

Practical approach to screen vesicoureteral reflux after a first urinary tract infection

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ABSTRACT

Introduction: Vesicoureteral reflux (VUR) is a common pediatric urologic disorder. After the first urinary tract infection (UTI), imaging studies are recommended, starting with a renal ultrasound (RUS). Voiding cystourethrography (VCUG) and dimercaptosuccinic acid (DMSA) scan are the other main radiologic studies used to detect VUR. We evaluated the use of RUS as a screening method for VUR in children below 2 years of age, in order to avoid unnecessary VCUG.

Materials and Methods: Medical records and imaging studies of infants (<2 years) who had their first UTI in a 6 year period were retrospectively reviewed. We evaluated the sensitivity, specificity, and negative predictive values of RUS and DMSA for diagnosing VUR.

Results: Among 155 children (51% males) with their first UTI, 148 RUS were performed, 128 VCUG and 29 DMSA. VUR was detected in 21% patients; 14.5% low grade and 6.5% high grade. One hundred and twenty-one patients underwent both RUS and VCUG, 101 RUS were normal and 20 abnormal. Of the normal RUS 98% had no or low grade VUR. Among those with an abnormality on RUS 30% had high grade VUR ($P < 0.001$).

Conclusions: After the first UTI in infants (<2 years) RUS is a good screening method for VUR. Among such children with a normal RUS, we do not recommend VCUG or DMSA. In our opinion, VCUG should be performed only in patients with abnormal findings in RUS or in recurrent UTI.

Key words: Dimercaptosuccinic acid scan, vesicoureteral reflux, voiding cystourethrography, urinary tract infection

INTRODUCTION

Urinary tract infection is a very common condition in pediatric patients, affecting up to 2% of children in their first year of life.^[1] On an average 30-40% of children with their first UTI episode have associated VUR).^[1-3] This relationship is stronger in infants and lesser in newborns and continent children.^[4] High grade VUR (defined as Grades IV and V following the International Reflux Study in Children classification^[5]) has been associated with renal scars, which cause

hypertension and renal failure at adult age.^[6] On an average, 20-25% of children above the age of 15 years who are included in transplant and dialysis programs have renal scars due to UTI, often related to VUR.^[7-12] Guidelines agree that after the first UTI, imaging the child's urinary tract is recommended to search for VUR.^[10,11]

VCUG is considered the gold standard investigation for VUR.^[6,13] Unfortunately, this technique has drawbacks. It requires urethral catheterization, which causes pain, risk of infection, and radiation. DMSA is the ideal technique to image the renal parenchyma, diagnose acute pyelonephritis (APN) and to identify the presence of renal scars.

All these techniques are used to optimize the management of children after their first UTI. Patients with VUR grades III-V could require surgical treatment, while those with low grade reflux (I and II) require only a clinical follow-up.^[14] Therefore, it is important to distinguish between these two groups. Guidelines, such as the one proposed by the American Academy of Pediatrics,^[3] recommend that after the first UTI, imaging should start with an RUS.^[15-18] Some studies suggest RUS as the only imaging test, other combine

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it with DMSA or VCUG.^[19,20] A common practice is to replace VCUG with DMSA.^[21] Some studies suggest that DMSA cannot replace VCUG in the diagnosis of VUR.^[19] NICE guidelines recommend imaging the urinary tract only in patients with atypical UTI, poor responses to treatment, or recurrent UTI.^[23] Till date, there is no consensus on how to proceed in this matter.

Our study analyzes the negative predictive value of RUS for VUR, in order to propose a more practical approach in the diagnosis of high grade VUR. Among this background, the objective of our study is to avoid all unnecessary diagnostic tests.

MATERIALS AND METHODS

Over a 6 year period between January 2003 and December 2008, we selected a cohort of children, between 1 day and 2-years of age, admitted in our hospital with their first UTI episode, defined as positive urine culture by urethral catheterization (>100,000 bacterial colonies). We excluded patients already diagnosed with urinary tract pathology and those with previous UTI diagnosis.

The study variables were sex, date of admission, age at admission (in months), urine culture, maximum temperature during the UTI (°C), C-reactive protein (CRP) (mg/dL), creatinine, and imaging diagnostic procedures, which were all done by two experienced pediatric radiologists.

