

Predicting Breakthrough Urinary Tract Infection: Comparative Analysis of Vesicoureteral Reflux Index, Reflux Grade and Ureteral Diameter Ratio



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Abbreviations and Acronyms

BBD = bladder and bowel dysfunction
DMSA = dimercaptosuccinic acid
fUTI = febrile urinary tract infection
UDR = ureteral diameter ratio
UTI = urinary tract infection
VCUG = voiding cystourethrogram
VUR = vesicoureteral reflux
VURx = vesicoureteral reflux index

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Purpose: The vesicoureteral reflux index is a simple, validated tool for predicting resolution of reflux. Along with likelihood of spontaneous resolution identification of children at risk for febrile urinary tract infection impacts management. We evaluated the usefulness of the vesicoureteral reflux index as a predictive factor for breakthrough febrile urinary tract infection compared to reflux grade and distal ureteral diameter ratio.

Materials and Methods: Children with primary vesicoureteral reflux and detailed voiding cystourethrogram data were identified. A 1 to 6-point index was assigned, and ureteral diameter ratio was computed by measuring largest ureteral diameter within the pelvis and dividing by the distance between L1 to L3 vertebral bodies. Random forest modeling and logistic multivariable regression were employed to estimate the predictive ability of grade, ureteral diameter ratio and vesicoureteral reflux index with regard to breakthrough febrile urinary tract infection.

Results: We analyzed 94 girls and 45 boys with a mean±SD age of 5.4±4.7 months at diagnosis. Mean±SD length of followup was 32.1±24.5 months. A total of 13 children (9.4%) experienced breakthrough febrile urinary tract infection. On univariate analysis ureteral diameter ratio ($p=0.01$) and vesicoureteral reflux index ($p=0.0005$) were associated with breakthrough urinary tract infection, while grade ($p=0.09$) did not reach significance. Area under the curve was generated as a measure of accuracy for each variable and was 0.77 for the vesicoureteral reflux index, 0.71 for ureteral diameter ratio and 0.68 for grade, indicating superiority of the vesicoureteral reflux index for predicting breakthrough febrile urinary tract infection.

Conclusions: Children with higher vesicoureteral reflux index are at increased risk for breakthrough febrile urinary tract infection independent of reflux grade. The vesicoureteral reflux index provides valuable prognostic information about infection risk, facilitating improved clinical decision making.

Key Words: vesico-ureteral reflux, urinary tract infections, cystography

URINARY tract infection is among the most common serious bacterial infections in the pediatric population and is associated with a high incidence of recurrence.¹⁻⁶ Up to 40% of children with a history of febrile urinary tract

infection have vesicoureteral reflux.⁷ While reflux is associated with an increased risk of recurrent urinary tract infection and renal scarring, use of aggressive management in all primary reflux cases has come into

question, with a more selective approach increasingly gaining favor.^{6,8} Despite the tendency of reflux to improve/resolve over time, a subset of children with persistent reflux are at risk for recurrent pyelonephritis as well as potential sequelae of renal injury.⁶ Thus, factors influencing the decision to perform antireflux surgery include risk of recurrent pyelonephritis, new renal parenchymal scarring and persistent vesicoureteral reflux.

The vesicoureteral reflux index is a simple 6-point scale designed to predict time to reflux resolution.⁹ Assigned based on gender and interpretation of data obtained from a single VCUG, VURx was initially developed to predict resolution of primary reflux in cases diagnosed before age 2 years. UDR is an objective data point with high interrater reliability that has been shown to be predictive of spontaneous reflux resolution and breakthrough UTI.^{10,11} Given the inclusion of gender and the emphasis placed on volume at which reflux occurs, we hypothesized that children with a higher VURx would also have an increased risk of breakthrough febrile UTI. We evaluated VURx regarding risk of breakthrough fUTI and compared its predictive ability to reflux grade, which is the gold standard descriptor of reflux, and UDR, which is associated with breakthrough fUTI.

