



# Validation of the ureteral diameter ratio for predicting early spontaneous resolution of primary vesicoureteral reflux

Angela M. Arlen<sup>a</sup>, Andrew J. Kirsch<sup>b</sup>, Traci Leong<sup>c</sup>, Christopher S. Cooper<sup>d</sup>

<sup>a</sup>Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

<sup>b</sup>Department of Urology, Children's Healthcare of Atlanta, Atlanta, GA, USA

<sup>c</sup>Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University School of Medicine, Atlanta, GA, USA

<sup>d</sup>Department of Urology, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Correspondence to: C.S. Cooper, University of Iowa, Department of Urology, 200 Hawkins Drive, 3RCP, Iowa City, IA 52242–1089, USA

[christopher-cooper@uiowa.edu](mailto:christopher-cooper@uiowa.edu) (C.S. Cooper)

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## Summary

### Introduction and objective

Management of primary vesicoureteral reflux (VUR) remains controversial, and reflux grade currently constitutes an important prognostic factor. Previous reports have demonstrated that distal ureteral diameter ratio (UDR) may be more predictive of outcome than vesicoureteral reflux (VUR) grade. We performed an external validation study in young children, evaluating early spontaneous resolution rates relative to reflux grade and UDR.

### Study design

Voiding cystourethrograms (VCUGs) were reviewed. UDR was computed by measuring largest ureteral diameter within the pelvis and dividing by the distance between the L1 and L3 vertebral bodies (Figure). VUR grade and UDR were tested in univariate and multivariable analyses. Primary outcome was status of VUR at last clinical follow-up (i.e. resolution, persistence, or surgical intervention). Demographics, VUR timing, laterality, and imaging indication were also assessed.

### Results

One-hundred and forty-seven children (98 girls, 49 boys) were diagnosed with primary VUR at a mean age of  $5.5 \pm 4.7$  months. Sixty-seven (45.6%) resolved spontaneously, 55 (37.4%) had persistent disease, and 25 (17%) were surgically corrected. Patients who spontaneously resolved had

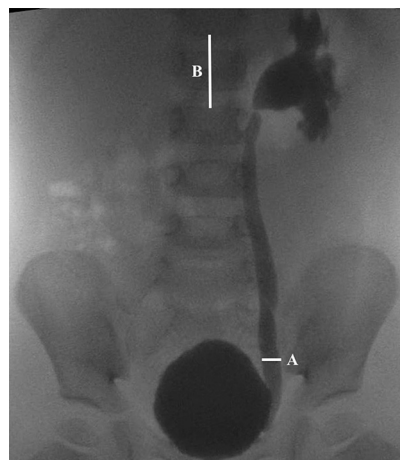
significantly lower VUR grade, refluxed later during bladder filling, and had significantly lower UDR. In a multivariable model, grade of VUR ( $p = 0.001$ ), age  $< 12$  months ( $p = 0.008$ ), ureteral diameter ( $p = 0.02$ ), and UDR ( $p < 0.0001$ ) achieved statistical significance. For every 0.1 unit increase in UDR, there was a 2.6 (95% CI 1.58–4.44) increased odds of persistent VUR, whereas a 1.6 (95% CI 0.9–3.0) increased odds was observed for every unit increase in grade.

### Discussion

Both grade of reflux and UDR were statistically significant in a multivariable model; however, UDR had a higher likelihood ratio and was more predictive of early spontaneous resolution than grade alone. Furthermore, unlike traditional VUR grading where children with grade 1–5 may outgrow reflux depending on other factors, there appears to be a consistent UDR cutoff whereby patients are unlikely to resolve. In the present study, no child with a UDR greater than 0.43 experienced early spontaneous resolution, and only three (4.5%) of those with spontaneous resolution had a UDR above 0.35.

### Conclusions

UDR correlates with reflux grade, and is predictive of early resolution in children with primary VUR. UDR is an objective measurement of VUR, and provides valuable prognostic information about spontaneous resolution, facilitating more individualized patient care.



**Summary figure** Ureteral diameter measurements taken at widest point in false pelvis (A) and divided by distance between L1 and L3 (B) to calculate UDR.

## Introduction

Vesicoureteral reflux (VUR) is one of the most common urologic diagnoses affecting children, with a prevalence of 0.4–1.8% in the general pediatric population and 30% in those with a history of febrile urinary tract infection [1,2]. Dilatation of the upper urinary tract on prenatal ultrasound may also be suggestive of VUR; numerous studies have demonstrated that reflux occurs in 10–20% of children with antenatally detected hydronephrosis [3]. Although there is a natural tendency for reflux to improve or resolve over time, there remains a subset of children with persistent VUR who are at risk for recurrent pyelonephritis as well as potential sequela from renal injury. Despite the high incidence of VUR, optimal management has become increasingly controversial, at least in part because of our inability to predict an individual child's specific prognosis.

