



# 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

significantly lower UD and UDR on their initial diagnostic VCUG (Table 1).

Only six children had grade 1 VUR, thus they were combined with grade 2 patients for statistical analysis. Correlation of both UDR and UD with VUR grade were significantly greater than 0 (i.e. positive linear relationship). Correlation with UDR was 0.68 (95% CI 0.58–0.76;  $p < 0.0001$ ) compared with 0.60 (95% CI 0.48–0.69;  $p < 0.0001$ ) for UD. The average UDR and UD by VUR grade is depicted in Table 2.

VUR grade (continuous and categorical), age (continuous and categorical), laterality, imaging indication, UDR, and UD were then considered in a multivariable model. Grade of VUR ( $p = 0.001$ ), age less than 12 months ( $p = 0.008$ ), UD ( $p = 0.02$ ), and UDR ( $p < 0.0001$ ) achieved statistical significance. When adjusting for all other variables, for every 0.1 unit increase in UDR, there was a 2.6 (95% CI 1.58–4.44) increased odds of persistent VUR compared with a 1.28 (95% CI 1.07–1.52) increased odds of persistent VUR for every unit increase in UD. Likewise, for every unit increase in grade, there was a 1.6 (95% CI 0.9–3.0) increased odds of persistent VUR. Children diagnosed at <12 months of age had 0.66 (95% CI 0.12–3.8) odds of persistent reflux.

Comparing the surgically corrected cohort to those with spontaneous resolution, a 0.1 unit increase in UDR was associated with a 3.7 (95% CI 1.9–7.0) increased odds of surgical intervention. A 1 unit increase in VUR grade was associated with a 5.6 (95% CI 2.1–15.4) increased odds of surgical correction. Patients that spontaneously resolved tended to be younger with low UDR. Children diagnosed at  $\geq 12$  months of age with spontaneous resolution had low UDR and VUR grade. There was rare spontaneous resolution

**Table 2** Mean UDR and UD according to VUR grade.

Reflux grade	UDR, mean (SEM)	UD, mean (SEM)
1–2	0.19 (0.01)	4.50 (0.29)
3	0.23 (0.01)	5.25 (0.32)
4	0.40 (0.03)	9.10 (0.66)
5	0.52 (0.05)	11.78 (1.62)

UD, ureteral diameter; UDR, ureteral diameter ratio; VUR, vesicoureteral reflux.

in children with a UDR greater than 0.35 at any age regardless of VUR grade (Fig. 1). High UD did not preclude early spontaneous resolution, but  $UDR \geq 0.43$  did.

The comparative effect of UDR and VUR grade on multivariable model is demonstrated in Table 3. To compare the effect size for UDR and grade of reflux, a multivariable analysis was performed in three models. The first model was with UDR and not grade, the second was with grade and not UDR, and the third model was with UDR and grade. Both grade of reflux and UDR were statistically significant; however, when testing UDR and grade in the same model, UDR was observed to have a larger effect on predicting failure to spontaneously resolve (chi-square 22.3;  $p < 0.0001$  versus 14.3;  $p = 0.0008$ ).