MATERIALS AND METHODS

Institutional review board approval was obtained. Children with primary reflux in whom VURx and UDR could be calculated on initial VCUG were identified. Patient demographics, volume at which reflux occurred, VUR grade and laterality were abstracted. VUR grade was determined using the International Reflux Study in Children classification system.¹² In cases of bilateral reflux the highest VUR grade was used for analysis. VURx (table 1) and UDR were calculated as described previously.^{9,13} High grade VUR was defined as grade 4 to 5.

VUR timing on VCUG was designated by the interpreting pediatric radiologist as early to mid filling, late filling or voiding only. Timing was indexed according to volume of contrast material infused and estimated bladder capacity according to age using the formula, $[\text{age} + 2] \times 30$ ml. Late filling VUR was defined as reflux onset at greater than 75% estimated bladder capacity. 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.

Patients were placed on prophylactic antibiotics and followed with annual cystograms until time of reflux resolution/significant improvement or operative repair. Significant improvement was defined as decrease of 2 or more grades. Children with secondary VUR, ectopic ureters, ureterocele, concomitant ureteropelvic junction or ureterovesical junction obstruction, or unknown clinical outcome/no followup VCUG were excluded from the study,

Table 1. Components of VUR index

	Score*
Gender:	0–1
Female	1
Male	0
VUR timing:	1–3
Early to mid filling	3
Late filling	2
Voiding	1
Ureteral anomalies present:†	0–1
Yes	1
No	0
VUR grade:	0–1
1–3	0
4–5	1

* Total score of 1 to 6 is possible.

† Periureteral diverticulum or complete ureteral duplication.

as were those not prescribed continuous antibiotic prophylaxis. Length of followup was defined as time from initial diagnostic VCUG to last cystogram and/or clinic visit. All patients had a minimum clinical followup of 6 months.

Patient demographics, UTI history and subsequent imaging were assessed. Febrile UTI was defined as a positive urine culture of more than 10^3 CFU/ml of a single organism associated with a body temperature of 101.5F or higher. Urine cultures were obtained via bag specimen, catheterization or clean catch depending on patient age. Catheterized specimens were obtained if bag specimens were positive (ie demonstrated pyuria or bacteriuria).

The Fisher exact test was used to compare categorical patient characteristics by breakthrough fUTI group, and 2 sample Wilcoxon tests were used for comparison of continuous variables. A random forest algorithm was used to estimate relative importance of VURx, UDR and reflux grade in classifying breakthrough fUTI. The variables were evaluated individually in 3 logistic regression models for area under the curve. AUC was calculated as a measure of accuracy for each variable. Statistical analysis was performed using R 3.1.1 software (R Project for Statistical Computing, <http://www.r-project.org>), with $p < 0.05$ representing statistical significance.

RESULTS

We identified 175 children who were diagnosed with primary reflux and had VURx and UDR data available. Of the patients 94 girls and 45 boys met all inclusion criteria with appropriate clinical followup (table 2). Indications for VCUG were fUTI in 94 patients (67.6%), UTI in 12 (8.6%), hydronephrosis in 32 (23%) and other in 1 (0.7%). Patients were diagnosed at a mean±SD age of 5.45±4.7 months. VUR was grade 1 to 2 in 47 cases (33.8%), 3 in 49 (35.2%), 4 in 30 (21.6%) and 5 in 13 (9.4%). Mean±SD VURx was 3.24±0.94, and UDR was 0.28±0.16. Mean±SD length of clinical followup was 32.1±24.5 months.

