unusual bacteria, poor urine flow, or renal insufficiency (see Table 2). Although not as specific, the AAP and AUA guidelines include similar recommendations, particularly regarding the routine use of VCUG.

The AAP recommends performing VCUG after a second UTI or if renal-bladder ultrasound reveals hydronephrosis, scarring, or other findings that suggest high-grade VUR, obstructive uropathy, or other atypical or complex clinical circumstances. The recommendation that VCUG not be routinely performed after fUTI, as Thomas Newman pointed out in a Commentary in Pediatrics, greatly from the earlier 1999 AAP guideline. Based on evidence accumulated during the 12 years since the earlier guideline, the AAP concluded that the use of VCUG is difficult to justify, given the risks, costs, and discomfort of the procedure and lack of benefit derived from having VUR diagnosed. However, this recommendation for minimal radiographic evaluation is controversial, because many physicians think that a significant number of children will have complications of UTI that otherwise could have been avoided.

Box 3
AAP imaging guidelines

- Febrile infants with UTIs should undergo renal and bladder ultrasonography
- VCUG should not be performed routinely after the first fUTI; VCUG is indicated if renal-bladder ultrasound reveals hydronephrosis, scarring, or other findings that suggest either high-grade VUR or obstructive uropathy, as well as in other atypical or complex clinical circumstances
- Further evaluation should be conducted if there is a recurrence of fUTI

DMSA renal scanning is a nuclear imaging procedure that enables visualization of the kidneys and assessment of their function, and identifies areas of decreased perfusion. DMSA can be used acutely to confirm pyelonephritis during the acute phase, although persistence of hypoperfusion on a follow-up scan performed months later (eg, 4–5 months after acute infection) represents scarring. The concept of a top-down approach incorporates a DMSA scan to identify upper tract involvement or APN during fUTI. As noted earlier, only 60% of patients with fUTI have confirmatory scans for APN. Only in cases with confirmed positive scans during the acute phase of a fUTI would a VCUG be performed in centers where the top-down approach is advocated.

Thus, in the conventional bottom-up approach, the initial diagnostic focus is the bladder, and primarily involves detection of urinary tract abnormalities and VUR, which is accomplished using VCUG. Detection of VUR on initial imaging leads to appropriate follow-up imaging and management, whereas normal imaging results indicate that no further work-up, at least for VUR, is required. This approach has the potential to produce a high yield of VUR cases. The criticism is that patients will be diagnosed with VUR, especially low grades, even if they have little risk of acquiring renal scars. The argument may be countered by the potential of identifying all VUR in patients who ultimately may suffer the morbidity of recurrent UTI.

The top-down approach focuses initially on the kidney and confirming the renal involvement in the setting of fUTI, APN. This confirmation is accomplished through DMSA renal scanning, or, in some cases, magnetic resonance imaging (MRI) or computed tomography (CT) have served as a substitute. Patients with cortical defects that indicate pyelonephritis go on to VCUG, whereas those with central photopenia that suggests hydronephrosis undergo RUS. Patients with normal DMSA results require no further work-up, with the exception of those with recurrent fUTI, who then undergo VCUG. The top-down approach has been praised for being more selective in determining acute renal involvement at the time of infection. Criticisms include the necessity of sedation, or even general anesthesia, in some younger children (not required with the bottom-up approach), a higher radiation dose compared with VCUG, and the requirement for repeat scanning if acute infection is identified.

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**Box 4**

**AUA imaging guidelines**

- Ultrasonography is recommended every 12 months to monitor renal growth and any parenchymal scarring.
- Voiding cystography (radionuclide cystogram or low-dose fluoroscopy, when available) is recommended every 12 to 24 months with longer intervals between follow-up studies in patients in whom evidence supports lower rates of spontaneous resolution (ie, those with higher grades of VUR [grades III–V], BBD, and older age).
- Option: follow-up cystography may be done after 1 year of age in patients with VUR grade I to II; these patients tend to have a high rate of spontaneous resolution and boys have a low risk of recurrent UTI.
- Option: a single normal voiding cystogram (ie, no evidence of VUR) may establish resolution. The clinical significance of grade I VUR and the need for ongoing evaluation is undefined.

