



ORIGINAL RESEARCH PAPER

Radiology

RENAL ULTRASOUND FOR INFANTS YOUNGER THAN 2 MONTHS WITH A FEBRILE URINARY TRACT INFECTION

KEY WORDS: neonate, ultrasound, urinary tract infection, vesicoureteral reflux, voiding cystourethrogram

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ABSTRACT

OBJECTIVE: The aim of this study is to determine the performance of renal ultrasound for detecting vesicoureteral reflux (VUR) and obstructive uropathies in infants younger than 2 months with a febrile urinary tract infection (UTI).

MATERIALS AND METHODS: We performed a retrospective cohort study of infants younger than 2 months with fever and culture-proven UTI presenting from July 1, 2015, through December 31, 2017, with renal ultrasound and voiding cystourethrogram (VCUG) performed within 30 days of UTI diagnosis. A single radiologist independently reviewed the renal ultrasound and VCUG findings. Results of the renal ultrasound were deemed abnormal if collecting system dilation, renal size asymmetry, collecting system duplication, urothelial thickening, ureteral dilation, or bladder anomalies were present. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of renal ultrasound were calculated using VCUG as reference standard.

RESULTS: Of the 208 patients included (mean [SD] age, 31.8[13] days; male-to-female ratio, 3:1, 25% (n = 54) had VUR grades I–V, with 16% (n = 35) having VUR grades III–V and 8% (n = 18) having VUR grades IV–V. For grades I–V VUR, sensitivity was 32.5% (95% CI, 20.0–47.5%), specificity was 69.5% (95% CI, 61.5–76.9%), PPV was 26.1% (95% CI, 15.8–39.1%), and NPV was 75.7% (95% CI, 67.6–82.7%). No obstructive uropathies were diagnosed by VCUG in patients with normal renal ultrasound findings.

CONCLUSION: In infants younger than 2 months, a normal renal ultrasound makes the presence of grades IV and V VUR highly unlikely but does not rule out lower grades of VUR.

Introduction:

The newly revised American Academy of Pediatrics guideline for infants 2–24 months old with first febrile urinary tract infection (UTI) stated in 2011 the following¹:

After first episode of UTI, a voiding cystourethrography (VCUG) is not recommended routinely. VCUG is specifically indicated if renal and bladder ultrasonography tells hydronephrosis, scarring, or other findings that would suggest either high-grade VUR or obstructive uropathy and in other atypical or complex clinical circumstances.

As neonates are more vulnerable to recurrent UTIs and more prone to severe renal damage, this age group were excluded from the American Academy of Pediatrics guideline.¹

Infants younger than 2 months may be more vulnerable to UTI than older children for a number of reasons. The likelihood of urinary pathogen ascent may be increased by colonization of the genital area after birth and immature local defense mechanisms.² Young infants with UTIs may develop more Vesicoureteral reflux (VUR) and anatomic anomalies.² For these reasons and because UTI in infants younger than 2 months occurs more often in boys than girls, many studies with an older cohort of patients may not be generalizable to patients younger than 2 months given the large percentage of female patients and lower rates of anatomic anomalies found in these studies.³⁻¹³ Few studies have concerned on infants younger than 2 months to evaluate the accuracy of renal ultrasound for detecting VUR, and in the present studies, the findings were mixed. Two small prospective studies found that renal ultrasound had poor sensitivity for detecting grades I–III VUR but good sensitivity for detecting higher grades of VUR.^{14,15} Other studies have found that renal ultrasound has only moderate sensitivity for detection of VUR and cases of grade IV VUR were being missed.^{16,17}

Because of the limited evidence to inform practice for infants younger than 2 months with a febrile UTI, practice varies. Some

pediatricians use a selective approach and perform a VCUG only after an abnormal renal ultrasound examination, whereas others continue to perform VCUG for all patients. We performed this study to evaluate the diagnostic accuracy of renal ultrasound for detecting VUR and obstructive uropathies in infants younger than 2 months with febrile UTI.

