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Computer model predicting breakthrough febrile urinary tract infection in children with primary vesicoureteral reflux

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Summary

Introduction and objective
Factors influencing the decision to surgically correct vesicoureteral reflux (VUR) include risk of breakthrough febrile urinary tract infection (fUTI) or renal scarring, and decreased likelihood of spontaneous resolution. Improved identification of children at risk for recurrent fUTI may impact management decisions, and allow for more individualized VUR management. We have developed and investigated the accuracy of a multivariable computational model to predict probability of breakthrough fUTI in children with primary VUR.

Study design
Children with primary VUR and detailed clinical and voiding cystourethrogram (VCUG) data were identified. Patient demographics, VCUG findings including grade, laterality, and bladder volume at onset of VUR, UTI history, presence of bladder–bowel dysfunction (BBD), and breakthrough fUTI were assessed. The VCUG dataset was randomized into a training set of 288 with a separate representational cross-validation set of 96. Various model types and architectures were investigated using neUROn++, a set of C++ programs.

Results
Two hundred fifty-five children (208 girls, 47 boys) diagnosed with primary VUR at a mean age of 3.1 years (±2.6) met all inclusion criteria. A total 384 VCUGs were analyzed. Median follow-up was 24 months (interquartile range 12–52 months). Sixty-eight children (26.7%) experienced 90 breakthrough fUTI events. Dilating VUR, reflux occurring at low bladder volumes, BBD, and history of multiple infections/fUTI were associated with breakthrough fUTI (Table). A 2-hidden node neural network model had the best fit with a receiver operating characteristic curve area of 0.755 for predicting breakthrough fUTI.

Discussion
The risk of recurrent febrile infections, renal parenchymal scarring, and likelihood of spontaneous resolution, as well as parental preference all influence management of primary VUR. The genesis of UTI is multifactorial, making precise prediction of an individual child's risk of breakthrough fUTI challenging. Demonstrated risk factors for UTI include age, gender, VUR grade, reflux at low bladder volume, BBD, and UTI history. We developed a prognostic calculator using a multivariable model with 76% accuracy that can be deployed for availability on the Internet, allowing input variables to be entered to calculate the odds of an individual child developing a breakthrough fUTI.

Conclusions
A computational model using multiple variables including bladder volume at onset of VUR provides individualized prediction of children at risk for breakthrough fUTI. A web-based prognostic calculator based on this model will provide a useful tool for assessing personalized risk of breakthrough fUTI in children with primary VUR.

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Table Univariate analysis of clinical variables with associated HR of developing breakthrough fUTI. Dilating VUR defined as grades 3–5.

Variable	HR	HR 95% CI	*p*
Age	0.98	0.90, 1.07	0.69
Gender (female)	2.72	0.84, 8.77	0.09
Dilating VUR	1.60	1.05, 2.42	0.03
Bilateral VUR	1.50	0.97, 2.30	0.07
BBD	1.66	0.99, 2.75	0.05
History UTI			
1	1.72	0.57, 5.16	0.34
≥2	2.98	0.98, 9.03	0.05
History of fUTI	2.17	1.22, 3.85	0.01
VUR onset bladder volume (≤35% PBC)	1.74	1.15, 2.63	0.01

BBD = bladder–bowel dysfunction; fUTI = febrile urinary tract infection; HR = hazard ratio; PBC = predicted bladder capacity; VCUG = voiding cystourethrogram; VUR = vesicoureteral reflux.

Introduction

Urinary tract infection (UTI) is a common bacterial infection of childhood [1–3]. The prevalence of vesicoureteral reflux (VUR) in children with a history of febrile urinary tract infection (fUTI) approaches 30% [4]. VUR is an important risk factor for pyelonephritis. Although sterile reflux is not thought to injure the kidney, pyelonephritis does increase the risk of renal scarring and subsequent sequelae such as hypertension, proteinuria, and chronic kidney disease. This potential for significant morbidity has placed emphasis on early and accurate diagnosis, as well as appropriate antibiotic therapy [5]. VUR treatment goals include prevention of febrile infections, prevention of renal injury, and minimizing morbidity of treatment and follow-up [6]. A multitude of factors influence the decision to surgically correct VUR including further risk of fUTI, risk of developing new renal parenchymal scarring, and decreased chance of spontaneous VUR resolution [7–10].

Identifying children at increased risk for developing breakthrough fUTI/pyelonephritis would aid clinical decision-making regarding the option for corrective surgery in these patients. Children with high-grade VUR are at increased risk for developing pyelonephritis and renal scarring [11,12]. In addition, children with VUR occurring at low bladder volumes are at increased risk for breakthrough febrile urinary tract infections independent of reflux grade [13]. In the current study, we developed a prognostic calculator using a multivariable model, allowing input variables to be entered to calculate the odds of an individual child developing a breakthrough fUTI.

Materials and methods

Approval was obtained from the University of Iowa Hospitals & Clinics IRB (2014-04766). Between 1984 and 2010, 255 children with primary VUR in whom detailed VCUG and clinical data was documented were identified. VCUG protocol at our institution routinely includes two filling and voiding cycles in a non-sedated child. Cystogram findings including grade, laterality, volume of contrast instilled, and bladder volume at VUR onset were abstracted. VUR grade was determined using the International Reflux Study classification system [8]. Dilating VUR was defined as grades 3–5. In cases of bilateral reflux, the highest VUR grade was utilized for analysis. Bladder volume at VUR onset was normalized for age predicted bladder capacity (PBC) for all patients using the formula (age + 2) × 30 mL. All children were placed on prophylactic antibiotics and followed with subsequent cystograms on an annual basis until reflux resolution or operative repair, and updated PBC according to age were used with each subsequent VCUG. VUR resolution was defined as a single negative VCUG. Children with secondary VUR or not prescribed continuous antibiotic prophylaxis were excluded from study.

Clinical variables recorded included age, gender, number of UTIs prior to VUR diagnosis, history of fUTI, documentation of complete ureteral duplication noted on ultrasound, and the presence of bowel or bladder dysfunction (BBD). Febrile UTI was defined as a positive urine culture of >100,000 colony-forming units (CFU) of a single organism associated with a body temperature of >101.4 °F (38.5 °C) documented in the medical record. Urine specimens were obtained via bag specimen, catheterization, or clean catch depending upon patient age. Catheterized specimens were obtained if bag specimens were positive. Both outpatient and inpatient urine specimens were included in the analysis. BBD was defined as incontinence episodes more than expected for age or requiring a prescription of anticholinergic medication or laxatives.

Input features other than bladder volume at onset of VUR, grade and age of patient were converted into a binary numerical code and a model created with the outcome being development of a breakthrough fUTI. Input features used included: patient age, gender, laterality, percentage PBC at VUR onset, VUR grade right/left, VUR onset right/left (filling or voiding), complete ureteral duplication, number of UTIs prior to VUR diagnosis (≥2 vs. <2), history of fUTI, and history of BBD. The number of infections was employed to determine the significance of multiple infections compared with a single documented infection as it has previously been shown that a child with multiple infections is more likely to have recurrent infections. The data was randomized into a training set of 288 and a

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