## Table 2
**NICE guidelines: recommended imaging schedule**

<table>
<thead>
<tr>
<th>Test</th>
<th>Responds Well to Treatment Within 48 h</th>
<th>Atypical UTI&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Recurrent UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants &lt;6 mo old</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound during the acute infection</td>
<td>No</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>Ultrasound within 6 wk</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>DMSA 4–6 mo following the acute infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>VCUG</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Infants and children 6 mo to &lt;3 y old</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound during the acute infection</td>
<td>No</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Ultrasound within 6 wk</td>
<td>No</td>
<td>No</td>
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</tr>
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<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>VCUG</td>
<td>No</td>
<td>No&lt;sup&gt;d&lt;/sup&gt;</td>
<td>No&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children ≥3 y old</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound during the acute infection</td>
<td>No</td>
<td>Yes&lt;sup&gt;b,e&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Ultrasound within 6 wk</td>
<td>No</td>
<td>No</td>
<td>Yes&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>DMSA 4–6 mo following the acute infection</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>VCUG</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>a</sup> Atypical UTI includes patients with 1 or more of the following: seriously ill, poor urine flow, abdominal or bladder mass, raised creatinine, septicemia, failure to respond to treatment with suitable antibiotics within 48 hours, or infection with non-<i>Escherichia coli</i> organisms. Recurrent UTI includes patients with 1 of the following: 2 or more episodes of UTI with APN/upper UTI, 1 episode of UTI with APN/upper UTI plus 1 or more episodes of UTI with cystitis/lower UTI, or 3 or more episodes of UTI with cystitis/lower UTI.

<sup>b</sup> In an infant or child with a non-<i>E coli</i> UTI, responding well to antibiotics and with no other features of atypical infection, the ultrasound can be requested on a nonurgent basis to take place within 6 weeks.

<sup>c</sup> If abnormal, consider VCUG.

<sup>d</sup> Although VCUG should not be performed routinely, it should be considered if the following features are present: dilatation on ultrasound, poor urine flow, non-<i>E coli</i> infection, or family history of VUR.

<sup>e</sup> Ultrasound in toilet-trained children should be performed with a full bladder with an estimate of bladder volume before and after micturition.

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### ISSUES IN PEDIATRIC UTI: RENAL SCARRING

The impact of renal scarring in pediatric patients with UTI has been the subject of much discussion in recent years. As mentioned elsewhere in this issue, the natural history of VUR is resolution with time (and patience). However, the presence of renal scarring in patients with VUR, and especially in those patients experiencing recurrent fUTI, becomes a challenge. The issue of protecting renal reserve becomes paramount in this select group of patients. In the patient with normal kidneys before an fUTI, the presence of a new scar, or a hypoperfused area on scan, likely has little long-term
impact on renal reserve. However, that does not mean that an fUTI does not lead to other traumatic sequelae and expense. Furthermore, although the short-term effects of renal scarring, including hypertension in up to 30% of patients, are known, the long-term consequences are less well understood. In one study comparing children with and without scars at 16 to 26 years after their initial diagnosis of UTI, patients with non-scarred kidneys had equivalent blood pressure measurements to those with unilateral or bilateral scars, whereas the glomerular filtration rate was only negatively affected in those with bilateral scars compared with those with unilateral scars or no scars. In addition, increased use of antenatal ultrasonography has revealed that many of the scars attributed to VUR reflect a developmental abnormality and not acquired APN-associated damage; this has been confirmed by prenatal ultrasonographic studies. Thus, the necessity of routinely screening the kidneys for reflux-related renal scarring in patients with VUR remains unclarified and has become an area of uncertainty that is beyond the scope of this article.

ISSUES IN PEDIATRIC UTI: BBD

BBD describes any abnormalities of storage as well as emptying, and also includes constipation. BBD has become a more common source of pediatric urology referrals in the past 2 decades. It constitutes a spectrum. Because BBD has been shown to negatively affect VUR spontaneous resolution rates and even surgical outcomes, the AUA guidelines state, “Symptoms indicative of BBD should be sought in the initial evaluation (including urinary frequency and urgency, prolonged voiding intervals, daytime wetting, perineal/penile pain, holding maneuvers [posturing to prevent wetting] and constipation/encopresis).”

The rationale for addressing BBD in management of VUR is based on several factors. The risk of fUTI in children with VUR on CAP is greater in patients with BBD compared with those without BBD. In addition, children with BBD experience lower rates of reflux resolution within 24 months after diagnosis, lower cure rates following endoscopic therapy, and a higher rate of postoperative UTI compared with children without BBD. Treatment of BBD is therefore urged before addressing VUR. However, no standardized treatment algorithm for BBD exists, and the impact of treating BBD on VUR

