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Kidney Stone Recurrence among Children and Adolescents

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Abstract

Purpose—Kidney stone disease has become increasingly common during childhood and adolescence; however, the rate of symptomatic kidney stone recurrence for pediatric patients is uncertain.

Materials and Methods—We performed a retrospective cohort study of patients aged 3–18 years without anatomic abnormalities or genetic causes of nephrolithiasis who presented with a first symptomatic kidney stone between 2008 and 2014. We determined recurrence rates of symptomatic nephrolithiasis, defined as a new kidney stone on ultrasound and/or CT associated with pain and/or vomiting. We also estimated associations between completing 24-hour urine analyses and symptomatic kidney stone recurrence using Kaplan-Meier curves and multivariable Cox regression models.

Results—Among 285 children with a median age at nephrolithiasis diagnosis of 14.8 years (IQR 11.3–16.6) who were followed for 492 person-years, 68 patients (24%) developed 86 symptomatic recurrent stones over the follow-up period. The probability of symptomatic stone recurrence was 50% three years after the index kidney stone. The median time to stone recurrence was 3 and 5 years to the first and second stone recurrence, respectively. Adjusting for confounders, including

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adherence to follow-up, completing a 24-hour urine analysis after a kidney stone episode was associated with a 60% decreased risk of recurrence (hazard ratio 0.40; 95% CI, 0.18–0.91).

Conclusions—The risk of kidney stone recurrence is high during childhood, with approximately 50% presenting with a symptomatic recurrence within three years of the first stone. The role and utility of analyzing 24-hour urine chemistries in decreasing kidney stone recurrence should be explored in future prospective studies.

Keywords

Nephrolithiasis; Children; Kidney stone recurrence; Twenty-four hour urinalysis

Introduction

Nephrolithiasis is a systemic disorder characterized by symptomatic recurrences that is associated with an increased risk of cardiovascular disease[1] and chronic kidney disease among adults[2] and fracture among children and adults.[3] The incidence of nephrolithiasis among children and adolescents has increased rapidly over the last 25 years, which has produced a new population of pediatric patients at risk for kidney stone recurrence.[4–7] Among adults, approximately 50% of patients with incident nephrolithiasis will develop a recurrent stone within five to ten years of the first kidney stone.[8] Although nephrolithiasis is now increasingly a disease that begins during childhood, little is known about the risk of recurrence among children and adolescents.

Additionally, there is a lack of consensus regarding recommended evaluation and treatment practices to decrease kidney stone recurrence among children. The European Association of Urology recommend analyzing 24-hour urine collections for high-risk patients to assess metabolic risk and target therapy to reduce recurrence.[9] The American Urological Association guidelines do not specifically address children.[10] The American College of Physicians does not endorse performing 24-hour urine collections as the panel deemed there was insufficient evidence that assessing urine chemistry before initiating preventive pharmacologic therapy (PPT) or dietary interventions reduces stone recurrence.[11]

The goal of this study was to determine the recurrence rate of symptomatic kidney stones in a cohort of children with incident symptomatic nephrolithiasis. Our secondary objective was to estimate the association between completion of 24-hour urine analyses and kidney stone recurrence. We hypothesized that completion of 24-hour urine analyses is associated with decreased risk of recurrence.

Materials and Methods

Study Design and Patient Population

We performed a retrospective cohort study of patients aged 3–18 years who presented with a first symptomatic kidney stone, defined as abdominal or flank pain and/or nausea/vomiting with a kidney stone on ultrasound and/or computerized tomography between January 1, 2008 and April 1, 2014. All patients were treated at our institution, and were identified by searching the outpatient and hospital billing databases for International Classification of

Diseases, ninth edition codes for nephrolithiasis (592.0, 592.1, 592.9, 274.11). Electronic medical records were reviewed and data were entered into Research Electronic Data Capture hosted at The Children's Hospital of Philadelphia using standardized abstraction forms.[12] This study was approved by the local Institutional Review Board.

