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Predicting the Risk of Breakthrough Urinary Tract Infections: Primary Vesicoureteral Reflux

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Abbreviations and Acronyms

BBD = bladder and bowel dysfunction

BTUTI = breakthrough urinary tract infection

CAP = continuous antibiotic prophylaxis

DMSA = dimercaptosuccinic acid

UTI = urinary tract infection

VCUG = voiding cystourethrogram

VUR = vesicoureteral reflux

Purpose: We constructed a risk prediction instrument stratifying patients with primary vesicoureteral reflux into groups according to their 2-year probability of breakthrough urinary tract infection.

Materials and Methods: Demographic and clinical information was retrospectively collected in children diagnosed with primary vesicoureteral reflux and followed for 2 years. Bivariate and binary logistic regression analyses were performed to identify factors associated with breakthrough urinary tract infection. The final regression model was used to compute an estimation of the 2-year probability of breakthrough urinary tract infection for each subject. Accuracy of the binary classifier for breakthrough urinary tract infection was evaluated using receiver operator curve analysis. Three distinct risk groups were identified. The model was then validated in a prospective cohort.

Results: A total of 252 bivariate analyses showed that high grade (IV or V) vesicoureteral reflux (OR 9.4, 95% CI 3.8–23.5, p <0.001), presentation after urinary tract infection (OR 5.3, 95% CI 1.1–24.7, p = 0.034) and female gender (OR 2.6, 95% CI 0.097–7.11, p <0.054) were important risk factors for breakthrough urinary tract infection. Subgroup analysis revealed bladder and bowel dysfunction was a significant risk factor more pronounced in low grade (I to III) vesicoureteral reflux (OR 2.8, p = 0.018). The estimation model was applied for prospective validation, which demonstrated predicted vs actual 2-year breakthrough urinary tract infection rates of 19% vs 21%. Stratifying the patients into 3 risk groups based on parameters in the risk model showed 2-year risk for breakthrough urinary tract infection was 8.6%, 26.0% and 62.5% in the low, intermediate and high risk groups, respectively.

Conclusions: This proposed risk stratification and probability model allows prediction of 2-year risk of patient breakthrough urinary tract infection to better inform parents of possible outcomes and treatment strategies.

Key Words: risk assessment, urinary tract infections, vesico-ureteral reflux

VESICOURETERAL reflux is a common pediatric urology diagnosis with a spectrum of severity ranging from an asymptomatic, self-limiting incidental finding to a condition associated with acute pyelonephritis, sepsis, renal scarring and deterioration of kidney function.[1–3] Variability in disease

presentation, outcome and health effects creates controversy regarding diagnosis and management.

Several large-scale studies have revealed that the factors associated with persistent, nonresolving VUR include demographic and clinical characteristics such as age at presentation, gender, race and reflux grade.[4–8] The clinical condition prompting the diagnosis of VUR, unilateral vs bilateral reflux, presence of renal scarring, number of past UTIs, and the presence of bladder and bowel dysfunction are other frequently studied risk factors for non-resolving VUR. Risk of future UTI and renal injury should drive the clinical treatment of patients with primary VUR, rather than its resolution.

We created a risk prediction instrument that stratifies patients with primary VUR into risk groups according to their 2-year probability of having a BTUTI. We constructed a formula that predicts individual risk of BTUTI. This instrument will provide clinicians and parents with guidance in determining optimal management.

METHODS

Definition of UTI and BTUTI
Based on the 2011 American Academy of Pediatrics guidelines, a UTI is defined as an infection characterized by fever, positive urinalysis and positive urine culture. In this study urinalysis was performed on clean intermittent catheterization sample, clean catch specimen or bagged urine sample. Urinalysis was deemed positive if pyuria, bacteria and leukocyte esterase were confirmed. A culture was positive by having more than 50,000 cfu/ml of a single uropathogenic organism.[6] BTUTI was defined as a UTI while taking prophylactic antibiotics. We collected data in 2 cohorts of patients following approval of the Children's Hospital of Orange County review board.

Retrospective Cohort
The hospital VCUG log from June 2008 to December 2010 was used to generate subjects diagnosed with primary VUR. Patients who were lost to followup were invited for followup. Families that failed to follow up in person were interviewed by telephone. Only patients with at least 2 years of followup were included.

Prospective Cohort
A total of 56 patients with primary VUR were followed for a minimum of 2 years at our facility. Final followup data were collected from January to December 2012.

