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

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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

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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 nonresolving 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, $\text{Odds(BTUTI)}_i = e^{RSi}$. Odds were then converted to a probability [Pr(BTUTI)_i], $\text{Pr(BTUTI)}_i = \text{Odds(BTUTI)}_i/1 + \text{Odds(BTUTI)}_i$. 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.