The goal of this study was to define the risk of symptomatic stone recurrence for the "typical" child with an incident symptomatic kidney stone. To do this, we had to balance including children with diseases that are associated with nephrolithiasis, but exclude those children with diseases who would likely have drastically different recurrence rates than other patients. We thus included patients with cystic fibrosis, inflammatory bowel disease, diabetes, nephrocalcinosis, renal dysplasia, and hypertension. We excluded patients with myelomeningocele, monogenic causes of nephrolithiasis (cystinuria, HPRT mutations, primary xanthinuria, and primary hyperoxaluria), renal tubular acidosis, and inborn errors of metabolism. We also excluded patients who had not achieved continence, those with diseases that produce stone symptoms (*e.g.* ureteropelvic junction obstruction), and patients with asymptomatic stones in order to eliminate lead-time bias introduced by more frequent imaging among some patients.

All patients were treated and followed at the Pediatric Kidney Stone Center at The Children's Hospital of Philadelphia using our clinical care pathway for children with nephrolithiasis.[13] The care pathway includes ordering 24-hour urine chemistries every 6 months beginning at the initial stone event regardless of the perceived risk of recurrence and providing all patients dietary counseling.

Outcome

The primary outcome was symptomatic kidney stone recurrence, defined as pain, and/or vomiting with a new stone on ultrasound and/or CT. We used strict criteria to define kidney stone clearance to determine patients eligible for stone recurrence. Kidney stone clearance was defined as resolution of symptoms with clearance of the offending stone on imaging following ureteroscopy, shock wave lithotripsy, percutaneous nephrolithotomy, or spontaneous stone passage. Because residual symptoms may occur after surgery or stone passage, a minimum of 30 days was required after stone clearance before a patient could be "eligible" for recurrence. A kidney stone episode was the time between presentation and recurrence after clearance of the initial stone, or between initial presentation and last follow-up for those without a recurrence. Patients were censored at time of last follow-up in urology, nephrology, or primary care, transfer to adult care, or death.

Exposures

Completion of 24-hour urine analyses and prescription of PPT were the primary exposures. We assessed the initiation and discontinuation of PPT by reviewing the clinical documentation and electronic medication list at each encounter. The following values were used to define abnormalities on 24-hour urines: hypercalciuria (>4mg/kg), hypocitraturia (<130mg citrate/gr creatinine for boys and <300 for girls), hyperoxaluria (>40mg/1.73m^2), and low urine volume (<1cc/kg/hr × 24hrs).

Statistical Analysis

Kaplan-Meier curves were used to estimate unadjusted recurrence rates for the overall population and cohorts stratified by completion of 24-hour urine analysis. Multivariable Cox proportional hazard regression using conditional risk set models[14] were used to estimate the association between completion of 24-hour urine analyses, PPT prescription, and stone recurrence. We used these models because kidney stones can recur multiple times for each individual and recurrences may be correlated within individual patients.

The first model estimated the association between completion of at least one 24-hour urine analysis after a stone episode and stone recurrence. The second model included an interaction term between completion of a 24-hour urine analysis and initiation of PPT to test the *a priori* hypothesis that assessing urine chemistry before initiating PPT is associated with decreased stone recurrence. 24-hour urine collections and PPT were considered time-varying covariates because they could occur at any time after the index stone. Regression models were built using manual backwards selection of covariates. Covariates assessed for inclusion in the models were age at diagnosis (years), age- and sex-specific body mass index (BMI) percentile, comorbidities (presence or absence of any one of the following: cystic fibrosis, inflammatory bowel disease, diabetes, nephrocalcinosis, renal dysplasia, and hypertension), family history of nephrolithiasis, stone analysis, insurance status (commercial versus public/uninsured), and adherence to follow-up. BMI percentile was determined using CDC growth curves. Adherence was a continuous variable defined as the proportion of attended outpatient visits over the total number of scheduled visits (attended plus missed).[15] We included in the final models all covariates with face validity (sex, age, adherence) and those that exhibited significant confounding, defined as ≥ 15% change in the hazard ratio for recurrence and completion of 24-hour urine collection (model 1) and the interaction between 24-hour urine collection and PPT (model 2). Proportionality of hazards was assessed using Kaplan Meier curves for time-fixed covariates and evaluating the interaction between time and each time-varying covariate.