Materials and Methods

Dhaka Shishu Hospital Ethical Review Committee approved this prospective study, and the need for informed consent was obtained. All infants younger than 2 months who presented to the radiology and imaging department of this academic tertiary care children’s hospital from July 1, 2015, through December 31, 2017, with a febrile ($\geq 38^{\circ}\text{C}$) UTI were eligible for inclusion in this study. This time frame was chosen because, before publication of the American Academy of Pediatrics guideline for management of febrile UTI in 2011,¹ almost all infants who received a diagnosis of febrile UTI at our institution underwent both renal ultrasound and VCUG. Children confirmatory diagnosis were identified through an institutional microbiology department, and the medical information were reviewed to verify eligibility and collect other patient-related data.

A UTI was defined by any bacterial growth on suprapubic specimen or greater than or equal to 10,000 colony-forming units on catheterized urine specimen with suggestive urinalysis findings or greater than or equal to 50,000 colony-forming units on catheterized urine specimen.¹⁸ Patients were excluded if they had a history of abnormal prenatal ultrasound, had a previous diagnosis of postnatal genitourinary anomaly, or did not have both renal ultrasound and VCUG performed within 30 days of UTI diagnosis. Patients were also excluded if they had been admitted directly to the neonatal ICU after birth because these patients were considered to be a different population, with many being extremely premature or having a genetic syndrome.

Single radiologists (with 5 years of postgraduation experience) who was blinded to VCUG results independently reviewed all renal

ultrasound examinations. Gray-scale and color Doppler ultrasound imaging of the kidneys, urinary bladder, and ureters (if visible) was performed on an imaging system using Simens sonoline G-40, Simens acuson NX 3 Elite machines. Renal ultrasound findings were considered abnormal if any of the following were present: collecting system dilation (renal pelvic diameter \geq 4 mm measured on the mid transverse image or pelviectasis), renal size difference greater than 10%, findings of collecting system duplication, urothelial thickening, ureteral dilation, or bladder abnormalities. The percentage renal size difference was defined as the difference in length between the right and left kidneys divided by the mean renal length. Bladder abnormalities included wall trabeculation, wall thickening, diverticula, and ureteroceles. Designation of collecting system duplication, urothelial thickening, ureteral dilation, and bladder abnormalities was left to the option of the reviewing radiologist.

single radiologists blinded to the renal ultrasound results subsequently reviewed the VCUG examinations. For VCUG examinations, the bladder was catheterized using a 5- or 8-French soft plastic catheter, was instilled via gravity with the patient supine. Intermittent fluoroscopic images and exposures were obtained during bladder filling and voiding and after voiding. VUR grade was reported using the 5-point international reflux grading scale.¹⁹

A standardized data sheet was used to record the findings for renal ultrasound and VCUG examinations and included findings of additional obstructive uropathies, including posterior urethral valves. Urinary tract anomalies diagnosed by either renal ultrasound or VCUG were specified and recorded. Any discrepant readings between the two primary readers on renal ultrasound or VCUG examinations were resolved by a third pediatric radiologist with 5 years of postgraduation experience.

Statistical Analysis

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of renal ultrasound were calculated for grades I-V VUR, grades III-V VUR, and grades IV-V VUR using VCUG as the reference standard. Likelihood ratios with 95% CIs were also calculated for these categories of VUR.²⁰ Test performance measures were calculated for both grades III-V and grades IV-V VUR, because the definition of high-grade VUR varies in the literature.^{4,6,8,16,21,22} Renal ultrasound examinations were considered positive for purposes of calculating test performance measures if any renal, ureteral, or bladder abnormality was present. To determine the effect of the threshold greater than or equal to 4 mm for abnormal renal pelvic dilation on the NPV of renal ultrasound, we calculated NPV for grades I-V VUR, grades III-V VUR, and grades IV-V VUR for abnormal renal pelvis dilation thresholds of greater than or equal to 5 mm, greater than or equal to 6 mm, and greater than or equal to 7 mm.

