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Fever, Hip Pain, and Vomiting in a 7-Year-Old Boy

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CASE PRESENTATION

Initial Presentation

A 7-year-old boy presented to a community hospital with vomiting and abdominal pain. His past medical history was remarkable for an anaphylactic reaction to penicillin and a long-standing absence seizure disorder, which was well-controlled on phenytoin. The patient had been well until 9 days prior to presentation when he was seen in the nurse's office at his school after an apparent absence seizure. In the nurse's office, he complained of fatigue and a severe headache and was found to have a fever of 104.3°F (40.2°C). The patient's parents spoke with his neurologist and primary care physician, who advised them to take the boy to the emergency department. In the emergency department, a lumbar puncture was unremarkable, and the patient's fever decreased to 99.0°F (37.2°C). The patient was sent home for follow-up with his primary care physician.

Follow-up Presentation

On follow-up the next day, the patient had new tenderness to palpation in his lower abdomen. The primary care physician started the patient on azithromycin for an unknown presumptive diagnosis. The following day, the patient began to experience soreness in his hips. He developed nausea and vomiting, which prevented him from continuing the azithromycin, and he continued to run a fever, which peaked at 106.1°F (41.2°C). The patient was treated at home with alternating ibuprofen and acetaminophen, but the next day, the patient could not take any medications orally and began to have difficulty walking due to increased hip pain. The patient again presented to the emergency department and was admitted. He did not have dysuria or diarrhea at any point.

Key Point

Gastroenteritis is a very common pediatric cause of fever, vomiting, and abdominal pain in nontoxic patients and is often a default diagnosis. However, the absence of diarrhea should raise concern for alternate etiologies.

- How accurately does subjective acute pain localization in the abdomen or hip predict the true location of diseasein children?

ETIOLOGY OF ABDOMINAL AND HIP PAIN

Several large studies that evaluated discharge diagnoses of children who originally presented with abdominal pain (localization not further specified) suggest that the etiology is extra-abdominal in nearly half of all cases. In 2 studies, upper respiratory infection/otitis media/sinusitis was the final diagnosis in 25% to 30% of cases of pediatric acute abdominal pain,[1,2] and another study found that urinary tract infection (UTI) was the final diagnosis in approximately 8% of cases.[1] The most common intra-abdominal diagnoses were gastroenteritis (10%–15%) and constipation (approximately 10%), with about 15% of cases remaining undiagnosed.[1,2] Appendicitis represented only 1% to 4% of cases of acute abdominal pain in pediatric patients. Unsurprisingly, appendicitis does correlate strongly with right lower quadrant pain,[3] although this finding can also represent referred pain caused by right lower lobe pneumonia.

In comparison with abdominal pain, pediatric hip pain is significantly more location-specific. Some studies

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found hip pathology in 83% to 100% of children complaining of hip pain. Transient synovitis was found in the majority of cases, followed by septic arthritis and Perthes disease; rheumatoid arthritis was found in some cases.[4–7] However, these studies may be biased because they included patients who were referred for imaging. The literature on nonarticular causes of pediatric hip pain suggests that there are no predominant diagnoses. Most diagnoses are described by case reports and include neuroblastoma, adductor myositis, myositis ossificans, abscesses of the psoas/epidural spine/peripelvic area, omental torsion, scrotal pathology, lumbar discitis, pyogenic sacroiliitis, and coccygeal disease.