A total of 13 children (9.4%) experienced 28 breakthrough fUTI events, of whom 9 (69.2%) had at

Table 2. Univariate analysis of patient characteristics by breakthrough urinary tract infection

	Overall	No Breakthrough UTI	Breakthrough UTI	p Value
No. pts	139	126	13	
Mean±SD age (mos)	5.45±4.7	5.48±4.74	5.13±4.54	0.79
No. gender (%):				1.00
Male	45 (32.4)	41 (32.5)	4 (30.8)	
Female	94 (67.6)	85 (67.5)	9 (69.2)	
No. male circumcision status (%):				0.11
Uncircumcised	22 (48.9)	18 (81.8)	4 (18.2)	
Circumcised	22 (48.9)	22 (100)	0 (0)	
Unknown	1 (2.2)	1 (100)	0 (0)	
No. laterality (%):				1.00
Unilat	55 (39.6)	50 (39.7)	5 (38.5)	
Bilat	84 (60.4)	76 (60.3)	8 (61.5)	
No. indication (%):				0.17
Febrile UTI	94 (67.6)	85 (67.5)	9 (69.2)	
UTI	12 (8.6)	9 (7.1)	3 (23.1)	
Hydronephrosis	32 (23.0)	31 (24.6)	1 (7.7)	
Other	1 (0.7)	1 (0.8)	0 (0)	
No. ureteral anomaly (%):				0.04
No	124 (89.2)	115 (91.3)	9 (69.2)	
Yes	15 (10.8)	11 (8.7)	4 (30.8)	
No. reflux timing (%):				0.06
Voiding only	16 (11.5)	16 (12.7)	0 (0)	
Late filling	86 (61.9)	80 (63.5)	6 (46.2)	
Early to mid filling	37 (26.6)	30 (23.8)	7 (53.8)	
No. high grade reflux (%):				0.11
No	96 (69.1)	90 (71.4)	6 (46.2)	
Yes	43 (30.9)	36 (28.6)	7 (53.8)	
No. reflux grade (%):				0.09
1–2	47 (33.8)	46 (36.5)	1 (7.7)	
3	49 (35.3)	44 (34.9)	5 (38.5)	
4	30 (21.6)	25 (19.8)	5 (38.5)	
5	13 (9.4)	11 (8.7)	2 (15.4)	
Mean±SD UDR	0.28±0.16	0.27±0.15	0.40±0.22	0.014
Mean±SD VURx	3.24±0.94	3.16±0.92	4.08±0.76	0.0005

least 1 documented infection within 2 years of reflux diagnosis. On univariate analysis both UDR ($p=0.01$) and VURx ($p=0.0005$) were associated with breakthrough UTI (table 2). Although all 4 males with breakthrough fUTI were uncircumcised, this result did not reach statistical significance. Children presenting with fUTI were not more likely to suffer a breakthrough UTI ($p=0.17$). A random forest model was employed to ascertain which variables (VURx, UDR, maximum VUR grade) were considered of highest importance in predicting breakthrough febrile urinary tract infection. Relative importance was based on mean decrease in model accuracy from permuting the values of each variable, with VURx being the most important. Logistic regression revealed the same order of importance (table 3). Figure 1 illustrates the increasing probability of a breakthrough fUTI in children with a higher VURx.

Area under the curve was generated as a measure of accuracy for each variable and was 0.77 (95% CI 0.661–0.887) for VURx, 0.71 for UDR (95% CI 0.558–0.857) and 0.68 for grade (95% CI 0.551–0.812; fig. 2). The AUC indicates that both VURx and UDR have fair discriminatory power, ie are significantly better at predicting breakthrough infection than chance alone.

DISCUSSION

Vesicoureteral reflux is among the most common urological diagnoses affecting children. Primary VUR is believed to result from failure of the ureterovesical junction to develop properly and is frequently associated with an abnormally short intramural ureteral tunnel. The condition is potentially self-limiting, and conservative management is often favored given the high rate of resolution. Several factors are known to impact the likelihood of spontaneous reflux resolution, including grade, age at diagnosis, laterality, presence of BBD, renal parenchymal scarring, bladder volume at which reflux occurs and distal ureteral diameter ratio.^{11,14–16} Reflux occurring early in the bladder filling cycle has been associated with anatomically incompetent ureteral orifices (as shown

