

UCSF

UC San Francisco Previously Published Works

Title

Clinical Outcomes for Cystinuria Patients with Unilateral Versus Bilateral Cystine Stone Disease.

Permalink

<https://escholarship.org/uc/item/1xv0g49s>

Journal

Journal of endourology, 32(2)

ISSN

0892-7790

Authors

Usawachintachit, Manint
Sherer, Benjamin
Hudnall, Matthew
[et al.](#)

Publication Date

2018-02-01

DOI

10.1089/end.2017.0335

Peer reviewed

Clinical Outcomes for Cystinuria Patients with Unilateral Versus Bilateral Cystine Stone Disease

Manint Usawachintachit, MD,^{1,2} Benjamin Sherer, MD,¹ Matthew Hudnall, MD,¹
David T. Tzou, MD,¹ Kazumi Taguchi, MD, PhD,^{1,3} Ryan S. Hsi, MD,^{1,4}
Marshall Stoller, MD,¹ and Thomas Chi, MD¹

Abstract

Introduction: Cystinuria is a genetic disorder marked by elevated urinary cystine excretion and recurrent cystine nephrolithiasis. Interestingly, despite seemingly similar contralateral renal anatomy, a subset of cystinuric patients consistently form stones in only one kidney. The aim of this study is to evaluate clinical outcomes in unilateral vs bilateral cystine stone formers.

Patients and Methods: We performed a retrospective case–control study of cystinuric patients evaluated and treated at the University of California, San Francisco between 1994 and 2015 and categorized patients as either unilateral or bilateral stone formers. Clinical presentation, baseline patient demographics, stone procedures, medical therapy regimens, and long-term renal function were compared between the two groups.

Results: A total of 42 cystine stone patients (22 female, 20 male) were included in the analysis. The median age at first presentation was 18.5 years and median age at study conclusion was 45.5 years. Two-thirds of patients ($n=28$) had a history of bilateral stones, whereas one-third ($n=14$) had unilateral stones. Medical therapy regimens were similar between groups. Despite an increased average number of lifetime surgeries (7.5 sessions for bilateral vs 3.7 sessions for unilateral, $p<0.05$), there was no significant difference in medians of the most recent glomerular filtration rate when compared with unilateral stone formers (81.5 vs 95 mL/min, respectively; $p=0.28$).

Conclusions: The majority of cystinuric patients within our cohort form stones bilaterally during their lifetime, and require more surgical interventions than unilateral stone formers. Despite this, overall renal function is well preserved in unilateral and bilateral cystinuric stone formers treated with minimally invasive stone extraction procedures.

Keywords: cystinuria, clinical outcomes, renal function

Introduction

CYSTINURIA IS A RARE AUTOSOMAL RECESSIVE genetic disease caused by defects in genes (*SLC3A1* and *SLC7A9*) that code for the transporters responsible for the reabsorption of filtered cystine, ornithine, lysine, and arginine in the proximal nephron. High concentrations of urinary cystine often lead to supersaturation, crystallization, and cystine nephrolithiasis. From an early age, cystinurics typically suffer from frequent and recurrent painful stone events, typically requiring multiple

emergency room visits and urologic procedures during their lifetimes. Approximately 1% of adult and 6% of pediatric nephrolithiasis patients are diagnosed with cystinuria, with males and females being equally affected.^{1,2}

Despite the life-long and systemic nature of cystinuria, a subset of cystinuric patients only form stones in one kidney, despite no obvious differences when compared with contralateral renal anatomy.³ The aim of this study was to determine baseline characteristics and clinical outcomes of unilateral vs bilateral cystine stone formers.

¹Department of Urology, University of California, San Francisco, San Francisco, California.

²Division of Urology, Department of Surgery, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, The Thai Red Cross Society, Bangkok, Thailand.

³Department of Nephro-Urology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

⁴Department of Urologic Surgery, Vanderbilt University, Nashville, Tennessee.

Patients and Methods

We performed a retrospective case-control study of all cystinuric patients evaluated and treated in at a university-based stone clinic (University of California, San Francisco or UCSF) between 1994 and 2015 after obtaining the Institutional Review Board approval (CHR No. 14-4533). Patients with at least two clinical visits and a confirmed history of cystine nephrolithiasis were included in the analysis. For all patients, a diagnosis of cystinuria was confirmed by routine laboratory stone analysis of *ex vivo* stone specimens obtained after stone passage or stone extraction procedures. Laterality of stone disease was determined by comprehensive review of all imaging studies, radiology reports, operative reports, and clinic notes. Patients were then categorized into two groups: unilateral (history of cystine stone formation in only one kidney) and bilateral (history of cystine stone formation in both kidneys). Baseline characteristics, including demographic data, clinical presentation, lifetime stone procedures, and current cystinuria medication regimens were obtained for each group.

