The VCUG for VUR: Looking Beyond the Reflux

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Vesicoureteral reflux (VUR) affects up to 40% of children with a history of febrile urinary tract infection (UTI) and occurs in 10%–20% of patients with prenatal hydronephrosis.[1] While the optimal management of VUR is controversial, treatment goals include prevention of febrile UTI and renal scarring, while minimizing the morbidity associated with treatment and followup. Accordingly, it is important that clinicians identify those patients with a higher risk of febrile UTI and renal scarring who warrant more aggressive treatment and followup protocols.

The international system of radiographic grading of VUR was described by Lebowitz in 1985 and is used in current voiding cystourethrogram (VCUG) reporting by radiologists and urologists alike.[2] This grading system was designed to quantify VUR severity by assigning a score of I–V based on specific radiologic findings. However, while VUR grade on VCUG may be important in predicting VUR severity and guiding treatment decisions, it is only one piece of the puzzle. VUR grade has been regarded as the gold standard for assessment of reflux severity, but other factors (fig. 1) influence likelihood of spontaneous resolution and breakthrough urinary tract infections.[3] As such, health care providers who use grade alone to make treatment decisions may be falsely reassured by low-grade, clinically significant reflux, leading to a delay in definitive treatment or, alternatively, be led to suggest early surgery for high-grade reflux. Thus, we must consider the role of other factors, in conjunction with reflux grade, in evaluation and management of our patients with primary VUR.

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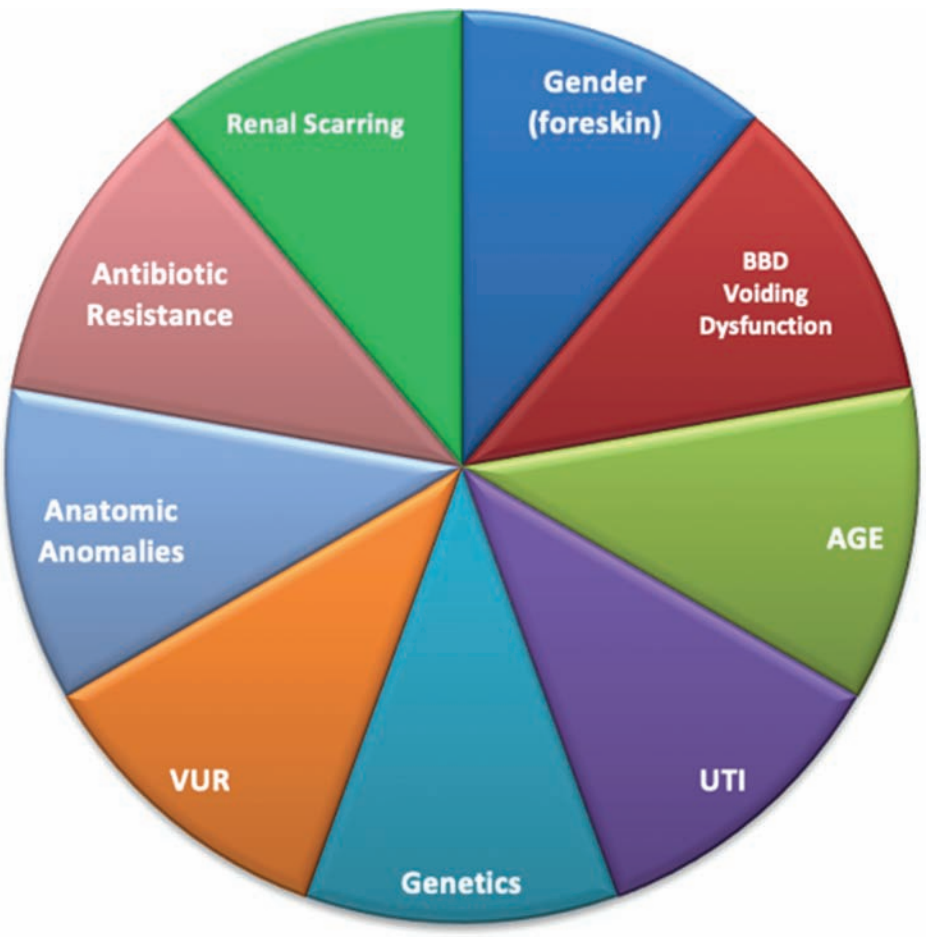

Figure 1. Factors associated with risk of febrile UTI *BBD*, bladder bowel dysfunction.