Management protocol included CAP using trimethoprim/sulfamethoxazole or nitrofurantoin initiated at first urological consultation for all patients. Education concerning BBD and UTI prevention was provided to each family. Patients who experienced BTUTI or new renal scarring during followup were excluded from the cohort.

Measures and Data Collection
Demographic and clinical information collected included current age, gender, age at presentation (plus or minus

12 months), reflux grade, laterality (on initial VCUG), initial presentation (after urinary infection or other), presence of BBD, history of BTUTI and hydronephrosis. Information was obtained through review of the medical record. Missing clinical information was obtained from followup visits or telephone calls to the family.

BBD was defined as presence of either daytime incontinence, symptoms of urgency and frequency, or holding maneuvers as assessed by clinical history, uroflowmetry with post-void residual and use of the validated Dysfunctional Voiding Symptom Score questionnaire in toilet trained children.[9] Constipation was defined as clinical history of difficult, incomplete or infrequent evacuations (less than 1 bowel movement daily). Since voiding function is difficult to evaluate in patients not yet toilet trained, BBD was limited to the presence of constipation in this population. Renal parenchymal defects were evaluated using ultrasound or DMSA scan.

VUR grade was determined using the International Reflux Study in Children grading system. A pediatric radiologist and a urologist reviewed all VCUGs to grade the VUR. When agreement was not reached regarding grade assessed independently, the higher of the 2 grades was assigned to the patient. The highest grade of VUR was used for categorization in those with bilateral VUR.

Statistical Analysis
Risk prediction model development. All statistical analyses were performed using SPSS®, version 21.0. Data collected from the retrospective cohort were used to develop the risk prediction model. We used descriptive statistics to characterize this cohort. Candidate variables for inclusion in the risk model were first evaluated by examining the bivariate associations with BTUTI using the Fisher exact test. Variables demonstrating association with BTUTI in the unadjusted bivariate analysis ($p < 0.2$) were included in an initial multivariable logistic regression model. A parsimonious model was then created, retaining only variables from the initial model that carried a significant independent association with BTUTI.

Subgroup analysis comparing associations of the risk factors with BTUTI in the low VUR grade (I to III) vs high grade (IV or V) subgroups was performed using stratified unadjusted bivariate analyses and binary logistic regression. This examination included an analysis of risk factor interactions.

Estimating risk of BTUTI. The final logistic regression model developed was used to estimate 2-year risk of BTUTI for each patient in the retrospective and prospective cohorts. We calculated a risk score (RS_i) by multiplying each variable in the multivariate model by its β coefficient (natural logarithm of odds ratio) and summing the products. The risk score was used to compute the odds of BTUTI using the formula, $Odds(BTUTI)_i = e^{RS_i}$. Odds were then converted to a probability [$Pr(BTUTI)_i$], $Pr(BTUTI)_i = Odds(BTUTI)_i/1 + Odds(BTUTI)_i$. ROC analysis was used to evaluate the performance of the continuous risk models in discriminating patients who would have a BTUTI on followup.

Categorical risk model. Results from the continuous risk model were used to define categorical risk groups.

Patients with factors associated with less than 10%, 10% to 30% and greater than 30% incidence of BTUTI were assigned to the low, intermediate and high risk groups, respectively. Odds ratios comparing the likelihood of BTUTI in the intermediate and high risk groups to the low risk group were estimated using logistic regression.

RESULTS

The retrospective cohort consisted of 252 patients. Of the patients 88% had low grade VUR, 74% were female and 84% were diagnosed with VUR after a UTI. Mean ± SD age at diagnosis was 22 ± 23 months (range 0 to 130). Males presented at an earlier age than females (mean ± SD 16 ± 27 vs 25 ± 26 months, p = 0.044). Males presented more commonly due to a condition other than UTI (26%) vs females (13%, p = 0.018). DMSA scan was performed in fewer than 10 subjects, and no correlation was noted between DMSA findings and BTUTI rates. DMSA scans were conducted only in subjects who had abnormal findings of parenchymal defects or significant size discrepancy of the kidneys on ultrasound.

Risk Prediction Model Development

Evaluating candidate risk factors. Bivariate associations between each baseline risk factor and onset of BTUTI are summarized for the retrospective cohort in the supplementary table (http://jurology. com/). BTUTI was more common in females (18.7%) than males (10.8%, p = 0.18). BTUTI occurred in 1 of the 23 circumcised males (4%). High grade VUR was significantly associated with BTUTI (46.9% vs 12.3% in low grade cases, p <0.001). This significant difference was lost when we defined high grade VUR as grade III to V (19.6% vs 14.4%, p = 0.31).