We considered an RUS as abnormal when it had anatomical changes such as hydronephrosis, dilated ureter, ureterocele or changes in the renal parenchyma. We considered high grade VUR when at least one of the two urinary tracts had grade III or higher reflux (even though Grade III is not considered high grade, the risk of renal damage is greater than in grades I and II).^[8,10,14] Based on the existing protocols of UTI management during the study years, VCUG was performed in many patients as routine after a first UTI and DMSA was subsequently performed in children with VUR of any grade. The timing of each imaging study was also recorded.

Our data were analyzed with IBM SPSS 15.0 Statistics software. We compared the contributions of different imaging techniques depending on the timing and compared the clinical variables in the high degree VUR group versus the low or no VUR group.

RESULTS

155 patients were included in the study, 51.2% boys (none circumcised), median age was 3 months (interquartile range [IQR] =2-7 months). The most frequent infectious agent was *Escherichia coli* (76%), followed by *Klebsiella* spp. (5.4%) and *Proteus* spp. (3.6%). The maximum temperature during

the UTI was 38.4°C, (standard deviation [SD] =0.965). The CRP median was 4.13 mg/dL (IQR = 1.37-8.45). No difference was observed between boys and girls.

The mean creatinine was 0.4 mg/dl (SD = 0.1), no patient had altered renal function and the hydration status was normal. Among 155 children with their first UTI, 148 RUS were performed, 128 VCUG and 29 DMSA. VUR was detected in 21% (36): 14.5% (25) low Grade (I-II) and 6.5% (11) high Grade (III-V), we distinguished these two groups regarding the dilation of the urinary tract.

Among the one hundred and twenty-one children who underwent both RUS and VCUG, 101 RUS were normal (83.5%) and 20 were abnormal (16.5%). 98% of children with a normal RUS had either no or low grade VUR. Two patients with normal RUS had high grade VUR on VCUG (2%). Of the 20 abnormal RUS, 6 patients (30%) had high grade VUR, the other 14 had a low grade VUR or none. The presence of VUR in patients with an altered ultrasound is 15.15 times more frequent (confidence interval [CI] =3.291-69.736) than in patients with a normal RUS ($P < 0.001$). RUS predicted VUR with a sensitivity of 83% (CI 95% =74-91%), specificity of 88% (CI 95% =87-89%) and a negative predictive value of 98% (CI 95% =97-99%).

During the study years, the imaging study protocols changed and the number of DMSA performed is limited. Both DMSA and VCUG were performed in only 27 patients. Of these 27, two patients had renal scars (7.4%), both with a high degree VUR. Of the 25 patients with normal DMSA (92.6%), 5 (20%) had a high degree VUR and 8 low grade. The risk of high degree VUR in patients with altered DMSA is 0.2 times higher than in those patients with a normal DMSA (CI: 0.091-0.438) ($P = 0.013$).

The timing of each of the image techniques was also analyzed. Ninety-one RUS were performed in the first 3 weeks of the UTI, and 57 between 3 weeks and 3 months after the UTI episode. No statistical difference was seen between these two groups; therefore, we found no difference in the timing of performing the RUS. All VCUG were performed 4 weeks after the UTI episode and all DMSA were performed between 4 and 6 months after the UTI in order to look for renal scars. DMSA was not used as a diagnostic method to diagnose APN.

Of the other variables that were analyzed, the infectious agent and the CRP could identify patients at risk of high grade VUR. UTI caused by microorganisms other than *E. coli* had 5 times more risk of having high grade VUR ($P = 0.011$). The median CRP in patients without high grade VUR was 4.00 mg/dL, and with high grade VUR was 7.20 mg/dL ($P = 0.026$). Temperature was also higher in the high grade VUR group, 39.04°C versus 38.35°C ($P = 0.06$). When analyzing the

receiver-operating characteristics curves for CRP and temperature, no optimal cut point was achieved.