CASE PATIENT: HOSPITAL COURSE

During the patient's hospital stay (6 hospital days), his fevers, nausea and vomiting, abdominal/hip pain, and headaches continued with a waxing and waning course. He was originally given naproxen to treat his fever and pain but was switched to acetaminophen due to concerns about gastrointestinal irritation. The patient's urine output and bowel movements were normal, but he was placed on intravenous (IV) fluids on hospital day 4 due to his continued minimal oral intake. Laboratory testing revealed a normal complete blood count and basic metabolic panel, negative blood culture, C-reactive protein (CRP) level of 38.56 mg/dL, and an erythrocyte sedimentation rate (ESR) of 78 mm/hr. Clean-catch midstream urinalysis (UA) micro and macro testing was remarkable for rare red blood cells (RBCs) and white blood cells (WBCs) with 2 to 5 epithelial cells and microproteinuria. Nitrite and leukocyte esterase (LE) tests were negative. An original urine culture demonstrated *Enterococcus faecalis (*20,000 colony-forming units [CFU]/mL), which was sensitive to nitrofurantoin, penicillin, and vancomycin. Results of multiple imaging studies, including a bone scan, kidney/bladder ultrasound, echocardiogram, and radiograph of the hip, were normal. An abdominal radiograph showed adynamic ileus. Magnetic resonance imaging (MRI) of the hips performed 4 days after the onset of symptoms (ie, hospital day 3) showed a minimal left hip joint effusion, which had resolved on a follow-up MRI 4 days later.

- What is the utility of clinical findings, UA, serum testing, and imaging for predicting UTI in children?

DIAGNOSIS OF URINARY TRACT INFECTION

Clinical Findings

Dysuria should not be used as an indicator of UTI in children. It has poor sensitivity and, as a result, UTI cannot be ruled out if dysuria is absent. In a study of 100 children with UTI, only 68% complained of dysuria. Because 92% were febrile, many of the children without dysuria probably had not only cystitis but also pyelonephritis.[8]

When UTI is suspected, clinical examination findings such as fever and flank pain are the major criteria to distinguish cystitis from acute pyelonephritis (APN), but clinical signs in children are often nonspecific. Studies have shown that fever has a 60% to 70% sensitivity and 71% specificity in distinguishing between cystitis and APN.[9,10] Thus, differentiating pyelonephritis from febrile UTI without renal involvement is a serious challenge. It has led some clinicians to recommend adding DMSA scanning (renal cortical scintigraphy using 99M-TC dimercaptosuccinic acid tracer) to the initial work-up of all children with a first UTI in order to accurately diagnose APN, although this is rarely done in current clinical practice.

Key Point

Over 30% of children who have UTI do not have dysuria.

UA Versus Culture

Urine culture is considered the gold standard for the diagnosis of UTI, but several studies have evaluated the use of various UA values for making immediate treatment decisions. Observation without antibiotic treatment until culture results are available is acceptable if UA results do not suggest UTI and clinical signs are mild. In 2 recent meta-analyses, the sensitivities and specificities (respectively) for the UA parameters were as follows: LE, 84% and 78%; nitrite, 50% and 98%; either LE or nitrite, 88% and 93%; uncentrifuged WBCs greater than 10 cells/mm^3, 77% and 89%; and bacteriuria on Gram stain, 93% and 95%.[11,12] The American Academy of Pediatrics (AAP) recommends against basing a final diagnosis of UTI on anything other than culture results.[13]

Serum Laboratory Tests

The utility of serum values for predicting UTIs appears to be poor to fair. Studies have suggested that 37%[14] to 77%[15] of patients with positive urine cultures also have leukocytosis. One study of febrile children younger than 8 weeks found that CRP and ESR levels and leukocytosis were all nonsignificant variables in predicting UTI.[16] CRP and ESR values and leukocytosis have a similarly mixed record in diagnosing pyelonephritis in known UTI. Studies that compared children with pyelonephritis and simple cystitis found differences in WBC

count values (11.7–17.3 × 10^3/μL for pyelonephritis versus 14.5–22.2 × 10^3/μL for cystitis, on average).[17] For values greater than 22 mm/hr,[9] ESR has a sensitivity of 64% and specificity of 67%; the average ESR in APN is 47.5 mm/hr compared with 28 mm/hr in simple cystitis. CRP is probably the best single marker for differentiating between APN and cystitis; average CRP levels in APN range from 10.6 to 11.9 mg/dL as compared with 3.6 to 3.8 mg/dL in cystitis (94% sensitivity and 32% specificity).[18]

Studies have also evaluated procalcitonin as an experimental marker of pyelonephritis in known UTI. Some have suggested that elevated procalcitonin has an approximately 83% to 94% sensitivity and 90% to 94% specificity for diagnosing pyelonephritis determined by DMSA.[18,19] Unlike CRP, procalcitonin also seems to correlate strongly with scarring on scanning 6 months later.[20,21] Procalcitonin measurement is not commonly used in practice.