Diagnosis of VUR following a UTI was significantly associated with BTUTI (19.1% vs 4.9%, p = 0.023). Although female gender and BBD were not significantly associated with BTUTI, both met our criteria for inclusion in the multivariable risk model (p <0.20).

In a multivariable logistic regression model including all variables that had evidence of a bivariate association with BTUTI (p <0.2) VUR grade IV or V (OR 8.9, 95% CI 3.4, 23.2) and presentation after UTI (OR 4.8, 95% CI 1.0, 22.4) were each significantly associated with BTUTI (table 1).

Subgroup analysis. Subgroup analyses were done comparing the association between each model covariate and BTUTI for high grade vs low grade VUR subgroups. Table 2 summarizes the clinical characteristic of each subgroup.

Of the 32 patients with high grade reflux BTUTI occurred in 15 (47%). Trends suggesting a higher

Table 1. *Adjusted logistic regression of factors associated with 2-year risk of BTUTI*

	OR (95% CI)	p Value
High grade VUR (IV or V)	8.9 (3.4, 23.2)	<0.001
Presentation as UTI	4.8 (1.0, 22.4)	0.045
Female gender	2.0 (0.7, 5.7)	0.19
BBD	1.8 (0.8, 4.0)	0.13

rate of BTUTI in females than males (61% vs 29%, p = 0.087) and in patients diagnosed after UTI (56% vs 14%, p = 0.088) were observed.

For those with low grade reflux BTUTI was significantly more common if BBD was present (21% vs 9%, OR 2.6, 95% CI 1.1, 6.1, table 2). Diagnosis after UTI was associated with BTUTI with a trend toward significance (19% vs 3%, OR 5.3, 95% CI 0.7, 41.1). The incidence of BTUTI was 14% in females and 6% in males (p = 0.145). In this subgroup BBD was associated with BTUTI (OR 2.6, 95% CI 1.1, 6.1).

Analysis comparing circumcised (23) to uncircumcised males (42) showed that none of the circumcised males with low grade VUR had a BTUTI. The only circumcised male with a BTUTI during followup had high grade VUR.

Estimating Risk of BTUTI

Based on the results of the regression models, a final parsimonious logistic regression model was created. Since the subgroup analyses revealed a trend suggesting an interaction between BBD and VUR grade, we included this interaction term in the model. Table 3 summarizes the model.

Assessing Model Performance

Training data set. The model was applied to the retrospective cohort to predict likelihood of BTUTI. ROC curve analysis demonstrated good discrimination of positive BTUTI (AUC 0.76). We developed the iReflux Risk Calculator, a Web based application to estimate BTUTI risk from patient characteristics (http://www.choc.org/programs-services/urology/ireflux-risk-calculator/, fig. 1).

Validation data set. We tested the risk model in a validation data set from the prospective cohort. Mean ± SD predicted probability of BTUTI was 19.5% ± 12% (range 1% to 51%). A total of 12 patients (21%) in this group experienced UTI. The model showed good discrimination between presence and absence of BTUTI (AUC 0.80).

Categorical Risk Stratification

To create a simplified categorical risk stratification algorithm for BTUTI, we generated a summary set of conclusions based on the results of the bivariate and multivariate analyses. Although no significant

Table 2. *BTUTI incidence in patients with high vs low grade VUR*

	High Grade VUR (IV or V)		Low Grade VUR (I-III)	
	BTUTI	OR (95% CI)*	BTUTI	OR (95% CI)*
No. gender/total No. (%):		3.1 (0.6–16.8)		1.8 (0.5–6.6)
Female	11/18 (61)		24/169 (14)	
Male	4/14 (29)		3/51 (6)	
No. BBD/total No. (%):		1.0 (0.9–1.0)		2.6 (1.1–6.1)
Present	10/20 (50)		13/61 (21)	
Absent	3/7 (43)		13/143 (9)	
No. diagnosis by UTI/total No. (%):		5.6 (0.5–58.3)		5.3 (0.7–41.1)
Yes	14/25 (56)		26/186 (19)	
No	1/7 (14)		1/34 (3)	

* Odds ratio for each factor derived from separate logistic regression models stratified by VUR grade subgroup.

association between gender and BTUTI incidence was observed in the final multivariate model, results from the bivariate analyses and other studies suggest that male gender may be a protective factor, particularly among circumcised males, and this was included in the algorithm.

