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Evaluation of children with urinary tract infection – Impact of the 2011 AAP guidelines on the diagnosis of vesicoureteral reflux using a historical series[☆]

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Abstract *Objective:* To clarify the impact of the updated American Academy of Pediatrics guidelines for the evaluation of children presenting with initial febrile urinary tract infection (UTI) on the diagnosis of vesicoureteral reflux (VUR) in children with normal renal sonograms. *Materials and methods:* Children with VUR followed between 2002 and 2004 were evaluated using criteria specified in the AAP guidelines. A total of 49 children (42 girls) who were 2–24 months of age at diagnosis of VUR made following initial febrile UTI were included.

Results: 40.8% of ultrasounds were abnormal. While children with abnormal ultrasounds were more likely to have scintigraphic evidence of renal damage than children with normal ultrasounds (50% vs 17%, $p = 0.026$), one third of the children with abnormal renal scans had normal RBUS. There was no statistically significant difference in diagnosis of grade 3 or higher VUR between groups ($p = 0.136$).

Conclusions: Most children in this series would not have been diagnosed with VUR after initial febrile UTI. More worrisome, 17.2% of children with normal ultrasound had renal injury identified on renal scanning, and 62.1% had grade 3 or higher VUR. These findings reinforce concerns that the new guidelines may miss or delay diagnosis of clinically significant VUR.

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Introduction

In 2011, the American Academy of Pediatrics (AAP) released an updated clinical practice guideline for the diagnosis and management of first febrile urinary tract infection (fUTI) in patients 2–24 months of age [1]. Previously, infants and children with initial fUTI were recommended renal and bladder ultrasound (RBUS), and voiding cystourethrogram (VCUG) or radionuclide cystogram to identify VUR. Antibiotic prophylaxis was recommended until evaluation for VUR was completed [2]. While the new guidelines continue to recommend RBUS after initial fUTI, the recommendations for performance of VCUG and commencement of prophylaxis have changed. Evaluation for VUR is now only suggested after a second febrile infection or if abnormalities such as hydronephrosis or scarring are noted on ultrasound [1]. This change in the guidelines has raised concerns that some children with clinically significant VUR may have delay in diagnosis and develop new or worsening renal injury.

Materials and methods

After obtaining institutional review board approval, a retrospective review of charts and radiographic studies was performed on a cohort of 329 consecutive children with a diagnosis of VUR seen in the Pediatric Urology Clinic between January 1, 2002, and December 31, 2004. To be included for analysis, complete VCUG and RBUS data were required, as was a minimum of one follow-up appointment. Sixty children (51 girls) were identified who were 2–24 months of age and had VUR diagnosed following a first fUTI. Of those, 56 children (48 girls) had RBUS and VCUG data. The 49 children (42 girls) who kept at least one follow-up appointment were included for analysis.

Data extracted included age at presentation, radiographic evaluation, and management of VUR. Radiographic evaluation included RBUS, VCUG, and dimercaptosuccinate renal scanning (DMSA). Ultrasounds were considered normal if there was no evidence of hydronephrosis, collecting system duplication, or scarring. Grading of VUR was performed using standard fluoroscopic VCUG according to the International Reflux Study grading system [3]. Grades 4 and 5 were considered high-grade VUR. DMSA scans were considered normal if there were no parenchymal defects and the differential function was greater than 45%. Clinically significant disease was that which resulted either in identifiable renal injury, or grade 3 or higher VUR.

Statistical analyses included Student *t* test, and 2 × 2 contingency tables with 95% confidence intervals (CI) and two-tailed Fisher exact probability test. A *p*-value ≤ 0.05 was considered statistically significant.

Results

The mean age at presentation was 10.0 ± 0.9 months (range 2.6–23.1 months; median 8.6 months). The mean duration of management was 35.9 ± 3.4 months (range 2.1–106.3 months; median 35.9 months). RBUS results are presented in Table 1. There was no difference in age at presentation

Table 1 Patient characteristics.

	Normal ultrasound	Abnormal ultrasound	<i>p</i> Value
<i>N</i>	29	20	
Age at presentation	10.11 ± 1.20	9.90 ± 1.39	0.908
Duration of management	36.20 ± 4.58	35.37 ± 5.26	0.906
Gender (M/F)	3/29	4/16	0.422

or duration of management between children with normal and abnormal RBUS. There was no difference in sonographic abnormalities by gender (*p* = 0.235).