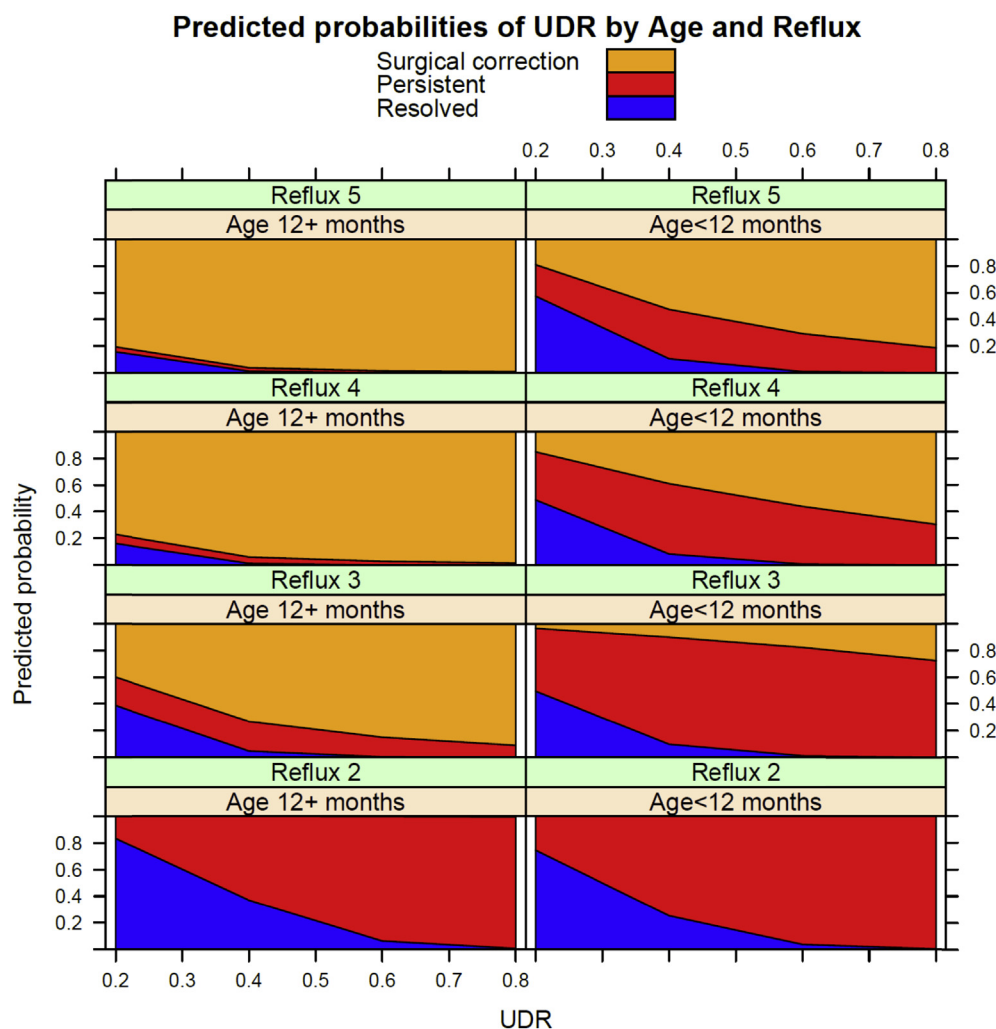
### Discussion

Management goals of VUR include prevention of recurrent pyelonephritis and renal injury as well as minimizing the

**Table 1** Univariate relationship between patient characteristics and spontaneous resolution.

Variable	Overall (n = 147)	Spontaneous resolution (n = 67)	Persistent (n = 55)	Surgical correction (n = 25)	p
Gender, n (%)					0.49
Male	49 (33.3)	19 (28.4)	21 (38.2)	9 (36.0)	
Female	98 (66.7)	48 (71.6)	34 (61.8)	16 (64.0)	
Bilateral, n (%)					0.05
No	59 (40.1)	34 (50.7)	18 (32.7)	7 (28.0)	
Yes	88 (59.9)	33 (49.3)	37 (67.3)	18 (72.0)	
Reflux grade, Mean (SD)	2.97 (1.08)	2.40 (0.89)	3.13 (0.94)	4.12 (0.73)	<0.001
Reflux grade, n (%)					0.0005
1	6 (4.1)	4 (6.0)	2 (3.6)	0 (0)	
2	46 (31.3)	35 (52.2)	11 (20.0)	0 (0)	
3	51 (34.7)	22 (32.8)	24 (43.6)	5 (20.0)	
4	31 (21.1)	5 (7.5)	14 (25.5)	12 (48.0)	
5	13 (8.8)	1 (1.5)	4 (7.3)	8 (32.0)	
Time of reflux, n (%)					<0.001
Voiding only	16 (10.9)	9 (13.4)	6 (10.9)	1 (4.0)	
Late filling	93 (63.3)	54 (80.6)	30 (54.5)	9 (36.0)	
Early to mid-filling	38 (25.9)	4 (6.0)	19 (34.5)	15 (60.0)	
Age group, n (%)					0.07
<12 months	131 (89.1)	62 (92.5)	49 (89.1)	20 (80.0)	
$\geq 12$ months	16 (10.9)	5 (7.5)	6 (10.9)	5 (20)	
UDR, Mean (SD)	0.28 (0.16)	0.19 (0.08)	0.31 (0.14)	0.45 (0.18)	<0.001
UD, Mean (SD)	6.37 (3.85)	4.55 (2.44)	7.01 (3.32)	9.86 (5.11)	<0.001

UD, ureteral diameter; UDR, ureteral diameter ratio.