Imaging

Although certain nuclear medicine findings are associated with active pyelonephritis, imaging is not often used in the initial evaluation of UTIs in pediatric patients, except as indicated to rule out other diseases. Imaging is central to the posttreatment work-up for UTI to evaluate for anatomic risk factors.

- What methods of obtaining urine samples are appropriate at which ages?

Accepted methods of obtaining urine samples vary with the patient's developmental level. In toilet-trained children, clean-catch midstream samples can be used for UA and culture. The standard collecting method involves cleaning the local area and spreading the labia in girls and pulling back uncircumcised foreskin in boys. Many girls who are toilet-trained may be unable to use this clean technique independently; this technique can be facilitated by having a girl sit in reverse position on the toilet seat and pulling the labia away from the urethral meatus.[22] In some cases, catheterization may be necessary to obtain a culturable sample. In non–toilet-trained children, the gold standard for obtaining a specimen suitable for culture is suprapubic aspiration (SPA), but this can be technically challenging. In a study by Pollack et al,[23] 54% of SPA attempts failed. Alternative methods include clean-catch bag samples, which are noninvasive but should not be used for culture due to an unacceptably high false-positive rate,[24] and bladder catheterization. Available data suggest that catheterization is almost equivalent to SPA in avoiding false-positive results (98% agreement, with sterility defined as colony counts < 10,000 CFU/mL) and can be attempted with almost 100% success.[25]

AAP recommendations for the management of children younger than 2 years who are ill enough to warrant immediate antimicrobial therapy are to obtain a sample through catheterization or SPA and then begin treatment. Children who are well enough to wait for treatment can have a sample obtained in any way convenient and can be examined by UA. If the results suggest infection, a repeat sample for culture should be obtained by catheterization/SPA.[13] These recommendations can be extrapolated to older children, in whom obtaining an acceptable sample is much easier.

- How should bacteriuria with a low colony count be interpreted?

Urine cultures from acceptable samples have traditionally been considered positive at 100,000 CFU/mL or greater. Another commonly used standard is more than 10,000 CFU/mL of a single organism in catheterized/SPA samples. A large prospective study of 2181 specimens obtained by catheter determined 50,000 CFU/mL to be the optimal cut-off; 65% of cultures with colony counts below 50,000 CFU/mL grew mixed species or saprophytes (ie, presumed contaminants) versus 17% of cultures with higher colony counts.[26] However, there is controversy over whether *Staphylococcus saprophyticus* should more often be accepted as a true pathogen. In stable, mildly symptomatic children, some experts recommend that UAs with low CFUs (< 50,000–100,000 CFU/mL) be confirmed by repeat urine culture.[27] The case patient (UA revealed 20,000 CFU/mL) fell into this category and was not treated immediately. There are conflicting findings on whether different pathogens carry different probabilities of causing renal scarring.[28]

CASE PATIENT: CONTINUED MANAGEMENT

On hospital day 6, the patient was transferred to a hospitalist general pediatrics service for further work-up and management. Prior to transfer, a follow-up UA (4 days after the original culture) was notable for a macro test with minimal LE and micro test with rare RBCs and bacteria. This culture grew over 100,000 CFU/mL of *Enterococcus* species, and upon transfer, the patient was diagnosed with *Enterococcus* pyelonephritis and started on vancomycin due to his penicillin allergy. IV fluids were continued as well as seizure precautions.