Clinical outcomes were evaluated by comparing need for operative intervention and long-term renal function. Procedures were only included in the analysis if they were performed for stone removal; these included percutaneous nephrolithotomy (PCNL), ureteroscopy (URS), shockwave lithotripsy (SWL), and open stone surgery. Stone-related procedures, such as percutaneous nephrostomy tube placement, ureteral stent insertion, or diagnostic cystoscopy were not included in the analysis. Cystinuria duration was defined as the time from initial diagnosis through January 1, 2017. Follow-up duration was defined as time from first presentation at our institution through January 1, 2017. Long-term renal function was determined by glomerular filtration rate (GFR) obtained at initial presentation compared with GFR obtained at the most recent follow-up. Baseline characteristics and clinical outcomes were evaluated through comparative statistical analyses utilizing Chi-squared test, Fisher's exact test, Student's *t*-test, and Mann-Whitney *U*-test using Stata version 14.1 (StataCorp, College Station, TX).

Results

A total of 42 cystine stone patients (22 females, 20 males) met criteria and were included in the analysis. The majority of patients were Caucasian and median body mass index (BMI) was 28.6 kg/m². The median age at the first presentation was 18.5 years [interquartile range (IQR): 13–30 years], the median age at study completion was 45.5 years (IQR: 28–63 years), and the median disease duration since diagnosis was 17.5 years (IQR: 12–31 years). Most (*n* = 33, 78.6%) cystinurics experienced their first stone event at an age ≤30 years. The most common presenting symptoms were flank pain (62.0%), recent stone passage (24.0%), hematuria (3.5%), urinary tract infection (3.5%), acute renal failure (3.5%), and urinary retention (3.5%). The median follow-up period within our institution was 8.8 years. Family history was available in 40 (95.2%) patients and revealed a positive history of stone disease in first-degree relatives of 42.5% of the patients (Table 1). Detailed family medical history was unknown for two adopted patients and we did not differentiate between cystine and noncystine stones for family history.

Of the 42 patients, 28 patients (66.7%) had bilateral stones, whereas 14 patients (33.3%) developed unilateral stones.

Among the unilateral stone formers, nine patients experienced stones solely on the left side, and five patients exclusively experienced stone on the right side. Staghorn stones in at least one kidney were present in 14 patients (33.3%). These included 11 bilateral stone formers and three unilateral stone formers. Bilaterality of stone formation did not significantly correlate to gender (*p* = 0.38), age of first presentation (*p* = 0.84), presenting symptoms (*p* = 0.60), BMI (*p* = 0.07), presence of Staghorn stone (*p* = 0.31), or family history of stone disease (*p* = 0.32). While follow-up duration was comparable between the two groups, median cystinuria follow-up duration was significantly longer in the bilateral stone disease group (20 vs 12 years, *p* = 0.02) (Table 1).

Collectively, the entire cystinuric cohort underwent 261 lifetime stone removal procedures (median 5 surgeries per patient, IQR: 2–9 per patient). Procedures included 112 (42.9%) PCNLs, 90 (34.5%) URSs with laser lithotripsy and/or basket extraction, 44 (16.9%) SWLs, and 15 (5.7%) open stone surgeries. Figure 1 illustrates the mean number of each procedure type for patients with either unilateral or bilateral cystine stone disease. All open nephrolithotomy and SWL procedures were performed outside of our tertiary care center. Three patients in the bilateral stone group required nephrectomy due to stone-related complications and all of them had at some point formed stones in the contralateral kidney. Two cystine stone patients (4.8%) had reported no stone-related surgery in their lifetimes. One of them experienced bilateral small ureteral stones, which routinely passed spontaneously. The other developed bilateral nephrocalcinosis with frequent passage of small stone fragments. Both patients have been treated conservatively with aggressive hydration and urinary alkalization. Bilateral cystine stone formation was associated with a higher median number of lifetime stone surgeries (6.5 vs 2 sessions, *p* < 0.05). Bilaterality also correlated with median number of lifetime URS sessions compared with unilateral stone formers (2 vs 1 sessions, respectively; *p* < 0.05), but there was no significant difference in lifetime need for PCNL (*p* = 0.55) or SWL (*p* = 0.35) (Fig. 1).

For the entire cohort of cystinuria patients, median GFR at most recent follow-up was 85 mL/min. Median change in GFR from the initial presentation was –2 mL/min. Despite the increased number of lifetime surgeries in patients with bilateral stone formation, there was no significant difference in the median of the most recent GFR when compared with unilateral stone formers (81.5 vs 95 mL/min, respectively; *p* = 0.28). Furthermore, there was no significant difference in the median change in GFR between groups over the follow-up period (–1 unilateral vs –3 mL/min bilateral, *p* = 0.64).