**Figure 1** Plot demonstrating probability of spontaneous resolution, persistent VUR, or surgical repair according to age, UDR, and VUR grade. X axis is UDR and Y axis is outcome at time of last follow-up. Grades 1 and 2 were combined for analysis. Children with high UDR are unlikely to resolve regardless of age or VUR grade.

**Table 3** Results of multivariable models comparing effect of ureteral diameter ratio without grade, grade with UDR, and combination of UDR and VUR grade.

	Likelihood ratio chi-square statistic	<i>p</i> value
UDR in model (VUR grade not in model)		
UDR	77.123	<0.0001
Age	8.746	0.0126
VUR grade in model (UDR not in model)		
Grade	64.224	<0.0001
Age	7.27	0.026
Both UDR and VUR grade in model		
UDR	22.2956	<0.0001
Grade	14.3973	0.0008
Age	9.6619	0.008

UDR, ureteral diameter ratio; VUR, vesicoureteral reflux.

cost, inconvenience, and morbidity of treatment and follow-up [13]. Thus, the key in selecting patients for either continuous antibiotic prophylaxis or surgical correction is identifying those children unlikely to resolve as well as those at greatest risk for recurrent infections, which remains a challenge. Factors impacting the chance for spontaneous resolution of VUR include the grade of reflux, gender, age, laterality, presence of bladder and bowel dysfunction, renal scarring, distal ureteral dilation, and bladder volume at which reflux occurs. An individualized risk-based approach that takes into consideration a complement of demographic, radiographic, and clinical factors should thus guide management [13–15]. Despite the multitude of factors contributing to the natural course of VUR, grade has long been acclaimed as the gold-standard descriptor of reflux as well as an important predictor of clinical outcomes.

Need for surgical correction is influenced by a particular child’s risk for further infections, risk of renal scarring/ chronic kidney disease, and likelihood of spontaneous

resolution. Although continuous antibiotic prophylaxis is considered safe and well-tolerated in general, the emergence of bacteria with high rates of resistance has been reported [16]. Parental preference regarding long-term antibiotic use also plays a role in opting for surgical intervention in children with persistent reflux. It is well-documented that high-grade reflux is associated with increased risk of renal scarring as well as lower resolution rates [14,17–20]. Despite common use and standardization, the subjective nature of the presently accepted system of grading VUR leads to significant inter-observer variability and discrepancies particularly with intermediate grades [6]. The subjectivity of VUR grading is one reason for the development of UDR as a predictive tool for clinical outcomes. Previous studies using UDR demonstrated high inter-rater reliability and improved predictability of clinical outcomes relative to grade alone [8–10]. As patients undergoing operative intervention were included, and the length of follow-up varied between patients, the purpose of the current study was not to determine the natural history of spontaneous resolution but rather to compare grade and UDR in predicting early clinical outcomes.

Although not all children are subject to the potentially harmful sequelae of reflux, accurate identification of those patients unlikely to resolve may impact management decisions and prevent recurrent pyelonephritis, renal scarring, and loss of renal function. In the present series, 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. This is consistent with previously published data, in which spontaneous resolution rarely occurred with UDR >0.35 [9]. Of note, the mean patient age at diagnosis in the previous study was 2.7 years, compared with a younger cohort in the present study.

The increment of 0.1 was previously determined to be a conservative cut-off for clinical significance, where a 0.1 increase in UDR resulted in a significantly increased risk of persistent VUR [9]. Specifically, our prior study demonstrated a 1.73 increased odds of failure to resolve with each 0.1 increment increase in UDR compared with 2.6 increased odds in the current study, confirming the predictive power of UDR. Although both grade and UDR were statistically significant in a multivariable model, UDR had a higher likelihood ratio and was thus more predictive than grade alone. Furthermore, unlike traditional VUR grading in which 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 spontaneously resolve. A reliable, reproducible UDR value over which spontaneous resolution is unlikely to occur, independent of grade, may be of particular benefit when counseling parents. Determination of such a cutoff will require larger numbers of patients so that values can be established in conjunction with other factors known to impact resolution such as age and laterality. The authors recognize, however, that confirmation of this statement would require a study with much longer period of follow-up in patients not subjected to surgical intervention.