VCUG data are presented in Table 2. The mean grade per affected renal unit was higher with abnormal RBUS (3.3 ± 0.2 vs 2.5 ± 0.1, *p* = 0.002). Although patients with abnormal RBUS were much more likely to have grade 4 or 5 VUR (OR 7.2, 0.95 CI 1.9–26.8, *p* = 0.002), 5 renal units in 5 patients with normal RBUS had high-grade VUR. There was no statistically significant difference in likelihood of having grade 3 or higher VUR (*p* = 0.136); 65% of female patients with normal RBUS had grade 3 or higher VUR, along with one of the three boys.

DMSA scans were performed on 29 of the patients, 15 of which were abnormal (Fig. 1). While children with sonographic abnormalities were more likely to have abnormal DMSA scans (50% vs 17%, *p* = 0.026), there was no association between high-grade VUR and presence of renal damage (*p* = 0.284). VUR grade per renal unit stratified by normal or abnormal DMSA is presented in Table 3. The mean grade of reflux per affected kidney in patients with normal and abnormal DMSA scans did not differ significantly (3.05 ± 0.28 vs 3.32 ± 0.20, *p* = 0.419).

The impact of the 2011 AAP guidelines on diagnosis of VUR or renal damage in children with normal RBUS is summarized in Table 4.

Discussion

The 2011 AAP guideline addresses the evaluation of children with fUTI that are 2–24 months at presentation [1]. The guideline was an update of the prior 1999 guidelines [2]. Based on review of the current literature, it seeks to help pediatricians and primary care physicians provide consistent care for children in this age group [1]. All children in our cohort met the criteria for evaluation and had culture proven UTI based on the suggested guidelines.

Table 2 Ultrasound findings and grade of reflux per renal unit.

Grade of reflux	Normal ultrasound	Abnormal ultrasound
No reflux	14	9
Grade 1	8	4
Grade 2	12	4
Grade 3	19	6
Grade 4	5	14
Grade 5	0	3

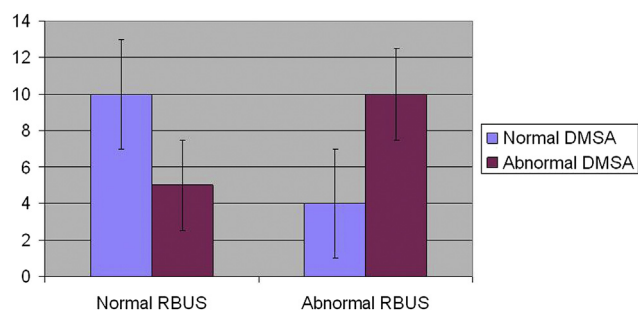


Figure 1 Dimercaptosuccinate renal scanning (DMSA) and ultrasound results. While children with abnormal renal and bladder ultrasound (RBUS) were more likely to have scintigraphic abnormalities [OR 4.8 (1.3–17.7), $p = 0.026$], one-third of the children with abnormal DMSA had normal RBUS.

The change in recommended evaluation of fUTI and potential for missed clinically significant VUR prompted this study. The current guidelines recommend limiting initial evaluation to RBUS, with additional studies only in children with abnormal RBUS or repeat fUTI [1]. Ultrasonography has poor sensitivity for the identification of renal injury [4]. Although children in this cohort with abnormal RBUS were more likely to have renal damage, one third of those with damage had normal sonograms. More than 1 in every 6 patients with a normal RBUS had scintigraphic evidence of renal damage. Müller et al. [5] evaluated the use of ultrasonography as a predictor for renal injury in children with fUTI. RBUS, VCUG and DMSA were performed in 191 infants less than 1 year to evaluate the ability of RBUS at first fUTI to predict scintigraphic evidence of renal damage at 1 year. A total of 28 children with DMSA-proven renal damage had normal RBUS; 44% of children with dilating reflux had no evidence of dilatation on RBUS. They conclude that while RBUS abnormalities may indicate permanent renal damage, only half of those with renal damage had abnormalities [5]. A retrospective study of 208 children with primary VUR found that abnormal renal scan is an independent risk factor for breakthrough UTI [6]. The children who were most likely to develop recurrent infections were those in whom it was most critical that they be prevented. Ultrasound is also limited in its ability to identify VUR. Prior studies that have evaluated the capacity of RBUS to predict VUR indicated low sensitivity for the diagnosis of even high grade VUR [7]. The recommendation to utilize this as the only modality for evaluation has the potential to miss children with high grade VUR, as 17% of patients in our cohort with normal RBUS had grade 4 VUR; 30% of all children with high grade VUR in this study had normal RBUS.

Table 3 Dimercaptosuccinate renal scanning (DMSA) findings and grade of reflux per renal unit.