Fig. 1. Bottom-up versus top-down approaches for imaging follow-up in pediatric UTI. (A) The bottom-up, North American standard approach, and (B) the top-down approach to imaging evaluation of the child presenting with a UTI. Hydro, hydronephrosis; MAG-3, mercaptoacetyl-triglycine; MR, magnetic resonance; Pyelo, pyelonephritis. (From Koyle MA, Elder JS, Skoog SJ, et al. Febrile urinary tract infection, vesicoureteral reflux, and renal scarring: current controversies in approach to evaluation. Pediatr Surg Int 2011;27(4):337–46; with permission from Springer Science and Business Media.)
outcomes has not been established. It is also important to recognize that the presence of VUR and BBD in the same patient may indicate a genetic component; this warrants further investigation.7

In the author’s experience, many children referred with UTI for management have never had a UTI confirmed by urinalysis and culture. Many have dysuria or abdominal pain, but are often labeled as UTI or as needing reflux to be ruled out. Such misdiagnosis may occur in 50% or more referred for UTI. Furthermore, many parents are unaware that their child has constipation, as long they are not encopretic. When these families are counseled, we stress the mantra: “A happy bladder is an empty bladder. An even happier bladder is an empty rectum.”

ISSUES IN PEDIATRIC UTI: RISK OF CHRONIC KIDNEY DISEASE

A perceived risk of chronic kidney disease (CKD) in patients with fUTI has existed for decades.35 However, the contribution of UTI and VUR to the development of end-stage renal disease (ESRD; ie, stage 5 CKD) is difficult to ascertain and likely has been exaggerated. The risk of a child with a UTI developing ESRD is estimated to be 1 in 10,000 based on the incidence of UTI and the incidence of ESRD resulting from VUR, which is, at worst, a weak association.27

In the most recent study to evaluate the correlation between childhood UTI and ESRD, a Finnish group performed a systematic literature search as well as a retrospective single-center case series.36 Together, the data indicated recurrent childhood UTI as a main cause of ESRD in 0.3% of patients. The study investigators thus concluded that a child with normal kidneys is not at significant risk of developing ESRD because of UTIs. Although this study has been cited for methodological concerns, such as a small data set, a lack of details about eligible study types and extraction steps, and no assessment of potential bias, the results add to the growing body of evidence that UTI in childhood does not cause CKD.

ISSUES IN PEDIATRIC UTI: CIRCUMCISION

The risk of UTI is higher in uncircumcised versus circumcised boys before the age of 1 year, and circumcision has been associated with a reduced risk of UTI.37–39 However, this difference is diminished in older boys, because the overall frequency of UTI tends to decrease with increased age.40 Whether or not circumcision should be performed to reduce the likelihood of UTI has been the subject of debate for many years. The results of a meta-analysis published in 2005 indicated that, to prevent 1 UTI, 111 circumcisions would need to be performed.39 The study investigators concluded that, based on these results, circumcision as a means to prevent UTI may only be warranted in boys at high risk of UTI, such as those with high-grade VUR. Of the recently published pediatric UTI guidelines, only the AUA guidelines directly address circumcision in male infants.10 The guidelines state that circumcision of the male infant with VUR may be considered based on an increased risk of UTI in boys who are not circumcised.

ISSUES IN PEDIATRIC UTI: WHEN TO REFER

Despite the current controversies and issues in pediatric UTI and VUR management, it is likely that some children will benefit from further evaluation by a pediatric urologist or nephrologist. The role of the pediatric urologist is to identify any contributory underlying conditions or issues, such as BBD, that may be promoting recurrent infections. Many centers have elimination dysfunction centers, using the skills of midlevel providers and even physical therapists and psychologists to assess and manage
these children, because they are time consuming, and the care may require long-term follow-up. BBD is rarely 1-stop shopping and can be frustrating for the clinician and parents alike. Common elements of BBD treatment programs include bladder training with timed voiding, behavior therapy, relaxation measures, biofeedback anticholinergic medications, α-blockers, and treatment of constipation.\textsuperscript{10,41}

In particular, referral should be considered for complex cases or patients at high risk of recurrent UTIs or renal damage. Such patients include infants less than 3 months old; infants and children 3 months or older with APN or upper UTI; children with congenital abnormalities; patients with symptoms that are nonspecific to UTI; and infants and children with a high risk of serious illness.\textsuperscript{11}

**SUMMARY**

There is no single algorithm that fits every patient with fUTI. Although guidelines provide some help, they should serve only as learned opinions that are based on data scrutinized by a committed panel of experts. They should not serve as rigid rules requiring emphatic adherence. The understanding of fUTI and VUR and how they are evaluated and managed is in evolution. This evolution mandates a cooperative, open approach between the primary care provider, pediatric urologist/nephrologist, and the patient/parents to tailor a thoughtful, agreed-on therapeutic option for each individual patient.

**REFERENCES**