Table 3. Order of relative importance logistic regression

	Mean±SE Beta	OR (95% CI)	p Value
Intercept	−7.19±1.69	-	<0.001
UDR	3.69±2.46	39.99 (0.27–5293.09)	0.13
VURx	0.96±0.44	2.61 (1.12–6.59)	0.03
VUR grade*			
3	0.90±1.17	2.45 (0.31–50.74)	0.45
4	−0.24±1.49	0.79 (0.05–23.29)	0.87
5	−0.52±1.74	0.59 (0.02–23.65)	0.76

* Reference is VUR grade 1-2.

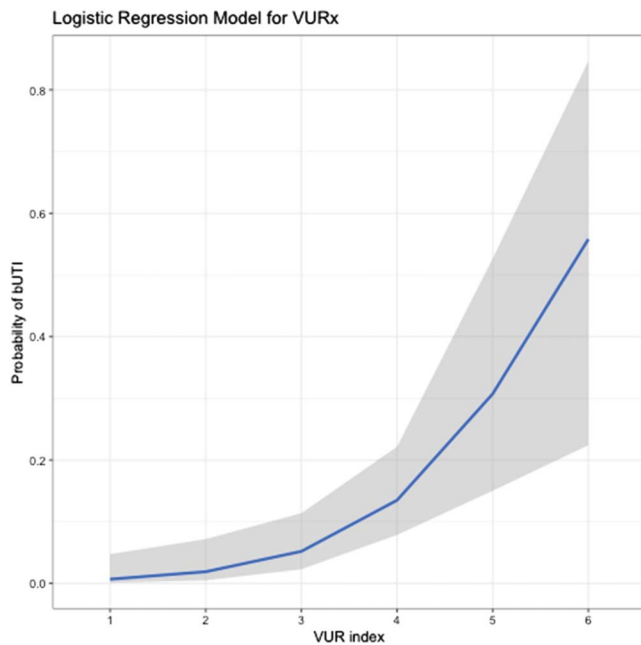


Figure 1. Probability of breakthrough febrile UTI (bUTI) based on VURx.

by dynamic ureteral hydrodistention), likely contributing to lower spontaneous resolution rates.¹⁷ Many of these characteristics also contribute to ongoing UTI risk. In general, clinicians must distinguish which cases are most likely to resolve without intervention from those harboring VUR with the potential to cause irreversible renal damage over time, thus placing the emphasis on the ability to predict the likelihood of recurrent febrile infections rather than merely resolution.¹⁸

VURx is a simple, validated tool that reliably predicts significant improvement and spontaneous resolution of primary reflux in children.^{19,20} If the 2016 American Academy of Pediatrics Sections on Radiology and Urology consensus standardized protocol is adhered to,²¹ data used to formulate a given child's VURx are readily available at initial VCUG, making the information accessible to primary care providers as well as specialists at the time of diagnosis.

Previous studies have indicated that VURx is superior at predicting spontaneous resolution compared to reflux grade alone.^{9,19,20} The present study suggests that VURx is also a better predictor of breakthrough fUTIs than grade alone. UDR, an objective measure reflective of ureterovesical junction anatomy, has been observed to predict breakthrough infections.¹¹ Both VURx and UDR were superior to reflux grade in this series, again suggesting that while grade has been the gold standard descriptor of reflux, it is not the ideal predictor of anticipated clinical course. Just under 10% of our patients experienced a febrile breakthrough infection. Our findings indicate that higher VURx at diagnosis is more

predictive of a breakthrough fUTI than either UDR or reflux grade alone. For example a child with a VURx of 5 had a 30% probability of a breakthrough febrile infection, compared to 5% for a patient with a VURx of 3. Grade was not significantly associated with breakthrough infections, suggesting that it is less important than other variables regarding risk of fUTI.