On transfer, a repeat urine culture again grew more than 100,000 CFU/mL of *Enterococcus* species, susceptible to ampicillin, nitrofurantoin, doxycycline, and levofloxacin; the next repeat culture on posttransfer

day 5 was negative. The patient's pain decreased, his oral intake improved, and fever resolved 2 days after antibiotics were started. The patient was discharged on oral levofloxacin (14 total days of antibiotics) for pyelonephritis. Voiding cystourethrogram (VCUG) was planned for outpatient follow-up.

- What is the approach to management of children diagnosed with pyelonephritis?

PYELONEPHRITIS

An estimated 1% of prepubertal boys (versus 3% of prepubertal girls) are diagnosed with UTI[29]; the highest incidence is in infants younger than 1 year. Approximately 70% of children with febrile UTI evidently also have APN; there is some evidence that girls are more susceptible to APN.[30] Constipation is a risk factor, and developmental delay with the attendant risk of poor toilet hygiene may be a risk factor as well. Among children with UTI, vesicoureteral reflux (VUR) is the best-known risk factor for further development of pyelonephritis. A 2003 study found that therapeutic delay of 48 hours or more, pathogens other than *Escherichia coli*, percentage of polymorphonuclear cells of 60% or greater, and CRP of 30 mg/dL or greater were all associated with a higher likelihood of developing lesions indicating pyelonephritis on DMSA scanning.[31]

Disposition and Therapy

Children who are toxic, dehydrated, or unable to tolerate oral medications require IV antibiotics. The AAP recommends that these groups be considered for admission to the hospital.[13] Children and older infants who are not toxic can be safely treated for pyelonephritis as outpatients.[32] Traditionally, young infants have been managed as inpatients. However, a randomized controlled trial involving over 300 children ages 1 month to 2 years found no difference between those given oral antibiotics versus IV antibiotics in symptom resolution, reinfection, or renal scarring.[27]

Regardless of inpatient or outpatient setting, timing of treatment may have greater long-term impact than any post-treatment prophylaxis. While delaying treatment in children with work-up not suggestive of UTI is reasonable, there is some evidence that a few days' delay in treatment of febrile children can affect the risk for renal scarring. A small prospective study involving 22 febrile children with UTI found renal scarring at 6 months in 0 of 14 patients treated within 24 hours of fever, 1 of 3 patients treated at 24 to 48 hours, and 2 of 5 patients treated at 48 to 72 hours.[33]

The AAP recommends a 7- to 14-day antibiotic course for pyelonephritis,[13] with some experts preferring 14 days. Most studies have found that *E. coli* causes the majority of pediatric UTIs (60%–80%).[34–36] Antibiotic choices should ultimately be guided by culture and sensitivities of bacteria found on culture; appropriate initial drugs vary with local sensitivity patterns, and selection can be aided with urine Gram stains. Studies in various regions internationally have noted that 55% of UTIs in general are sensitive to ampicillin,[37] with *E. coli* isolates 80% sensitive[38]; and 70% of UTIs are sensitive to trimethoprim-sulfamethoxazole,[39] with gram-negative bacteria over 93% sensitive.[38] *E. coli* are 65% to 81% sensitive to cephalexin.[40] (The second- and third-generation cephalosporins are effective against *E. coli* but not *Enterococcus* species.) Although quinolones have been a therapeutic mainstay for adults, their safety in children is uncertain and they have not been used as first-line drugs. Evidence for their safety is accumulating, and practice may change.[41] Quinolones remain very effective, with susceptibilities of approximately 89% to 98% across all pathogens and near-unique efficacy against *Pseudomonas* species.[38] The AAP recommends that no test of cure be performed in children with a clinical response within 48 hours of treatment.[13] The available evidence suggests that in such children repeat cultures are uniformly negative.[42]

Work-up for urinary tract abnormalities is usually done on an outpatient basis. However, pediatric patients referred for outpatient work-up are about half as likely to have the work-up performed as are inpatients.[43]

Key Point

Inpatient management of pediatric UTIs should focus on early treatment to prevent scarring and consideration of post-diagnostic imaging. Less than half of children referred for outpatient work-up of VUR after a UTI diagnosis have the work-up performed.