The chi squared test was used to measure the association between high-grade (grades III-V and grades IV-V) VUR and each of the following four renal ultrasound abnormalities: pelvic diameter greater than or equal to 4 mm or pelviectasis, renal size difference greater than 10%, renal collecting system duplication, and urothelial thickening.

The number needed to test was calculated for all grades of VUR, grades III-V VUR, and grades IV-V VUR and is defined as the number of VCUG examinations that would need to be performed on infants with a normal renal ultrasound examination to detect one case of VUR. The number needed to test was calculated as $1 / (1 - NPV)$, rounded up to the nearest integer.

Results

During the study period, 387 patients younger than 2 months received a diagnosis of febrile UTI, and 208 were included in the final study cohort. The following patients were excluded: 26 with a history of an abnormal genitourinary tract, 43 who were admitted directly to the neonatal ICU, 75 with incomplete or missing medical records, 26 with either a missing VCUG or renal

ultrasound, and 9 with an interval between renal ultrasound and VCUG exceeding 30 days. Most of the patients were male (157/208; 75.48%). Additional demographic information is shown in Table 1.

Table 1: Demographic characteristics in the study infants(n=208)

Characteristics	Value
Age	31.8±13
Male	157(75.48)
Prematurity,< 37 weeks gestational age	18(8.65)

Thirty-one percent (65/208) of renal ultrasound examinations were abnormal (patients could have more than one abnormality) and included pelvic diameter greater than or equal to 4 mm or pelviectasis ($n = 38$), renal size difference greater than 10% ($n = 15$), urothelial thickening ($n = 16$), renal collecting system duplication ($n = 9$), and ureter or bladder abnormalities ($n = 19$). Twenty-five percent (54/208) of patients had VUR grades I-V, 16% (35/208) had grades III-V VUR, and 8% (18/208) had grades IV-V VUR. The sensitivity, specificity, PPV, NPV for renal ultrasound for grades I-V VUR, grades III-V VUR, and grades IV-V VUR are shown in Table 2.

Table 2: Diagnostic performance of renal sonography by VesicoureteralReflux(VUR) Grade

parameter	All Grades VUR	Grade III- V VUR	Grade IV-V VUR
Sensitivity(%)	32.5 (20.0-47.5)	51.6 (33.1-69.9)	86.7 (59.5-98.3)
Specificity(%)	69.5 (61.5-76.9)	72.7 (65.5-79.5)	73.4 (66.6-79.7)
Positive Predictive Value(PPV)(%)	26.1 (15.8-39.1)	26.2 (15.8-39.1)	21.3 (11.9-33.7)
Negative Predictive Value(NPV)(%)	75.7 (67.6-82.7)	89.0 (82.5-93.7)	98.5 (94.8-99.8)

Five patients had abnormalities diagnosed by VCUG only. Four VCUGs showed periureteral (Hutch) diverticula: two with normal renal ultrasound examinations and no VUR, one with urothelial thickening on renal ultrasound and no VUR, and one with findings of renal collecting system duplication on renal ultrasound and bilateral grade IV VUR. One patient with a normal renal ultrasound examination was diagnosed with a urogenital sinus on VCUG. Among infants with normal renal ultrasound findings, the number needed to test was five for grades I-V VUR, 10 for grades III-V VUR, and 67 for grades IV-V VUR.

Discussion:

We found that renal ultrasound has low sensitivity (33%) and moderate NPV (76%) for detecting low-grade VUR, moderate sensitivity (52%) and moderately high NPV (89%) for detecting grades III-V VUR, and moderately high sensitivity (87%) and high NPV (99%) for detecting grades IV-V VUR. Furthermore, no obstructive uropathies were diagnosed by VCUG in patients with normal renal ultrasound findings. From our data, we were able to calculate the number needed to test and likelihood ratios, which may be helpful for physicians and parents when deciding whether to perform a VCUG on an infant with normal renal ultrasound findings.