The following sensitivity analyses were performed: 1) excluding patients with comorbid diseases listed in our inclusion criteria; 2) Modeling recurrence as time from previous event rather than time from study entry.

At 90% power, 74 recurrent stones among patients who did and did not complete 24-hour urine collections would be needed to detect a 45% difference in the hazard rates for stone recurrence, which is the relative risk reduction of stone growth observed among children treated with citrate therapy.[16] Analyses were performed on patients for whom complete data were available using Stata 13. Tests were two-sided and $p < .05$ was the threshold for statistical significance.

Results

Two hundred eighty-five patients were followed for 492 person-years (Figure 1 and Table 1). Twenty patients (7%) had 32 medical comorbidities. The most common were renal dysplasia (7), cystic fibrosis (7), inflammatory bowel disease (5), and either type 1 diabetes or diabetes associated with cystic fibrosis (4).

Including the index stone, 371 stones occurred, with 68 patients (24%) having 86 symptomatic recurrent stones over the follow-up period. Fifty-two patients had one recurrence, 14 patients had two recurrences, and 2 patients had three recurrences. The probability of recurrence was 50% three years after the index stone (Figure 2). The median time to stone recurrence was 3 and 5 years to the first and second recurrence, respectively. The overall recurrence rate was 197 stones per 1000 person years (95% CI 159–243). One hundred-one (35%) patients had surgery during the study period. One hundred sixty-six stones were collected at surgery or after spontaneous passage: One hundred twenty-four (93%) were at least 50% calcium oxalate, 5 (3%) were pure calcium phosphate, 3 (2%) were uric acid, 1 (1%) was struvite, and the composition was not available for 15 (9%).

One hundred ninety-six patients (69%) completed a 24-hour urine analysis: 20% had hypercalciuria, 15% had hypocitraturia, and 70% had inadequate urine volume on at least one 24-hour urine analysis. When stratified by stone episode, the proportion of children who had adequate urine output as measured on the first urine collection for each stone episode increased from 27% to 44% to 57%. Forty-two patients (17%) were prescribed PPT. Of those, 7 did not complete a 24-hour urine collection (Table 2).

Recurrence rates for patients who did and did not complete a 24-hour urine analysis were 185 and 242 stones per 1000 person years, respectively (Figure 3). The final Cox models were adjusted for age, sex, BMI percentile, comorbid disease, completion of stone analysis, and adherence to follow-up. In our primary analysis that examined the relationship between 24-hour urine analyses and recurrence, completing 24-hour urine analyses after the stone episode was associated with a 60% lower hazard of stone recurrence (HR 0.40; 95% CI 0.18–0.91). In our secondary analysis that examined the interaction between 24-hour urine analyses, PPT, and stone recurrence, PPT initiated after completing a 24-hour urine analysis was associated with an 85% lower risk of stone recurrence (HR 0.15; 95% CI 0.04–0.57), whereas PPT without a 24-hour urine analysis was not associated with decreased recurrence risk (Table 3).

In sensitivity analyses, the associations between completing a 24-hour urine analysis and stone recurrence changed minimally when patients with comorbidities were excluded. In the second model that included the interaction between 24-hour urine analysis and PPT, the association between completing a 24-hour urine analysis without PPT and stone recurrence became statistically significant (HR 0.40; 95% CI 0.17–0.98). Results were unchanged modeling recurrence as time from the previous event rather than time from study entry.