Post-UTI Work-up and Management

Sequelae of UTI. The relationship between the entities of pediatric UTI, VUR, pyelonephritis, scarring, and subsequent renal failure is complex and uncertain. Conditions promoting urinary stasis, which can include VUR, obstructive uropathy, renal calculi, and voiding disorders, are believed to promote the development of UTI in children. Once UTI is established, reflux is also believed to increase the risk of pyelonephritis and scarring, which are believed to be major causes of renal failure in young adults. VUR is categorized by severity. Grade I reflux (Figure 1) involves backup into the ureter only; grade II reflux (Figure 2) involves the renal pelvis without dilation and the calyxes without

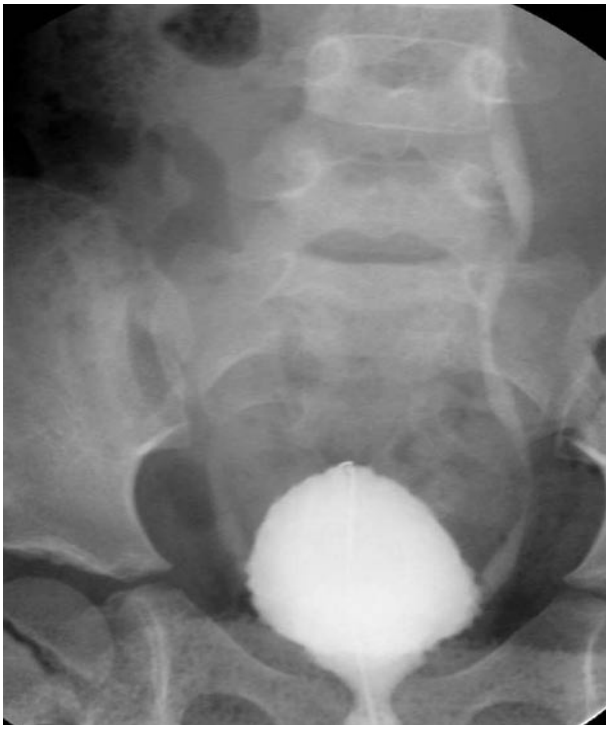

Figure 1. Voiding cystourethrogram demonstrating grade I vesicoureteral reflux in the right ureter. (Reflux on the left ascends past the figure border and cannot be assessed on this image.)

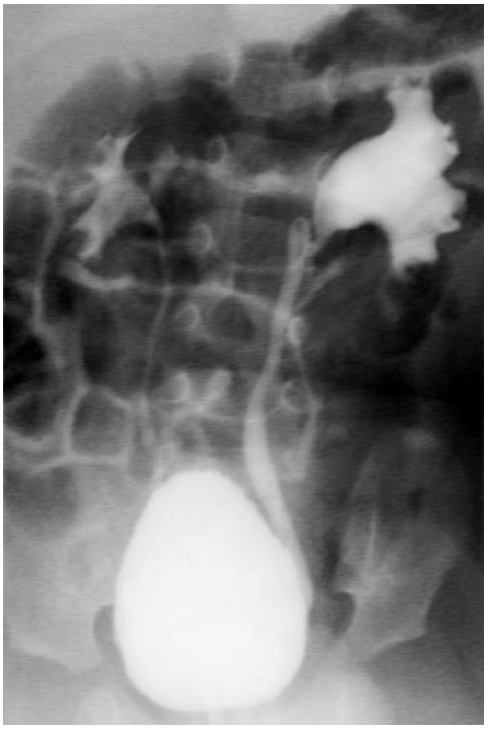

Figure 2. Voiding cystourethrogram demonstrating grade II vesicoureteral reflux in the right kidney and grade III vesicoureteral reflux in the left kidney.

blunting; grade III (Figure 2) involves mild dilation and blunting with additional involvement of the collecting system; grade IV has moderate blunting with collecting system involvement (Figure 3); grade V (Figure 4) involves severe blunting and dilation with tortuosity of the ureter.