VCUG DATA		SCORE
Timing of Reflux		
	Filling (Early-Mid)	3
	Filling (Late)	2
	Voiding (Only)	1
Ureteral Anomalies (Duplex/PUD)		
	Present	1
	Absent	0
VUR Grade		
	High (IV-V)	1
	Low-Mod (I-III)	0
Gender		
	Female	1
	Male	0
TOTAL	=	/ 6

Figure 2. VURx calculator.

In addition to identifying factors associated with spontaneous resolution, breakthrough UTI and protection from renal scarring are of paramount importance in VUR management. Between 15% and 52% of children with acute pyelonephritis and 23% and 59% of those with UTI have some degree of renal scarring.[4] Chen et al retrospectively reviewed a cohort of 173 children with primary VUR to identify risk factors for renal scarring and long-term renal outcomes. Multivariate analysis demonstrated that older age at VUR diagnosis (≥5 years vs <1 year, OR 2.8), higher grade (grade IV–V vs I–III, OR 15.2), and UTI events (≥2 vs 0, OR 3.2) were risk factors for renal scarring. Younger age at diagnosis (HR 0.2), presence of renal scarring (HR 3.7) and acute pyelonephritis (HR 3.1) were risk factors for development of CKD2 (stage 2 chronic kidney disease: mild loss of kidney function, eGFR 60-89) or greater.

It is well established that patients with VUR demonstrate aberrant ureterovesical junction anatomy, resulting in a shortened intramural tunnel and perpendicularly oriented ureteral insertion. Some patients demonstrate isolated distal ureteral dilation without upper tract dilation, making reflux grading difficult. This observation led to the development of the ureteral diameter ratio (UDR), a tool providing quantitative assessment of ureterovesical junction (UVJ) dilation as a surrogate measure of VUR severity. The UDR is calculated by measuring the largest ureteral diameter in the false pelvis divided by the distance from the bottom of L1 to the top of L3 vertebral bodies.[5] The UDR is significantly associated with VUR grade, is more predictive of reflux resolution than grade alone (chi-squared 22.3, p <0.0001 vs 14.3, p=0.0008) and is significantly correlated with risk of