Since pyelonephritis and its potential sequelae (such as scarring) are what cause concern in children with VUR rather than merely the presence of reflux itself, we assessed the utility of VURx to identify children at increased risk for breakthrough febrile urinary tract infections. The key focus in selecting patients for intervention should be identifying those unlikely to have resolution of VUR and those at greatest risk for recurrent pyelonephritis, underscoring the usefulness of VURx. We hypothesize the superiority of VURx over grade may be secondary to the impact that gender and volume at which reflux occurs have on breakthrough infection risk.^{22,23} Our current and prior publications support the notion that, as opposed to high pressure voiding only VUR, patients with early filling, low volume VUR have increased exposure of the kidney to urine and bacteria coming from the bladder, and thus are at increased risk for UTI.

Our study is not without limitations. Data were collected retrospectively and are subject to flaws inherent in such a study design. The current definition of UTI by the American Academy of Pediatrics reduces the required bacterial colony count from 10^3 CFU/ml to 5^3 CFU/ml and includes the requirement of pyuria.²⁴ Given the time at which patients in this study were diagnosed with reflux, the former definition of 10^3 CFU/ml was used. While some urine cultures were obtained via sterile catheterization, others were from voided specimens, which may have resulted in false-positive results. Although efforts were made to confirm patient clinical status, it is possible that not all UTIs were included in the analysis if children presented elsewhere and the records were not obtained.

The impact of BBD was not addressed in the current study, and while the included cohort was diagnosed before age 24 months, many of these patients likely underwent toilet training during the followup period. Renal scarring is also a known risk factor for febrile UTI. However, ^{99m}Tc -DMSA scans were not routinely obtained, and therefore the incidence of renal scarring/dysplasia and the impact on breakthrough fUTI rate in our patient cohort is unknown. The lack of DMSA data was in part due to lack of availability/national shortage of ^{99m}Tc technetium during the study period. In addition, while all children were placed on continuous antibiotic prophylaxis, compliance was not formally assessed with culture sensitivity profiling or assessment of medication refill status. Finally, some children were excluded due to lack of repeat VCUG or lack of clinical followup. It is unknown whether cases