UTI and reflux are not always coexistent risk factors, with some researchers emphasizing the risk of renal scarring from recurrent UTI without reflux, and others equally concerned about the risk of scarring from reflux in the absence of infection.[44] It is also possible that reflux and infection are markers rather than causes of susceptibility to long-term renal damage. Among all children with UTI, the frequency of scarring seems to be 10% to 15%.[45] Among those with the diagnosis of pyelonephritis, rates between 37% and 70% have been observed.[46,47] One study of risk factors for scarring in children with UTI found no significant effects from age, sex, or antibiotic type, but UTI was almost 20 times more likely in children with high-grade versus low-grade reflux.[28] Recurrent infection and, as discussed previously, treatment delay are also believed to increase the risk.

The relationship between scarring itself and long-term renal function is a separate and controversial issue. In the shorter term, 1 study of children with pyelonephritic scarring at ages 2 to 17 years found microalbuminuria in 51% but high-for-age serum creatinine concentrations in only 14%.[10] According to the United States Renal Data System, the risk of end-stage renal disease in children is almost negligible (66 per million), and only 2.7% of these cases are associated with reflux nephropathy or pyelonephritis. The longer-term outcome is a more difficult area to study; a small 27-year follow-up study of Swedish children with renal scarring from UTI found a 23% incidence of hypertension and 10% risk for end-stage renal disease in young adulthood. Importantly, within this small data set, even children with unilateral scarring were at risk for these complications.[48]

Patient selection. The question of which children need further evaluation contributes to the controversy that characterizes the post-UTI work-up. AAP recommendations only address children under 2 years of age and state that all children in this age-group should be imaged.[13] Others place the cut-off for indiscriminate VCUG for all children at 3 to 5 years or recommend evaluation for certain groups, such as all children under 5 years with febrile UTI, children with recurrent UTI, children who do not respond promptly to treatment,

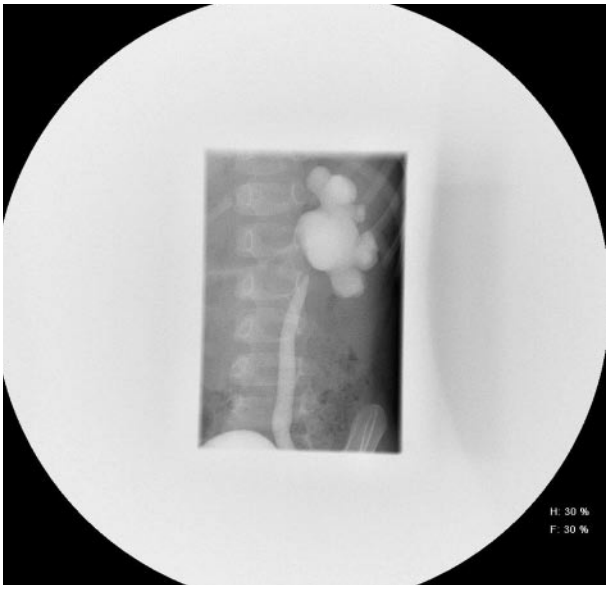

Figure 3. Voiding cystourethrogram of the left kidney demonstrating grade IV vesicoureteral reflux.