Based on these conclusions, we constructed categorical definitions for groups at low, intermediate and high risk for BTUTI (fig. 2). Table 4 outlines the distribution of the retrospective sample and the rate of BTUTI in the different risk groups.

In the prospective sample we found that 25 patients (44%) stratified into the low risk group had an actual BTUTI rate of 4%. A total of 30 patients (53%) fell into the intermediate risk group and had an actual BTUTI rate of 33%. Only 1 patient was in the high risk group, and she had a BTUTI.

DISCUSSION

We investigated the association of different clinical and demographic factors with the incidence of BTUTI during the first 2 years after the diagnosis of primary VUR. Results revealed that risk groups defined by VUR grade, gender, circumcision status, presence of BBD and cause of presentation of VUR differentiate patients at low, moderate and high risk for BTUTI. Females with high grade VUR diagnosed after urinary infection had the highest risk of BTUTI.

These findings are consistent with previous studies. Dias et al retrospectively followed 740

Table 3. *Final logistic regression model estimating 2-year risk of BTUTI*

	β Coefficient	OR	95% CI for Exp(B)		p Value
			Lower	Upper	
Female gender	0.800	2.226	0.749	6.614	0.15
Presentation (diagnosis by UTI)	1.811	6.114	1.226	30.483	0.03
Grade IV or V VUR	2.846	17.219	5.137	57.715	0
BBD	0.955	2.597	1.107	6.095	0.03
BBD + grade IV or V VUR	−1.985	0.137	0.018	1.055	0.06

patients for 37 years.[10] In that cohort clinical presentation after UTI, female gender, BBD and reflux grade were significantly associated with recurrent UTI. Interestingly, unlike our study, age less than 6 months at presentation was a significant risk factor. The larger cohort may explain this difference.
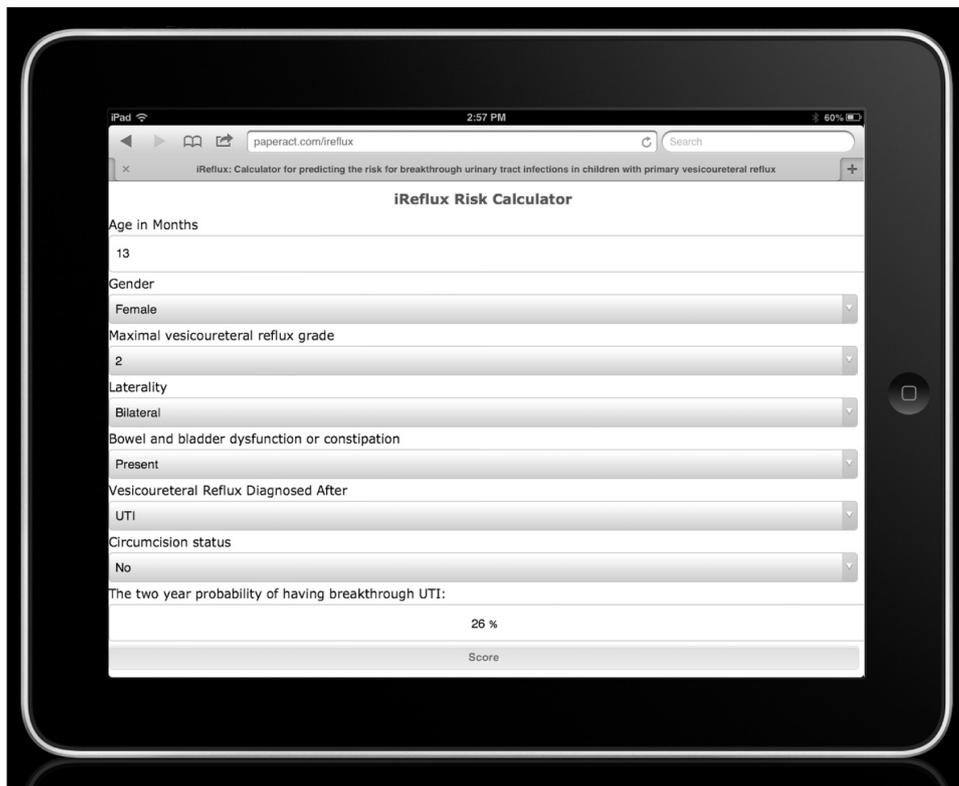
The important role of BBD in the rate of BTUTI is well documented. Based on a meta-analysis, the 2010 AUA guidelines panel reported that when managing primary vesicoureteral reflux in children the presence of BBD is associated with an increased risk of BTUTI during continuous antibiotic prophylaxis (44% vs 13%) and a decreased rate of spontaneous resolution of reflux (31% vs 61%).[8] Presence or absence of normal bladder function was also associated with reduced success of endoscopic correction therapy (57% vs 90%). Leslie et al demonstrated that after stopping CAP patients with BBD were at significantly increased risk for UTI.[11] In our cohort the role of BBD was confirmed in the low grade reflux population but could not be confirmed in patients with high grade disease, likely due to the small number of patients in our high grade category.