Grade of reflux has long been considered the predominant prognostic factor in children with primary VUR. The International Reflux Study, among others, demonstrated that initial VUR grade affects spontaneous resolution rates over a 5–10-year study period [4,5]. However, VUR grade has been associated with significant inter- and intra-observer discordance, particularly when evaluating intermediate grades of reflux [6,7]. Recent work suggests that distal ureteral diameter ratio (UDR) has higher inter-rater reliability and is predictive of clinical outcomes along with grade of reflux [8–10]. To further investigate these findings, and to help minimize the potential impact of institutional bias from practice patterns, we performed a validation study using patient data from an outside institution. Resolution rates over time were evaluated and compared relative to VUR grade and UDR; we hypothesized that UDR was more predictive of early spontaneous resolution than grade.

## Materials and methods

Voiding cystourethrograms (VCUGs) of all children diagnosed with primary VUR between January 1, 2011, and December 31, 2013, at a collaborating institution were retrospectively reviewed. Inclusion criteria included the ability to identify the distal ureter in the false pelvis and the L1–L3 vertebral bodies in the same image. Children with secondary reflux, ectopic ureters, complete ureteral duplication, ureterocele, concomitant ureteropelvic junction or ureterovesical junction obstruction, or unknown clinical outcomes/no follow-up VCUGs were excluded from study. Renal scintigraphy was performed only in cases with significant atrophy or concern for concomitant obstruction (i.e. moderate-severe hydronephrosis in the absence of hydroureter or absence of contrast drainage on postvoid images).

VUR grade was determined by a pediatric radiologist using the International Reflux Study classification system [11]. In cases of bilateral reflux, the highest VUR grade was used for analysis. The ureteral diameter ratio (UDR) was calculated as previously described [8]. In brief, the largest ureteral diameter within the false pelvis (defined as the area below the most superior aspect of the iliac crest) was obtained in millimeters; this measurement was divided by

the distance from the bottom of the L1 vertebral body to the top of L3 to control for patient size and radiographic magnification. UDR was calculated based on the widest distal ureteral diameter. Patient demographics, indication for initial VCUG (febrile urinary tract infection, hydronephrosis, etc.), and subsequent imaging were assessed. Patients were placed on antibiotic prophylaxis, and followed with annual ultrasounds and cystograms.

Clinical outcome was defined as surgical correction, persistent VUR, or spontaneous resolution. VUR resolution was defined as a single negative VCUG. Primary outcome was status of reflux at last clinical follow-up (i.e. spontaneous resolution, persistence, or surgical intervention). Comparison between categorical patient characteristics and outcome was tested using chi-square analysis and comparison between continuous characteristics such as UDR and outcome were tested using ANOVA. Variables controlled for included age, gender, VUR grade, an estimate of bladder volume at onset of VUR, laterality, ureteral diameter (UD), UDR, and UTI history prior to diagnosis of VUR. A generalized logit model for outcomes was fitted to compare the effect of UDR and VUR grade using Wald chi-square analysis. All models in the analyses were converged. Akaike's Information Criterion (AIC) was used to evaluate relative goodness-of-fit for the generalized logit models. Patients from a collaborating institution were used to evaluate model performance in a sample independent of that used to develop the model (i.e. external validation) [12]. Statistical analysis was performed by a professional biostatistician using R 3.1.1, with  $p < 0.05$  representing statistical significance.

## Ethical approval

Approved under University of Iowa Hospitals & Clinics IRB 2014–04766 and Children's Healthcare of Atlanta IRB 14–034.

## Results

The validation cohort included 165 children diagnosed with primary VUR who met inclusion criteria. One-hundred and forty-seven patients (89.1%; 98 girls, 49 boys) had initial VCUG images that allowed for calculation of UDR. Mean age at diagnosis was  $5.5 \pm 4.7$  months. Indications for obtaining VCUG included febrile UTI in 100 children (68%), UTI without documented fever in 14 (9.5%), hydronephrosis in 32 (21.8%), and hematuria in a single patient (0.7%). Children underwent an average of 2.2 cystograms, and mean time between initial and last VCUG was  $15.8 \pm 6.4$  months. Of the 147 patients, 67 (45.6%) resolved spontaneously, 55 (37.4%) had persistent disease at the end of the follow-up period, and 25 (17%) had undergone surgical correction. Surgical indications included persistent VUR in 17 (68%) and breakthrough fUTI in eight children (32%). Of the 25 children undergoing surgical correction, 13 (52%) had endoscopic repair and 12 (48%) underwent ureteral reimplantation. Median length of follow-up was 21.5 months (95% CI 17–25 months). Mean time to spontaneous resolution was  $14 \pm 5.3$  months. Patients who spontaneously resolved had lower VUR grade, refluxed later in the bladder cycle, and had

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