Discussion

Among patients who first presented with nephrolithiasis during childhood, the probability of symptomatic kidney stone recurrence was approximately 50% within three years of the index stone. This rate is similar or greater than stone recurrence rates for adults.[8]

Prior to this study, knowledge of recurrence rates for patients in whom nephrolithiasis began during childhood was limited. Two prior retrospective cohort studies reported that 16–19% of patients who formed stones in childhood developed a recurrence.[17, 18] However, these

studies did not account for differential follow-up, which would bias recurrence rates to appear lower than they really were. Other prior studies that examined stone recurrence were likely not representative of the contemporary population of children with nephrolithiasis,[18, 19] included many patients with infectious stones,[17] or included only children who underwent surgery.[20]

In exploratory analyses, we also found that completing 24-hour urine collections was associated with a decreased risk of recurrence. Although kidney stone recurrences cause substantial morbidity and health care expenditures, little is known about practices that decrease stone recurrence for children and adolescents. Our results provide preliminary evidence about the effectiveness of 24-hour urine collections in decreasing stone recurrence. Completing at least one 24-hour urine analysis after an incident stone was associated with a 60% lower risk of recurrence. Excluding patients with comorbid disease did not substantively change the association between completion of 24-hour urine analyses and stone recurrence. Our analyses, which should be considered hypothesis generating due to the observational nature of this study, also demonstrated that completing a 24-hour urine analysis modified the effectiveness of PPT. PPT initiated after completion of a 24-hour urine analysis was associated with an 81% decreased risk of kidney stone recurrence, whereas no association between empiric PPT and stone recurrence was detected. The association between completing a 24-hour urine analysis without prescription of PPT became significant after excluding patients with comorbid disease. This finding suggests that the benefit of assessing urine chemistries for healthy patients with “idiopathic” stones extends beyond targeting hypocitraturia and hypercalciuria with citrate therapy and thiazides, respectively.

There are multiple possible explanations for these results that should be explored in future studies. One possible explanation is that serial monitoring of 24-hour urine chemistries improves adherence to general recommendations to decrease stone recurrence. Patients who complete 24-hour urine collections may be more likely to be adherent to dietary recommendations and PPT. This hypothesis is supported by the observation that 24-hour urine volume increased on subsequent urine analyses. An alternative explanation is that assessing urine chemistries identifies specific metabolic abnormalities that could be treated with targeted therapy, such as lemonade or citrate for patients with hypocitraturia[21] and thiazides for patients with hypercalciuria[22–26] However, in successful clinical trials of adult participants, only 22% treated with citrate and 47% of those treated with thiazides met pre-specified cut points for hypocitraturia and hypercalciuria, respectively.[23] Our study highlights the need for well-designed randomized trials to test the efficacy of targeted PPT on stone recurrence among children and adolescents. Additionally, studies that determine the optimal dosage and point to begin PPT for children with nephrolithiasis are needed.

Limitations of this study include that patients were not followed prospectively for stone recurrence. However, we defined stone occurrence by the occurrence of pain and/or vomiting combined with diagnostic imaging findings. These outcome measures were reliably documented and able to be identified from chart review. Second, these results should be applied only to patients that share the characteristics of our study population; recurrence rates are likely different for patients with monogenic causes of stones and disorders such as spina bifida. Third, we may have underestimated recurrent stone formation because we did

not classify asymptomatic stones diagnosed on surveillance imaging as a recurrence. Although patients generally had ultrasounds every six months, we chose to measure symptomatic recurrence because it is a clinically important outcome and it mitigates lead-time bias for patients with more frequent follow-up and surveillance imaging. Fourth, there is the possibility of unmeasured differences in adherence between groups. It is possible that patients who did not complete 24-hour urine collections were also more likely to not adhere to general risk reduction recommendations (*e.g.* decrease salt intake) and thus were at higher risk of recurrence. However, 24-hour urine collections were ordered for all patients in this study, thus limiting any confounding by indication introduced by perceived risk of recurrence. Additionally, we adjusted for adherence to follow-up, which is an observable, although imperfect, measure of treatment adherence. Finally, the mean follow-up in this study was shorter than most randomized trials that assessed the efficacy of PPT to decrease stone recurrence among adults. However, this study had sufficient power to detect differences in stone recurrence.