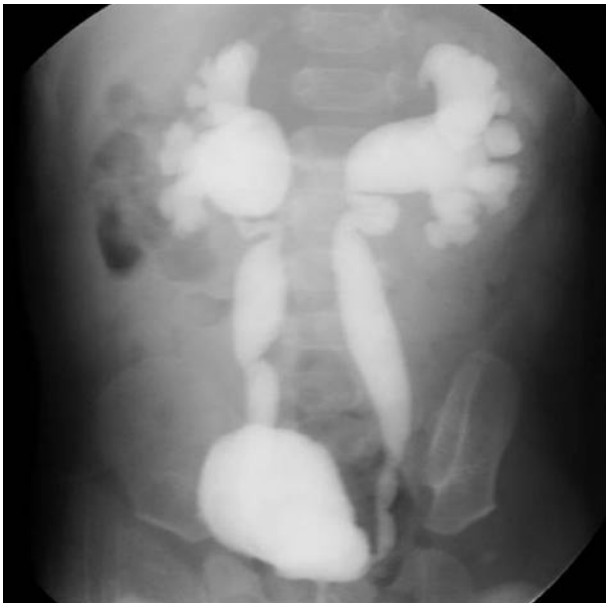

Figure 4. Voiding cystourethrogram demonstrating grade V vesicoureteral reflux in the left and right kidneys.

and girls over 3 years with abnormal voiding patterns, poor growth, high blood pressures, or abnormal pertinent physical examinations.

Work-up for reflux. The conventional approach to children whose UTIs mandate anatomic work-up is VCUG to diagnose reflux or abnormal urinary tract anatomy and renal ultrasound (RUS) to diagnose severe renal scarring. This work-up is the subject of great and multifaceted controversy. With VCUG, radiographic contrast dye is instilled through the urethra into the bladder and then voided, with images taken in both phases; contrast ascending into the ureters and/or kidneys indicates reflux. Direct radionuclide cystography uses the same principle, providing a lower gonadal radiation load and less anatomic detail. Indirect radionuclide cystography, in which IV contrast is processed by the kidneys and then voided, avoiding bladder catheterization, is rarely done due to its poor sensitivity.

RUS is approximately half as sensitive for detecting cortical defects as DMSA scanning[49]; however, it is a radiation-free and much less expensive modality. RUS is used to assess post-pyelonephritic parenchymal scarring (through cortical thinning with altered echogenicity) and gross renal anatomic abnormalities (eg, megaureters, ureteropelvic junction obstruction, ectopic ureters, ureteral/renal duplication). It can also show evidence of reflux even without scarring (through dilation of the pelvi-calyces, collecting ducts, or ureters), although its sensitivity seems to be poor (Figure 5).[50] However, studies have shown that RUS findings do not modify post-UTI management in a statistically significant way, possibly due to the rarity of anatomic abnormalities that escape prenatal ultrasound diagnosis.[51,52] Thus, some have recommended eliminating routine RUS from the work-up altogether, although including it remains the most commonly accepted approach.[51,53]

DMSA scanning is the gold standard rarely used in clinical practice, with a cost 5 to 10 times that of RUS. It also takes up to 5 hours to complete, thus often requiring sedation; requires IV access; and when done early cannot differentiate reliably between acute infection and scarring. DMSA scanning provides additional information about renal function. CT has similar sensitivity and specificity but a higher radiation burden, especially for serial follow-up; MRI is expensive. On DMSA scanning, APN shows as a cortical filling defect, often with indistinct margins; the defect of mature scarring at times can be differentiated by a sharper border, sometimes with retraction and shrinkage of the surrounding cortex (Figure 6).[54]

Management of VUR. The usual follow-up to a diagnosis of VUR, managed in the outpatient setting, is prophylactic antibiotic therapy with nitrofurantoin or trimethoprim-sulfamethoxazole, and, in high-grade cases, referral for ureteral reconstruction/reimplantation. A minimally invasive alternative to open surgery was approved by the US Food and Drug Administration for use in children in 2001. This procedure consists of

