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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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Abstract

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.

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Study received institutional review board approval.

Keywords

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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 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 observation off CAP was higher in the patients given a trial of observation off CAP. In other words, physicians were most likely to treat older children with VUR off CAP. Treatment with or without CAP was not significantly different based on patient gender, race/ethnicity, primary language or insurance carrier.

We also evaluated clinical factors associated with the diagnosis of VUR that might tend to bias providers to treat VUR with observation off CAP. Of the 529 patients in the study 230 were completely toilet trained, and adequately completed bladder and bowel function questionnaires. Although children treated with CAP and those observed off CAP had median bladder and bowel function questionnaire scores suggestive of BBD, children observed off CAP had less BBD. Children observed off CAP were also older at diagnosis, less likely to have febrile UTI as an initial presentation and less likely to have dilating VUR on most recent cystogram.

Of the 224 patients observed off antibiotics febrile UTI developed in 19 (8.5%) during the observation period. Of these children 6 went on to undergo surgical correction of VUR during the study period. The median time for febrile UTI to develop after cessation of CAP was 8 months (range 0 to 25). Median followup for children off CAP was 2.2 years (range 0.0 to 8.8), which included time on and off CAP. Our univariate survival analysis showed that an initial presentation with multiple febrile UTIs was associated with the development of febrile UTI during observation off CAP (table 2). Surprisingly older age at diagnosis and older age at the start of observation off CAP were also associated with a higher risk of febrile UTI developing during observation off CAP. The presence of dilating VUR or increased BBD symptom score was not associated with febrile UTI during observation off CAP. Of the 305 patients on CAP febrile UTI developed in 60 (19.5%) during the observation period. Median time to febrile UTI in this group on CAP was 12 months (range 0 to 39). Median followup for children on CAP was 1.2 years (range 0.0 to 8.4).

DISCUSSION

The primary goals for VUR treatment include reducing recurrent febrile UTI episodes and reducing renal scarring while minimizing morbidity. For years CAP has been the accepted medical treatment for children with VUR. Recently multiple randomized controlled trials have questioned the efficacy of CAP in decreasing recurrent UTIs in some children with VUR.^{8–10} However, some patients with VUR in randomized controlled trials clearly benefit from CAP. Notably in the Swedish Reflux Trial girls on CAP had a lower rate of febrile UTI recurrence¹¹ and new renal damage¹² compared to those observed off CAP.

The American Urological Association recently published revised guidelines on the management of VUR to reflect these new data.⁵ However, many questions are still unanswered. For children younger than age 12 months the guidelines recommend CAP. In older children the guidelines leave many options available to the physician, including CAP and observation off CAP. A recent study revealed that parents of children with VUR rate the urologist's opinion as extremely important in their decision making process.¹³ In this study we evaluated our own biases in observing patients older than 12 months off CAP.

It was not surprising that those patients observed off CAP tended to be the older children in our VUR population. Discontinuation of CAP in a select group of older children with persistent VUR has been previously reported with good short-term results,³ even in those who initially presented with a febrile UTI.¹⁴ Traditionally infants younger than 12 months old have been considered more susceptible to renal damage from infection,^{15,16} although this belief has been challenged.^{17,18} Older children can also more reliably report symptoms of a UTI, prompting early diagnosis and treatment.^{2,14}

We were also more likely to observe patients with VUR off CAP for milder VUR severity and initial presentations other than febrile UTI. Although dilating VUR is not a contraindication for observation off CAP, it carries a higher risk of subsequent pyelonephritis and renal scarring in the setting of a febrile UTI.¹⁹⁻²¹ We also saw patients with initial presentations of afebrile UTI or prenatal hydronephrosis who came to the pediatric urology clinic from their primary care physicians with an established VUR diagnosis. Many of these patients for whom we would not have pursued a VUR evaluation were also observed off CAP.

The children we observed off CAP also tended to have less bladder and bowel dysfunction as quantified by validated questionnaire. We currently distribute a validated BBD questionnaire to all our toilet trained patients with VUR during each office visit.⁶ The role of bladder and bowel dysfunction with regard to the persistence of VUR and the risk of renal cortical scarring is well established.^{5,16,22,23} However, bladder and bowel dysfunction has largely not been addressed in the published randomized controlled trials that questioned the efficacy of CAP.⁸⁻¹⁰ Although bladder and bowel dysfunction scores were lower in children observed off CAP, the CAP and observation off CAP groups had median questionnaire scores that surpassed the threshold for a diagnosis of bladder and bowel dysfunction.

In this study in addition to evaluating our own biases regarding patient selection, we also identified risk factors for recurrent febrile UTI in our cohort observed off CAP. Not surprisingly an initial presentation of multiple febrile UTIs was associated with recurrent febrile UTI while off CAP. We also found that older age at VUR diagnosis and older age at cessation of CAP were associated with recurrent febrile UTI. We speculate that these unexpected findings may be potentially related to well established poor bladder and bowel habits in these children. Because of the high prevalence of bladder and bowel dysfunction in this population, BBD was not itself a risk factor. We acknowledge that our followup for observation off CAP may not be sufficiently long to properly assess the risk of a febrile UTI while being observed off CAP, but our followup is within the range of other reports. We also cannot fairly compare the febrile UTI rate in our observation off CAP group to that of our CAP group. As discussed, the patients in our CAP group likely represent a cohort at higher risk for recurrent febrile UTI.

Although recent randomized controlled trials have changed our management of VUR, definitive conclusions about the role of CAP have been limited by study design. Results of the National Institutes of Health sponsored RIVUR (Randomized Intervention for Children

with Vesicoureteral Reflux) study may provide additional understanding. Nevertheless, all studies will be limited by our own biases regarding the patients for whom we consider observation off CAP to be safe.

CONCLUSIONS

With limited high level evidence to guide our use of CAP in patients with VUR, physician practice patterns are likely to vary dramatically. Physician willingness to enroll patients in studies involving observation off CAP could be limited by our own criteria and biases. Recognition of our current biases will aid in applying results from these studies to our own patient populations. Our study reinforces that observation off CAP is an acceptable treatment option, but there is a subset of patients with VUR in whom observation off CAP will fail. In our analysis of the children observed off CAP, children who initially presented with multiple febrile UTIs, older age at diagnosis and older age at discontinuation of CAP had a higher risk of febrile UTI.

Abbreviations and Acronyms

BBD	bladder/bowel dysfunction
CAP	continuous antibiotic prophylaxis
UTI	urinary tract infection
VUR	vesicoureteral reflux

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Table 1

Patient demographics

	Off CAP	On CAP	p Value
<i>Demographic factors</i>			
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)	
<i>VUR related factors</i>			
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

Table 2

Risk factors for febrile UTI in children off CAP

	p Value
Initial presentation with more than 1 febrile UTI	0.03
Older age when CAP stopped	0.003
Older age at VUR diagnosis	0.003
Gender	0.12
Primary language	0.96
Race/ethnicity	0.90
Insurance (public vs private)	0.81
VUR severity (dilating vs nondilating)	0.36
BBD score by questionnaire	0.69