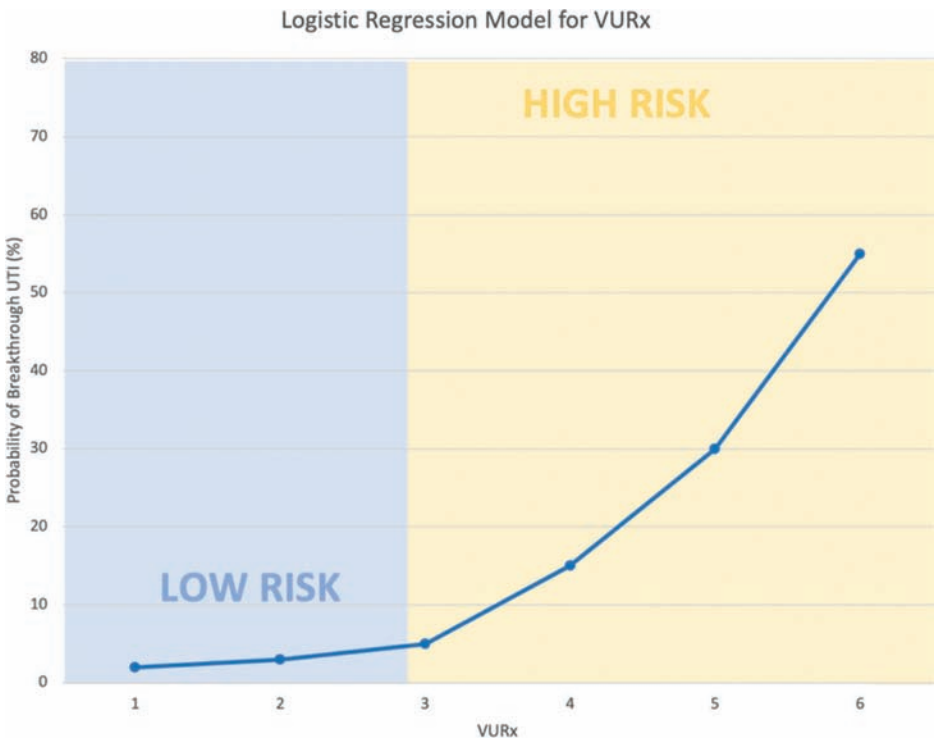

Figure 3. Risk of future or recurrent febrile UTI.

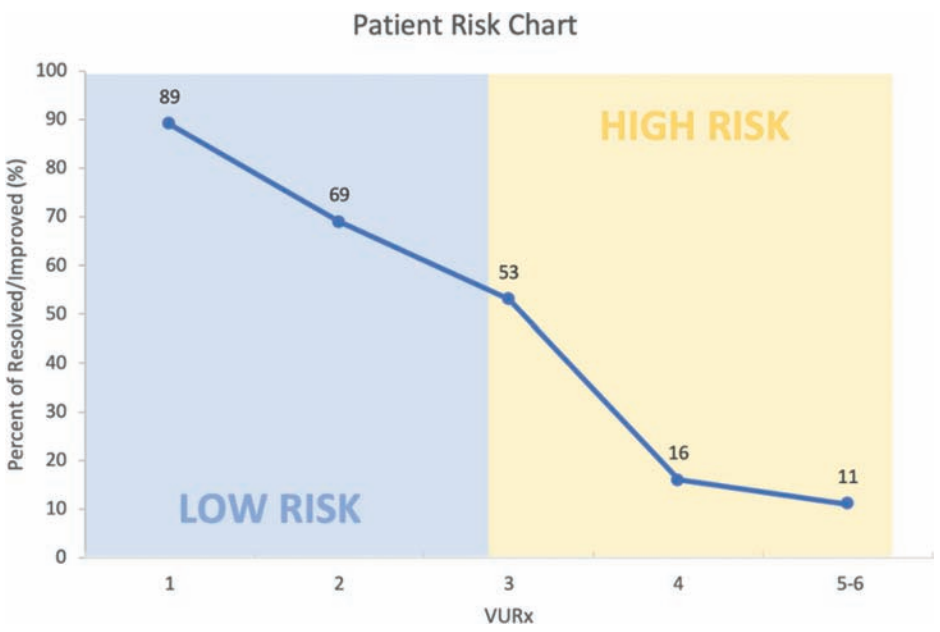

Figure 4. Probability of spontaneous resolution.

breakthrough febrile UTI.[5,6] Arlen et al demonstrated that for each 0.1 unit increase in UDR, there is a 2.6 increased odds of persistent VUR and 3.7 increased odds of surgical intervention.[5] In addition, the UDR demonstrates high inter-rater reliability among pediatric urologists.[7]