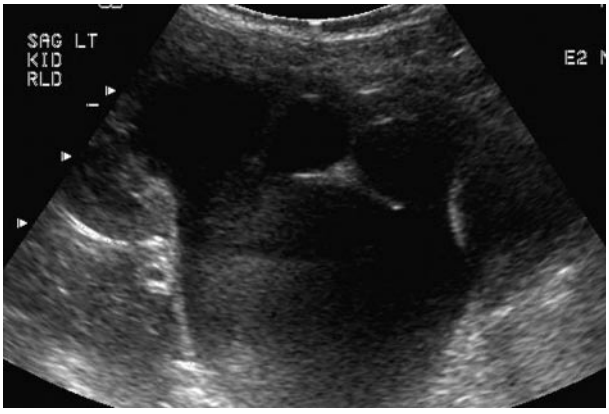

Figure 5. Renal ultrasound showing severe pelvicaliectasis, consistent with vesicoureteral reflux. (This patient's actual diagnosis was ureteropelvic junction obstruction.)

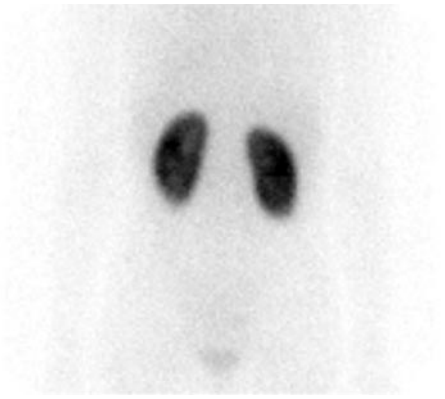

Figure 6. Renal cortical scanning using 99M-TC dimercaptosuccinic acid. The superior poles of both kidneys, particularly the left in this posterior view, show decreased tracer retention suspicious for focal pyelonephritis versus scarring.

endoscopic injection of a dual polysaccharide gel (trade name Deflux; Q-Med Scandinavia, Princeton, NJ) at the site of ureteral insertion into the bladder to form a bulge, which obstructs backflow. It sometimes serves as an alternative to antibiotic prophylaxis in lower-grade reflux as well.

The appropriate interval for repeat pediatric VCUG to assess the need to continue prophylaxis (or ultimate need for surgery) is also an issue under development. A recent review of previously published data found that widening the interval from annual to biannual in mild VUR and every 3 years in moderate/severe VUR reduces the average numbers of VCUGs by 23% to 64% and associated costs by 33% to 51%, at the cost of a 10% to 16% increase in antibiotic exposure.[55] These intervals allow for obvious decreases in radiation exposure as well.

Outcomes. Aside from the controversy over subjects, methods, and timing, the uncertainty at the core of post-UTI work-up and management is whether these interventions ultimately protect children from developing renal failure. A recent meta-analysis of 10 randomized controlled trials, none with over 10 years' follow-up, evaluated the relative effectiveness of observation, medical, and medical-surgical treatment in children with known VUR. The only study analyzed that used a nonintervention control group lasted 13 months and found no significant difference in its endpoint, renal scarring on DMSA, between groups.[56] Many other studies failed to show a certain difference between medical and combined medical-surgical therapy. The authors concluded that it remains uncertain whether any intervention makes a difference and that surgery is marginally more effective than medical therapy.[57]

SUMMARY

Pediatric UTIs are sometimes difficult to diagnose, usually straightforward to treat, and primarily concerning in selected patients as part of a clinical complex of infection and reflux that may ultimately cause kidney failure. The accepted initial work-up is RUS and VCUG, but almost every element of the diagnosis, follow-up, and management of VUR is undergoing rapid evolution. The most cautious approach is pursuing an inpatient initial work-up before discharge in appropriate patients, but more research on the vulnerable population is badly needed to identify the subset at long-term risk and the pathophysiology that affects them. **HP**

ACKNOWLEDGMENT

The authors thank Dr. Michael Dipietro and Donna Anderson for their help in obtaining VCUG and RUS images and Lahti Lahti for her help in obtaining DMSA images.

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