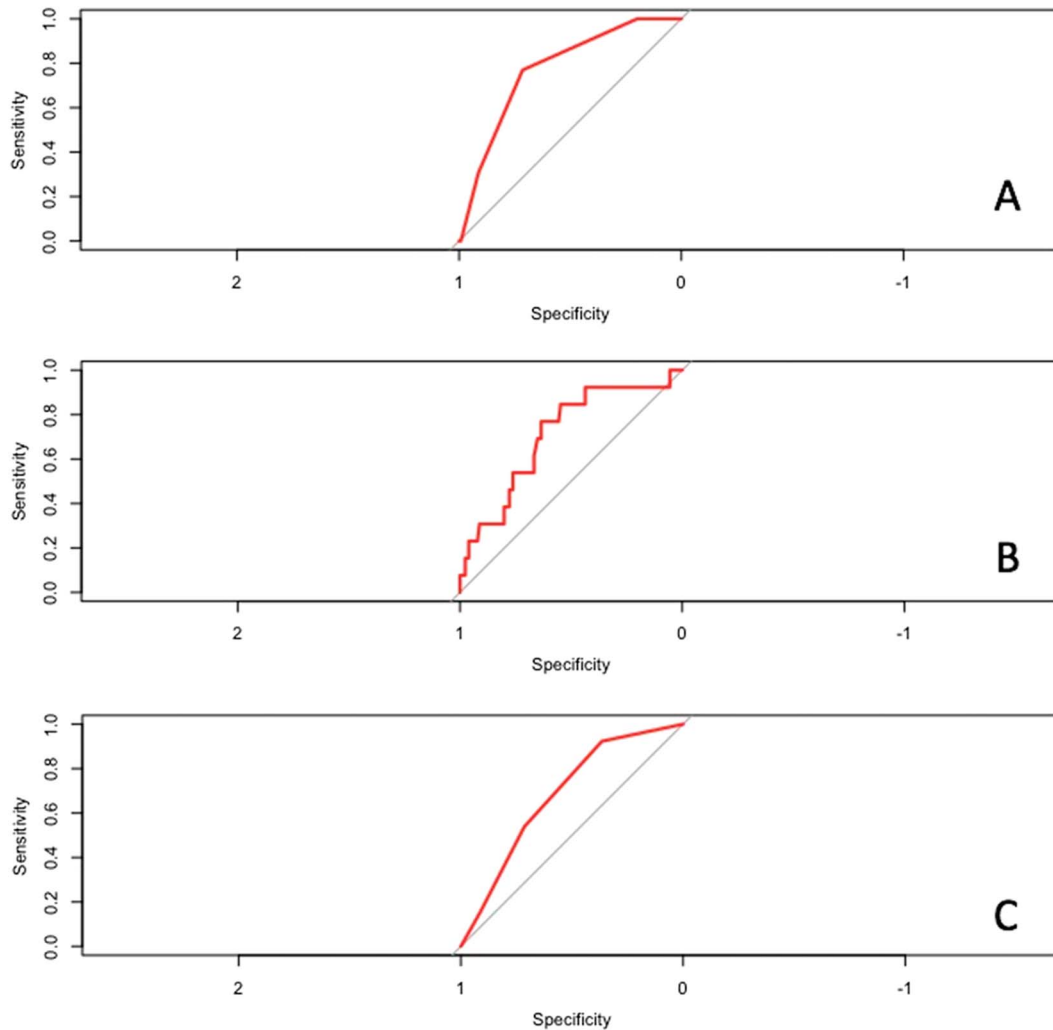


Figure 2. AUC of VURx (A), UDR (B) and VUR grade (C) for predicting breakthrough febrile UTI

that were excluded from the study would have altered the breakthrough infection rate.

Despite these limitations, our study demonstrates that VURx as a cumulative score of gender, reflux grade and timing, and ureteral anomalies is associated with breakthrough febrile UTI risk in patients diagnosed at a young age, and thus provides additional information to help assess projected clinical course. With antibiotic stewardship in mind future study will focus on the role of VURx in determining UTI risk off antibiotics.

CONCLUSIONS

Children who are diagnosed with primary vesicoureteral reflux before age 24 months and have a higher VURx are at increased risk for breakthrough febrile urinary tract infections. VURx was more predictive of breakthrough UTIs than either reflux grade or distal ureteral diameter ratio in our population. VURx is readily computable and provides valuable prognostic information about the risk of recurrent pyelonephritis, allowing for more individualized counseling and clinical decision making.

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EDITORIAL COMMENT

This study indicates that VURx is better than reflux grade or ureteral diameter ratio for predicting breakthrough fUTI in children with reflux. The authors concede it is unfortunate that BBD and the presence of renal dysplasia as measured by DMSA nuclear scan are absent from this study. Indeed, it has been clearly shown that the risk of febrile UTI in children with reflux is greater in those with BBD, and this condition should always be investigated and managed actively (reference 14 in article).¹ As concerns renal dysplasia, a recently published study from the United Kingdom of 61 patients, which also demonstrated an increased risk of breakthrough UTI in children with a high VURx, indicates an even greater association between breakthrough UTI and renal scarring/dysplasia on DMSA scan.² It is noteworthy that there was no analysis according to circumcision status in that series, while in the

current study all boys who presented with breakthrough fUTIs were uncircumcised. Nevertheless, as the authors correctly point out, DMSA scans are not always available, and decision making is based on the data we have. Furthermore, although ultrasound can yield information about BBD through estimated bladder capacity and post-void residual, actual bladder function can be difficult to evaluate in young children. So even if VURx does not reveal the whole picture, it can definitely be a useful adjunct for decision making and for counseling parents.



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