Grade of reflux	Normal DMSA	Abnormal DMSA
No reflux	8	5
Grade 1	3	2
Grade 2	3	2
Grade 3	6	8
Grade 4	6	12
Grade 5	2	1

Table 4 Impact of 2011 AAP guidelines on vesicoureteral reflux (VUR) diagnoses in children 2–24 months with initial febrile urinary tract infection and normal renal and bladder ultrasound (RBUS).

	Missed (%)
VUR, high grade	17.2
VUR, grade 3 or higher	62.1
VUR, grade 3 or higher, female	65.4
Scintigraphic renal damage	17.2

The Swedish reflux trial, a prospective open randomized control study, recruited children aged 1 to less than 2 years with grades 3–4 VUR and randomized them to antibiotic prophylaxis, endoscopic management, or surveillance [8]. At entry, 61% of the children had abnormal DMSA findings, with bilateral defects in 15%. New renal damage was seen in 15 of 203 patients, none of whom were on prophylactic antibiotics, indicating a potential benefit of prophylaxis. Female gender was a significant risk factor for renal deterioration, as was recurrent fUTI. Of note, there was a statistically significant increase in renal damage in girls with grade 3 reflux who were not on prophylaxis [9]. Nearly two-thirds of the girls with normal RBUS were diagnosed with grade 3 or higher VUR, suggesting that adherence to the guidelines would miss identifying a group who benefit from VUR management.

By waiting for a second fUTI to perform VCUG, the authors of the guidelines posit most children with high-grade VUR will be identified, while those with lower grades will not, thus avoiding overtreatment of insignificant disease [1]. Our data suggest that grade of VUR is not always correlated with renal damage. It is well established that renal damage can be present even in children with lower grades of VUR and if this puts them at increased risk of recurrent infection and scarring as concluded by Shiraishi et al. [6], it is important to identify them to prevent the additional insult of recurrent pyelonephritis. Furthermore, many children have had prior febrile infections that were not evaluated for UTI, possibly accounting for renal injury identified following first recognized fUTI. Under the previous guidelines, some have already expressed concern that treatment of VUR is delayed. In a retrospective review of 42 patients undergoing ureteral reimplantation after failing medical management, 58% of patients showed reduced renal function prior to starting medical management. By the time of surgery, 83% of kidneys had renal scarring, with 36% of kidneys showing decline in renal function during medical management [10]. Another study of 549 patients with VUR found that 55.7% had evidence of renal damage at diagnosis. On multivariate analysis, grades 3–5 VUR and age of diagnosis >24 months were most commonly associated with renal damage [11]. While the damage could certainly be congenital, the higher prevalence in the older children indicates that some of the injury may be acquired. In a prospective observational study of 115 children under 1 year with grades 3–5 VUR, renal abnormalities were detected in 90% of children; 30% of patients had a glomerular filtration rate (GFR) less than 80% of expected. Over the mean follow up period of 62 months, 18% of children had declining renal function [12].

In addition to the inherent drawbacks of a retrospective study, one limitation of this study is that the patient population was followed for reflux. It does not account for children between 2 and 24 months with normal RBUS and no reflux. The AAP guidelines estimate that in a hypothetical cohort of 100 infants with an initial fUTI, VUR would be detected in 35 and high-grade reflux would only be present in 6 [1], or 17% of the refluxing patients. Overall, high-grade VUR was found in 34% of our refluxing patients. This may demonstrate a referral bias, with community physicians feeling more comfortable managing infants and children with low-grade reflux and a solitary fUTI. Nonetheless, it does demonstrate that children in that age group with normal ultrasounds can have high-grade disease. Furthermore, children with grade 3 VUR were included with grades 1 and 2 [1]. Girls with grade 3 VUR benefit from prophylaxis, both in terms of recurrent UTI [13] and acquisition of new renal damage [9]. As DMSA scans were ordered according to the clinical indications of individual attending physicians, not from a standardized research protocol, the true incidence of renal damage and the temporal relationship in its acquisition are unknown, another limitation. However, we feel that the rates of renal damage and grade 3 or higher VUR identified in our population warrant additional prospective studies to determine if the suggested guidelines are appropriate moving forward.

Conclusions

In this series, 40.8% of children had abnormal ultrasounds at initial evaluation and therefore would have been identified by the current guidelines. However the majority of refluxing patients in our series would have gone undiagnosed. While some of those missed children may not have had clinically significant disease, it is worrisome that 17.2% with normal RBUS had VUR and renal injury identified on renal scanning. Furthermore, 62.1% of those with normal RBUS had grade 3 or higher VUR. These findings raise concern that the new guidelines may lead to some children with clinically significant VUR being missed or delaying their diagnosis until a second or third febrile infection and the potential for further renal injury.

Conflict of interest

None.

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None.

Ethical approval

This study was performed following institutional review board approval (NA_00034861).

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