Ultimately, the decision of whether to perform VCUG for an infant with normal renal ultrasound findings would be based on the clinical importance placed on the detection of low- or high-grade VUR. Several studies have suggested that the clinical course for most patients with VUR may be benign, with more than 50% of cases resolving within 2 years.^{23,24} Cases of higher-grade VUR are less likely to resolve and may have a higher chance of requiring surgical intervention.²⁵ In a prospective cohort study assessing practice patterns in a single institution, the percentages of children who underwent surgery for grades I-V VUR were 9%, 23%, 36%, 61%, and 67%, respectively.²⁵ It is questionable, however, whether the benefit of surgery outweighs the risk.²⁶ Several studies comparing surgical treatment with antibiotic prophylaxis

to antibiotic prophylaxis alone estimated the number needed to test to be eight or nine to prevent one UTI recurrence.^{27,28} Medical treatment with low-dose antibiotics for UTI prophylaxis is also controversial.^{26,29} Many of the early clinical trials were flawed because of a lack of blinding and poorly reported methods.^{26,27} Most recently, the RIVUR study investigators³³ evaluated whether antibiotic prophylaxis with trimethoprim and sulfamethoxazole (Bactrim, AR Scientific) in infants 2–24 months old may reduce recurrent UTI. Their results suggest that antibiotic prophylaxis may reduce the risk for recurrent UTI but does not reduce renal scarring and may confer higher rates of antibiotic resistance. If these findings are true for infants who present with UTI early in life, few patients with low-grade VUR would benefit from medical or surgical interventions.

Further studies are needed to assess whether infants younger than 2 months may be at higher risk for kidney injury related to VUR. A recent meta-analysis of children and adolescents performed to identify prognostic factors for the development of renal scarring after febrile UTI found abnormal renal ultrasound findings to be predictive of renal scarring, but studies of only infants were excluded [30]. One small retrospective study of 57 infants younger than 8 weeks showed that renal scars were present in 39% of infants who underwent dimercaptosuccinic acid-enhanced scans.³¹ Cleper et al.² suggested that creatinine levels may have been higher in these young infants, but their sample size was very small. Prospective studies are needed to follow outcomes in patients diagnosed with febrile UTI and VUR in the first 2 months of life. Studies are also needed to assess whether patients with genitourinary tract anomalies in addition to VUR may benefit from surgical or medical interventions for VUR. Most studies have excluded this population.^{23,27,28}

Our study has several limitations. First, 80% of renal ultrasound studies in our study were performed within 48 hours of UTI diagnosis. Because the findings seen during pyelonephritis can overlap with findings due to VUR or anatomic anomalies, the sensitivity of renal ultrasound in our study may be increased over the sensitivity that would be found if infants were imaged after UTI resolution.^{1,32} Second, defining collecting system dilation in this age group is challenging, because there is no set standard. Because we were evaluating the use of renal ultrasound as a screening examination, we chose a value of 4 mm or the presence of caliectasis, with the understanding that this threshold would likely be sensitive for VUR but not specific, as our results showed. Interestingly, varying the threshold for renal pelvic dilation did not affect the NPV for VUR, regardless of VUR grade. This is likely because many patients with VUR had either more than one abnormality on renal ultrasound or pelvic dilation greater than 4 mm; therefore, the designation of renal ultrasound examinations as normal or abnormal was not sensitive to the definition of renal pelvic dilation. Further research is needed to define normal renal pelvic diameters both for infants and older children.

In conclusion, the sensitivity and NPV of renal ultrasound for detecting VUR increase as VUR grade increases. In an infant younger than 2 months, a negative renal ultrasound result makes grades IV–V VUR highly unlikely but does not rule out low-grade VUR. Further studies are needed to assess patient outcomes in infants diagnosed with UTI and VUR in the first 2 months of life.

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