In 2014, we described the vesicoureteral reflux index (VURx), a novel tool utilizing an individualized risk-based approach to predict primary reflux resolution rates. A cohort of 229 children <2 years of age with primary VUR was evaluated, and factors associated with improvement and resolution of reflux were identified.[3] Multivariate analysis revealed early timing of reflux (ie low bladder volume and pressure) was the most important factor in determining time to resolution, with anatomic anomalies, female gender and high-grade reflux also significantly predictive. The VURx score ranges from 1–6 and is calculated as follows: VUR timing (early-mid filling: 3; late filling: 2; voiding only: 1), female gender: 1; VUR grade IV-V: 1; complete ureteral duplication or periureteral diverticulum (PUD): 1 (fig. 2). VURx score correlates with risk of breakthrough febrile UTI (fig. 3) and inversely correlates with rate of improvement or resolution (fig. 4).[3,8] In 2016, the scoring system was validated in children older than 2 years.[9] The VURx and UDR are both superior to international grade alone at predicting risk of breakthrough UTI, with the VURx being most predictive.[8]

> "We must look beyond reflux grade as the sole determinant of reflux severity and clinical course"

Studies demonstrate that not only reflux timing but more specifically bladder volume when reflux first occurs affect clinical outcomes. A retrospective analysis of 255 children with primary VUR demonstrated that lower median bladder volume was significantly associated with breakthrough febrile UTI on univariate analysis (33.1% vs 49.5% of predicted bladder capacity, p=0.003).[10] Additionally, VUR onset at a bladder volume of ≤35% predicted bladder capacity demonstrates a significant independent association with breakthrough febrile UTI (HR 1.58, p=0.03).[10] Therefore, as outlined in the 2016 American Academy of Pediatrics VCUG guidelines, it is critical that radiologists specify bladder volume when reflux occurs to accurately assess clinical outcomes.[11]

In summary, VCUG serves as an important diagnostic tool for evaluation of VUR, but we must look beyond reflux grade as the sole determinant of reflux severity and clinical course. As outlined above, other factors including bladder volume when reflux occurs, female gender, ureteral anomalies, age at diagnosis and number of UTIs have significant implications on clinical outcomes. Therefore, an individualized risk-based approach to primary VUR should be utilized to counsel families and guide evidence-based treatment decisions. ■

1. Roberts KB and the Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management: Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011; **128:** 595.
2. Lebowitz RL, Olbing H, Parkkulainen KV et al: International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol 1985; **15:** 105.
3. Kirsch AJ, Arlen AM, Leong T et al: Vesicoureteral reflux index (VURx): a novel tool to predict primary reflux improvement and resolution in children less than 2 years of age. J Pediatr Urol 2014; **10:** 1249.
4. Chen MJ, Cheng HL, Chiou YY: Risk factors for renal scarring and deterioration of renal function in primary vesico-ureteral reflux children: a long-term follow-up retrospective cohort study. PLoS One 2013; **8:** e57954.
5. Arlen AM, Kirsch AJ, Leong T et al: Validation of the ureteral diameter ratio for predicting early spontaneous resolution of primary vesicoureteral reflux. J Pediatr Urol 2017; **13:** 383e1.
6. Arlen AM, Leong T, Guidos PJ et al: Distal ureteral diameter ratio is predictive of breakthrough febrile urinary tract infection. J Urol 2017; **198:** 1418.
7. Swanton AR, Arlen AM, Alexander SE et al: Inter-rater reliability of distal ureteral diameter ratio compared to grade of VUR. J Pediatr Urol 2017; **13:** 207e1.
8. Arlen AM, Leong T, Wu CQ et al: Predicting breakthrough urinary tract infection: comparative analysis of vesicoureteral reflux index, reflux grade and ureteral diameter ratio. J Urol 2020; **204:** 572.
9. Garcia-Roig M, Ridley DE, McCraken C et al: Vesicoureteral reflux index: predicting primary vesicoureteral reflux resolution in children diagnosed after age 24 months. J Urol 2017; **194:** 1150.
10. Alexander SE, Arlen AM, Storm DW et al: Bladder volume at onset of vesicoureteral reflux is an independent risk factor for breakthrough febrile urinary tract infection. J Urol 2015; **193:** 1342.
11. Frimberger D and Mercado-Deane MG: Establishing a standard protocol for the voiding cystourethrography. Pediatrics 2016; **138:** e20162590.

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