Distal ureteral dilatation, defined as >7 mm on ultrasound, has been shown to influence resolution of VUR as well as need for surgical intervention [21,22]. These findings are

consistent with our findings, as well as the well documented outcomes with higher grades of VUR; however, the predictive accuracy of ultrasound measured distal ureteral diameter compared with grade and UDR is unknown at this time. Normalizing ureteral diameter via UDR controls for potential radiographic magnification and patient size. Controlling for these variables was more predictive than using distal ureteral diameter alone in our study. For every unit increase in UDR, there was a greater increased odds of persistent disease compared with UD (2.6 versus 1.28). While a UDR >0.5 precluded early spontaneous resolution, high UD did not, as some children with distal ureteral diameter >10 mm experienced early spontaneous resolution.

VCUG has the ability to provide detailed information about both the anatomical and functional status of the urinary tract, including UDR. Studies have demonstrated significant variability among institutions lacking standardized VCUG protocols, as well as inconsistent reporting practices [23,24]. In addition to potential child and parental distress, VCUGs also expose patients to ionizing radiation, albeit at low doses [25,26]. It is important to collaborate with the radiologist to optimize the quality and quantity of data obtained from a single VCUG. In the current study, nearly 90% of the VCUGs had adequate images for UDR without altering imaging protocol. Ensuring adequate images of the lumbar spine and distal ureter during reflux allows for easy calculation of UDR in all children, thereby adding valuable prognostic information without additional invasive testing. Several recent studies have also demonstrated the value of recording bladder volume at VUR onset, further emphasizing the need for standardized, complete VCUG reporting [27,28].

Our study has several limitations that warrant acknowledgement. The data were collected retrospectively, subjecting it to flaws inherent with such study design. The impact of hydration status, urinary flow rates, and ureteral peristalsis on maximal ureteral diameter were not addressed in the current study, and remain unknown. The data were analyzed by patient rather than by ureter, assuming that in cases of bilateral VUR, laterality had no relation to evaluated variables. Patients without a second VCUG were excluded from study, and it is unknown whether inclusion of these children would have altered resolution rates. The role of parental preference regarding timing of surgical intervention and comorbidities representing potential clinical risk factors were not included in our analysis, and it remains unknown how many children would have spontaneously resolved with longer follow-up. Renal scintigraphy was not routinely performed; therefore the role that undetected concomitant obstruction played in ureteral dilation was not assessed. Bladder and/or bowel dysfunction is known to affect the likelihood of spontaneous resolution in children with primary VUR and was not included in our analysis of these young children. Finally, as neither preoperative clinical risk factors such as parenchymal scarring and voiding dysfunction nor postoperative outcomes were included in our analysis, it should be emphasized that the risk of VUR non-resolution should not be interpreted to correlate with clinical risk of pyelonephritis.

Despite these limitations, our study provides validation of UDR in predicting early spontaneous resolution versus persistence or surgical correction of primary VUR. The

association between UDR and risk of recurrent infection is currently the source of ongoing study. Clinicians and parents often opt for intervention based on likelihood of spontaneous resolution as well as clinical course, thereby placing an emphasis on the ability to predict likelihood of recurrent febrile infections. Although no single factor alone can predict with absolute certainty the clinical outcome of any given child with reflux, UDR is readily available and adds potentially valuable information when counseling families about likelihood of spontaneous resolution.

## Conclusions

The distal ureteral diameter ratio is a readily accessible, objective, and validated measure of vesicoureteral reflux. UDR correlates with reflux grade, but is more predictive of early spontaneous resolution in children with primary VUR than grade alone. The ureteral diameter ratio provides valuable prognostic information regarding clinical outcomes, facilitating more individualized patient management.

## Conflict of interest

None.

## Funding

None.

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