DISCUSSION

In an infant with his first UTI, the aim is to start the correct treatment as soon as possible in order to lower the risk and damage of APN and its sequelae. Once the acute infection is solved, investigation into underlying pathologies are begun. The actual recommendations are to perform a RUS in all infants after their first UTI.^[4,16,18] Our results favor this recommendation, we consider RUS the first imaging study after a first UTI in infants, being a safe and inexpensive technique. In our study group RUS accurately predicted the presence of VUR and therefore, we consider it a good screening method for VUR, in agreement with the American Academy of Pediatrics and other study groups.^[3]

VUR and renal scars can originate during the fetal period, related with prenatal hydronephrosis, or can appear postnatally, in the context of an UTI.^[13] In a systematic review by Shaikh *et al.*, children with VUR appeared to have 1.5 times more risk of having findings consistent with APN evidence by technetium-99 DMSA.^[12] Furthermore, children with VUR had prevalence of renal scarring of 2.6 times higher than children with no VUR, being higher in VUR grades III–V. There is also evidence of renal scars in the absence of VUR, consequence to VUR suffered in the prenatal period or VUR with spontaneous resolution.^[9]

Many study groups recommend a DMSA in the acute phase of UTI to optimize the screening of APN, optimize treatment, and minimize the damage that APN can do to the kidney.^[22,23] Considering that DMSA is not available in all centers and that it cannot always be done as part of the initial diagnosis of a febrile infant, we argue that the lack of DMSA in the initial diagnosis should not be a handicap at the time of initiating adequate treatment. In addition, we believe that in many cases, DMSA is not required to initiate more aggressive treatment. In an infant with high fever and a suspicion of APN, a normal DMSA would not change our practical approach. In such cases, we would treat the patient as an APN, having in mind that infections in this age can extend easily and become an APN or even sepsis.

There is no agreement on the follow-up after a first UTI. We believe that the next step should rely on an imaging technique that can make a difference in the treatment and follow-up. Given the good correlation of RUS with high grade VUR, we suggest continuing investigations in only those patients with abnormal findings on the RUS. Some studies have shown a low sensitivity, specificity, and negative predictive value for RUS,^[23] These results may have been influenced by radiologist experience which is an important factor in order to perform a valid RUS.

Furthermore, additional factors like CRP, recurrent UTI or bacteria other than *E. coli*, can indicate a high risk UTI, which may require VCUG.

We propose that if an abnormal RUS is found, patients should undergo a VCUG, irrespective of sex of the patient. An abnormal VCUG with high-grade VUR would require close follow-up, antibiotic prophylaxis, or surgery.^[24] Further, these patients with high grade VUR have a higher risk of renal scars, and should undergo a DMSA.^[3,25] In our cohort, despite the low number of patients in which both DMSA and VCUG was performed, a high percentage of patients with high grade VUR had a normal DMSA (25/27). In our cohort, the performance of RUS by expert sonographers was sufficient to identify patients for a VCUG, missing only two patients (2%). One of these 2 patients was a 2-month-old male with VUR Grade III, 40°C fever, *E. coli* infection and a CRP of 23 mg/dL. These clinical parameters could indicate the risk of high grade VUR. Subsequently, this patient did not have any more UTI episodes, the DMSA was normal and the VUR resolved spontaneously. The other misdiagnosed patient with RUS was a 2-year-old female with a positive culture for *E. coli* and a CRP of 15 mg/dL. This patient had recurrent UTI episodes, but did not require surgical nor medical treatment because the VUR decreased to low grade. Both cases did not require additional intervention.

Other variables such as high fever, infectious agent or procalcitonin, should be considered as indicators of high grade VUR.^[26] In our cohort, high fever and microorganism different than *E. coli* were associated with high grade VUR.^[27]

Renal scarring after UTI is a fact, but we consider that our objective is to avoid the kidney from getting new scars. These new lesions can appear in the presence of VUR or with new UTI episodes. Therefore, diagnosing VUR would make a difference in the management.

The main limitation of our study is that this is a retrospective study; therefore, the protocols on imaging techniques were not uniform. However, we have a large amount of RUS which makes the results more reliable.

CONCLUSIONS

We support RUS as a screening method for high grade VUR in infants under 2 years of age after their first UTI. Given the high negative predictive value, we consider normal RUS enough to stop further imaging after a first UTI, postponing further investigations for recurrent UTI episodes. If the RUS is abnormal, we propose performing VCUG as the next step instead of a DMSA, because it can change our treatment. DMSA should be performed only for those patients with high grade VUR in order to complete the renal study and optimize therapy.

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