Our findings led us to identify 3 risk groups, stratifying patients according to the risk of BTUTI (fig. 1). When we validated these risk groups in 56 prospectively collected patients, we found similar results and good predictability. We validated this instrument in the prospective cohort with good predictability and accuracy (AUC 0.8).

Instruments for prediction of the probability of spontaneous resolution of VUR are available. Investigators at Boston Children's Hospital developed a calculator to predict probability using logistic regression analysis of retrospectively collected data in 2,462 patients.[12] The computational model from Iowa University predicts the same point.[13] VUR associated morbidity is mostly due to infections and related complications. Accordingly the goal of treatment should be prevention of complications, not resolution of VUR. In our study we constructed a prediction model that estimates the

Figure 1. iReflux Risk Calculator (Web based application to apply risk prediction model)

individual likelihood of BTUTI in a child with primary VUR.

There are several clinical implications for this study. Providers and parents will be able to appreciate the level of risk and probability of experiencing a BTUTI in the first 2 years after diagnosis. We hope that these findings will aid in determining optimal treatment and followup plans.[14]

Although the RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux) trial showed

a widening effect of treatment over prophylaxis, infection developed in 25% of those on placebo vs 13% in the treatment group.[15] In effect 8 patients would need to be treated so that 1 would benefit. The RIVUR trial actually revealed that higher grades of VUR, diagnosed after a febrile index infection, and presence of bowel and bladder dysfunction were modifiers that predicted for subsequent UTI. The advantage of our risk categorization system will be in helping to identify which patients would benefit most from prophylaxis, which will allow us to determine specifically who should receive CAP. BBD and circumcision status are modifiable factors that can increase the risk of BTUTI, and, therefore, they represent important treatment targets.

These results should be considered despite potential limitations associated with the retrospective design of this study. The main weakness is the difficulty in verifying parental adherence to CAP.
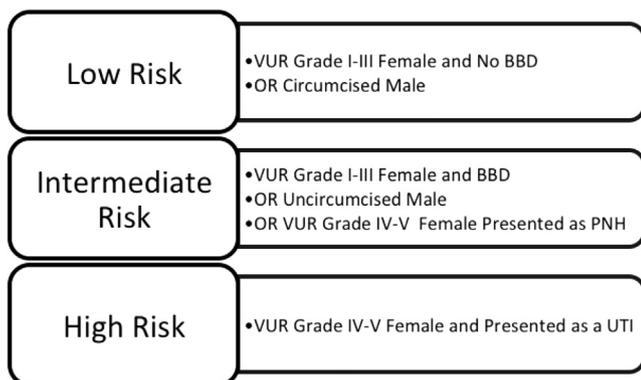
Figure 2. Stratification into low, intermediate and high risk groups according to 2-year risk of BTUTI. *PNH,* prenatally detected hydronephrosis.

Table 4. *Distribution of population and BTUTI incidence stratified by risk group in retrospective sample*

	Low Risk	Intermediate Risk	High Risk
% Population at risk	68.0	28.0	6.3
BTUTI risk	8.6	27.0	62.5
OR	1	4	17
p Value		<0.001	0.005

Furthermore, some patients were lost to followup and information was obtained via telephone, so recall bias may have occurred. Another limitation of the study is that all patients were treated with CAP. Rate of BTUTI in different patients treated with observation alone remains unknown.

Despite the relatively small cohort and preliminary nature of this study, we were able to highlight the weight of different variables on the risk of BTUTI. These results should be confirmed in a larger multicenter prospective trial.

The major strength of this study is validation of the risk stratification groups and the probability score completed in the prospective cohort, with encouraging results. Another strength is the homogeneous nonselected sample, which was managed by the same medical team.

In conclusion, this proposed risk stratification and probability model allows the clinician to predict 2-year risk of having a BTUTI on a more individualized basis to better inform parents of possible outcomes and treatment strategies.

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