Observation of Patients with Vesicoureteral Reflux Off Antibiotic Prophylaxis: Physician Bias on Patient Selection and Risk Factors for Recurrent Febrile Urinary Tract Infection

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Abbreviations and Acronyms

BBD = bladder/bowel dysfunction

CAP = continuous antibiotic prophylaxis

UTI = urinary tract infection

VUR = vesicoureteral reflux

Study received institutional review board approval.

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Purpose: Observation off continuous antibiotic prophylaxis is an option for vesicoureteral reflux. We evaluated the characteristics of patients observed off continuous antibiotic prophylaxis and risk factors for febrile urinary tract infection.

Materials and Methods: We identified children 1 to 18 years old with primary vesicoureteral reflux between January 1, 2010 and December 31, 2010. We excluded patients with prior surgical correction from analysis. We recorded age, gender, race/ethnicity, primary language, insurance carrier, age at vesicoureteral reflux diagnosis, initial presentation and vesicoureteral reflux severity. We quantified bladder and bowel dysfunction with a validated questionnaire if toilet trained. We compared patients off vs on continuous antibiotic prophylaxis with the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. We used a univariate Cox proportional hazards model to assess predictors of febrile urinary tract infection during observation off continuous antibiotic prophylaxis.

Results: Of 529 eligible patients 224 were observed off continuous antibiotic prophylaxis. Patients off continuous antibiotic prophylaxis tended to be older ($p < 0.001$), to be older at diagnosis ($p < 0.001$), to have an initial presentation other than febrile urinary tract infection ($p = 0.05$), to have nondilating vesicoureteral reflux on most recent cystogram ($p < 0.001$) and to have lower bladder/bowel dysfunction scores if toilet trained ($p < 0.001$). Of the patients off continuous antibiotic prophylaxis a febrile urinary tract infection developed in 19 (8.5%). Risk factors associated with febrile urinary tract infection included initial presentation of multiple febrile urinary tract infections ($p = 0.03$), older age at diagnosis ($p = 0.03$) and older age starting observation off continuous antibiotic prophylaxis ($p = 0.0003$).

Conclusions: Criteria to select patients with vesicoureteral reflux for observation off continuous antibiotic prophylaxis remain poorly defined in the literature. Observation will fail in a subset of patients with vesicoureteral reflux. Physician biases regarding patient selection for observation off continuous antibiotic prophylaxis should be considered when interpreting studies that evaluate treatment strategies.

Key Words: vesico-ureteral reflux, pediatrics

VESICOURETERAL reflux affects approximately 1% of the pediatric population. In contrast to the original AUA (American Urological Association) guidelines published in 1997,[1] cessation of continuous antibiotic prophylaxis in children

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with persistent VUR has been shown to be a reasonable treatment option in some children.[2–4] However, with limited high level evidence, the recent 2010 AUA guidelines could not offer explicit recommendations on how to determine which patients are better candidates for observation off CAP.[5] Ultimately care providers aim to reduce the number of children at risk for new renal scars and recurrent pyelonephritis, and define which, if any, benefit from CAP.

Beginning in January 2010 our pediatric urology clinic made a concerted effort to increase the number of patients with VUR older than age 12 months observed off CAP. Therefore, we identified the characteristics of children who we observed off CAP and identified risk factors for recurrent febrile UTI in our observation off CAP cohort.

MATERIALS AND METHODS

After receiving institutional review board approval, we identified all patients evaluated at our pediatric urology clinic with an ICD-9 diagnosis of VUR between January 1 and December 31, 2010. We excluded children from study who were younger than age 12 months at the visit (105); those with prior documentation of VUR resolution (210); with prior surgical repair of VUR (165); with secondary VUR from posterior urethral valves, neurogenic bladder or exstrophy (20); with no documentation of VUR (16); with only 1 clinic visit (10); with renal insufficiency/solitary kidney (3); or death from unrelated cause (1). Children were followed by 1 of 5 pediatric urologists or a pediatric urology nurse practitioner. Selection for observation off CAP followed careful discussion with the family regarding all treatment options for VUR including observation, CAP, and open and endoscopic surgical interventions. Some families had strong preferences for continuation or discontinuation of CAP at their visits. Parent preferences had a major role in decision making when there was not a well supported best option.

We recorded demographic data including age at last visit if CAP continued or age at which observation off CAP started, gender, race/ethnicity, primary language and insurance carrier (public vs private). We assessed bladder and bowel function in toilet trained children with the University of British Columbia symptom score questionnaire.[6] This questionnaire is a 14-item 5-point Likert scale questionnaire which addresses nonneuropathic pediatric bladder and bowel function. Scores of 11 or greater of 52 have been demonstrated as the threshold for BBD. We collected information pertaining to the VUR diagnosis of each patient including age at VUR diagnosis, initial presentation (febrile UTI, prenatal hydronephrosis vs other), most recent radiological VUR severity and management (observation off CAP, CAP vs surgical correction). If CAP was discontinued for a trial of observation, we noted the date off CAP. We tracked the occurrence of febrile UTI for all patients in the study whether on or off CAP. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Vanderbilt University. REDCap is a secure, web based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry, 2) audit trails for tracking data manipulation and export procedures, 3) automated export procedures for seamless data downloads to common statistical packages and 4) procedures for importing data from external sources.[7]

We compared characteristics of patients observed off CAP to characteristics of those on CAP with the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. We performed a univariate survival analysis with a log rank test of equality for categorical variables and Cox proportional hazards regression for continuous variables model to assess predictors of febrile urinary tract infection in children observed off CAP. In our survival analysis model, analysis started at the time of cessation of CAP.

RESULTS

A total of 529 patients met inclusion criteria. The majority of patients were girls (85% female, 15% male). Of the 529 eligible patients 224 underwent observation off CAP. Other treatments in the 305 children not observed off CAP were CAP (233), endoscopic correction with dextranomer/hyaluronic acid (12), open ureteroneocystotomy (54) and unknown (6).

We evaluated demographic factors that might tend to bias providers to treat VUR with observation off CAP (table 1). The median age at last clinical contact of patients still on CAP vs age at initiation of

Table 1. *Patient demographics*

	Off CAP		On CAP		p Value
Demographic factors					
Median age (range)	4.3 (1.0–9.8)		3.2 (1.0–14.3)		<0.001
No. gender (%):					
M	28	(12.5)	53	(17.4)	0.14
F	196	(87.5)	252	(82.6)	
No. race/ethnicity (%):					
White	101	(45)	163	(53.4)	0.11
Black	2	(0.1)	7	(2.3)	
Hispanic	14	(6.3)	13	(4.3)	
Not listed/other	107	(47.7)	122	(40)	
No. primary language (%):					
English	211	(94.2)	288	(94.4)	0.9
Spanish	12	(5.4)	13	(4.3)	
Other	1	(0.4)	4	(1.3)	
No. insurance carrier (%):					
Private	135	(60.3)	168	(55.1)	0.25
Public	89	(39.7)	137	(44.9)	
VUR related factors					
Median age at VUR diagnosis	1.8		0.9		<0.001
No. initial presentation (%):					
Febrile UTI	158	(70.5)	239	(78.4)	0.05
Prenatal hydronephrosis	15	(6.7)	33	(10.8)	
Other	51	(22.8)	33	(10.8)	
No. VUR severity (%):					
Dilating	55	(24.6)	129	(42.3)	<0.001
Nondilating	169	(75.4)	176	(57.7)	
Median BBD score	12		15		<0.001