Conclusion

The probability of kidney stone recurrence is high during childhood, with approximately 50% of children and adolescents presenting with a symptomatic recurrence within three years of the first kidney stone. The utility of 24-hour urine analysis in decreasing kidney stone recurrence should be explored in prospective studies.

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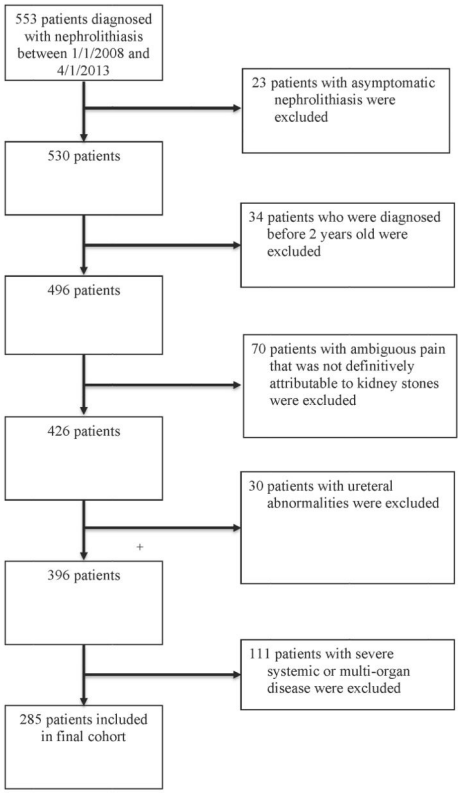

Figure 1.
Cohort selection

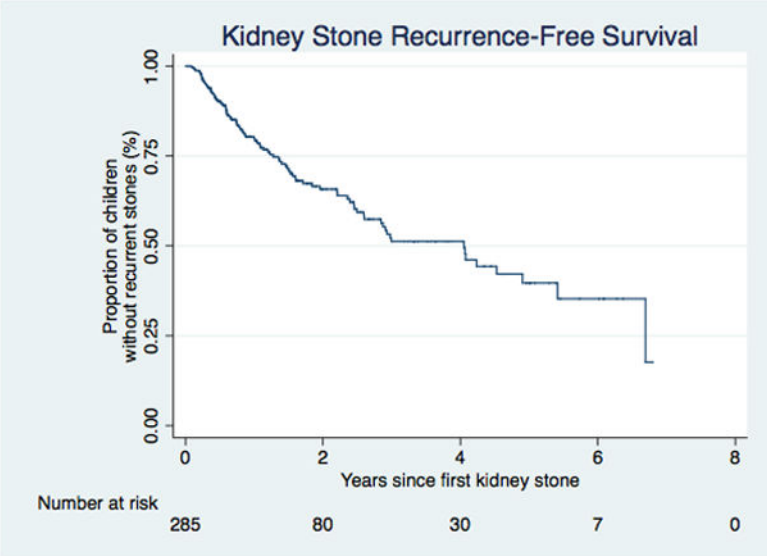

Figure 2. Kidney stone recurrence-free survival of children and adolescents with incident nephrolithiasis

The risk of symptomatic kidney stone recurrence was approximately 50% three years after the index stone.

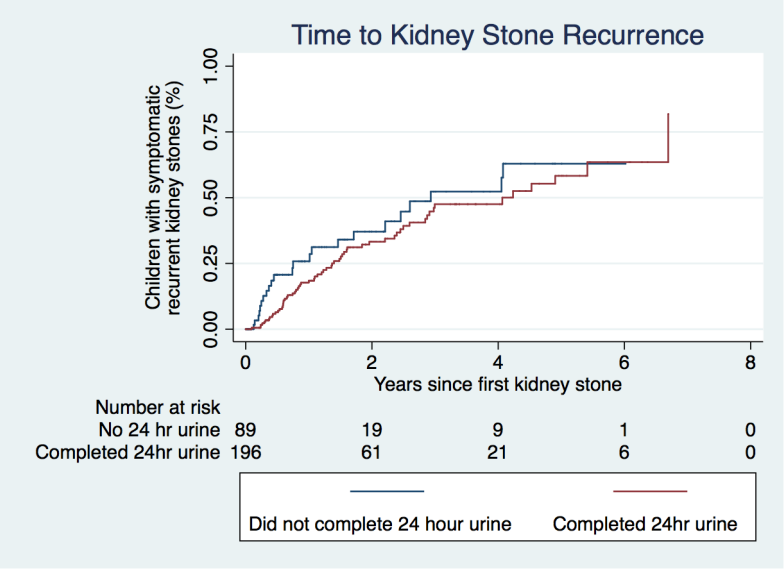

Figure 3. Time to recurrent kidney stone among children and adolescents who did and did not complete 24-hour urine analyses

Kidney stone recurrence was lower among children and adolescents who completed 24-hour urine analyses.

Table 1

Patient Characteristics

Total number of patients	285
Patients with no recurrence, n (%)	217 (76.1)
Patients with one recurrence, n (%)	52 (18.2)
Patients with two recurrences, n (%)	14 (4.9)
Patients with three recurrences, n (%)	2 (0.7)
Total number of stone events	371
Age in years, median (IQR)	14.8 (11.3–16.6)
Gender, n (%)	
Male	130 (45.6)
Female	155 (54.4)
BMI percentile, median (IQR)	**68 (40–87)**
Race, n (%)	
Asian	5 (1.8)
African American	23 (8.1)
White	231 (81.1)
Not Reported/Other	26 (9.1)
Ethnicity, n (%)	
Hispanic or Latino	7 (2.5)
Not Hispanic or latino	165 (57.9)
Unknown/Not reported	113 (39.7)
Family History of stones, n (%)	
Yes	165 (57.9)
No	85 (29.8)
Unknown	35 (12.3)
Insurance Type, n (%)	
Uninsured	3 (1.1)
Commercial insurance	245 (86.0)
Public insurance	37 (13.0)
Diagnosis made at CHOP per event, n (%)	
Yes	122 (32.9)
No	249 (67.1)
Comorbid disease (s) per event, n (%)	
Yes	28 (7.6)
No	343 (92.5)
Follow up in years, median (IQR)	**1.1 (0.4–6.7)**

Table 2

Frequency of PPT and 24-hour urine analysis

	Patients who did not complete 24-hour urine analyses (n=89)	Patients who completed 24-hour urine analyses (n=196)
Citrate therapy, n (%)	6 (7)	23 (11)
Hydrochlorothiazide, n (%)	1 (1)	12 (6)
Chlorthalidone, n (%)	0 (0)	2 (1)
1 or more PPT meds, n (%)	7 (8)	35 (18)
No PPT, n (%)	82 (92)	161 (82)
Total	89	196

Table 3

Multivariable Cox regression analysis of association between completion of 24-hour urine analysis, prescription of PPT, and stone recurrence

	Hazard ratio	**95 % CI**	**p-value**
24hr urinalysis & PPT			
No 24hr/No PPT	Ref	Ref	Ref
No 24hr/ + PPT	**1.07**	**0.23–5.0**	**0.93**
+ 24hr/ No PPT	0.44	0.19–1.02	0.055
+24hr/+PPT	**0.19**	**0.06–0.62**	**0.007**
Age at diagnosis (years)	**1.08**	**1.01–1.16**	**0.04**
Female sex	0.97	0.62–1.51	0.88
Medical comorbidity	0.6	0.28–1.54	0.34
Stone analysis completion	0.79	0.49–1.30	0.36
BMI **percentile**	**1.52**	**0.67–3.45**	**0.31**
Adherence	**1.64**	**0.76–3.54**	**0.21**