Most cystinurics reported taking medical therapy at most recent follow-up; 36 (85.7%) were taking potassium citrate, 11 (26.2%) were on thiol therapy, and 2 (4.8%) patients were receiving D-penicillamine. Comparing bilateral vs unilateral cystinurics, there was no significant correlation with medication use and stone laterality (Table 2).

Given the difference in median cystinuria follow-up duration between the two groups, a matched pair subgroup analysis was performed to examine whether duration of disease impacted results. From the original cohort of 42 patients, 14 bilateral stone formers matched to the unilateral stone-forming group for age, gender, and cystinuria disease duration were selected and compared. In this subgroup of patients,

TABLE 1. BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF CYSTINE STONE PATIENTS

Parameters	Overall (n = 42)	Bilateral stone disease (n = 28)	Unilateral stone disease (n = 14)	p
Current age (years), median [IQR]	45.5 [28 to 63]	48.5 [31 to 65]	42 [23 to 49]	0.14
Gender, n (%)				
Male	20 (47.6)	12 (42.9)	8 (57.1)	0.38
Female	22 (53.4)	16 (57.1)	6 (42.9)	
BMI (kg/m ²), median [IQR]	28.6 [23.6 to 30.9]	29.0 [25.0 to 31.5]	24.9 [20.7 to 29.3]	0.07
Ethnicity, n (%)				
Caucasian	32 (76.2)	23 (82.1)	9 (64.3)	0.14
Hispanic	6 (14.3)	4 (14.3)	2 (14.3)	
African American	2 (4.7)	0	2 (14.3)	
Indian	1 (2.4)	1 (3.6)	0	
Asian	1 (2.4)	0	1 (7.1)	
Age at presentation (years), median [IQR]	18.5 [13 to 30]	19.5 [13 to 28.5]	18 [8 to 30]	0.84
Presenting symptom, n (%) (data available in 29 patients)				
Flank pain	18 (62.0)	12 (63.1)	6 (60.0)	0.60
Passed stone	7 (24.0)	5 (26.3)	2 (20.0)	
Hematuria	1 (3.5)	0	1 (10.0)	
UTI	1 (3.5)	1 (5.3)	0	
Acute renal failure	1 (3.5)	1 (5.3)	0	
Urinary retention	1 (3.5)	0	1 (10.0)	
Duration of follow-up (years), median [IQR]	8.8 [0.9 to 13.6]	9.8 [2.1 to 14.8]	6.6 [0.5 to 11.4]	
Duration of clinical cystinuria (years), median [IQR]	17.5 [12 to 31]	20 [15 to 35.5]	12 [10 to 18]	0.02*
Positive history of urinary stone in other family members, n (%) (data available in 39 patients)	17 (42.5)	13 (50.0)	4 (28.6)	0.32
Presence of Staghorn stone, n (%)	14 (33.3)	11 (39.3)	3 (21.4)	0.31

*Statistically significant difference.

BMI=body mass index; IQR=interquartile range; UTI=urinary tract infection.

median lifetime stone surgery was still significantly higher in bilateral stone formers compared with unilateral stone formers (7.5 vs 2 sessions, $p < 0.05$), although comparable medication usage and median current GFR were observed (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/end).

Discussion

Cystinuria is an autosomal recessive metabolic disorder, with known disruption of dibasic amino acid transporters in both kidneys. Encoding for the defective *SLC3A1* (classic cystinuria or type I) or *SLC7A9* (nontype I cystinuria) genes is ubiquitously conserved among cystinuric patients.⁴ The resulting excessive renal excretion of cystine leads to lifetime recurrent stone events for most patients.⁵ However, it remains a curiosity that approximately one-third of cystinuric stone formers only form stones in one kidney. Our cohort ($n = 42$) demonstrated bilateral stone disease in 66.7% of cystinurics. Similarly, in previous work, we reported a series of cystinurics ($n = 34$) with a bilateral stone formation rate of 70.6%,³ and a smaller study ($n = 22$) of cystinurics from Iran identified bilateral disease in 59% of patients.⁶ By comparison, in a generalized sample of calcium-based stone formers, bilateral stone formation is estimated at ~25% in contemporary series.⁷ Certainly, higher rates of bilateral stone disease are expected in cystinurics given the near-constant presence of elevated urinary cystine. Yet, the question remains: why do some patients only form stones in one kidney?

Genotypes, transport gene defects, hydration status, and urine pH should theoretically be similar in each kidney. While it is assumed that the phenotypic distribution of defective

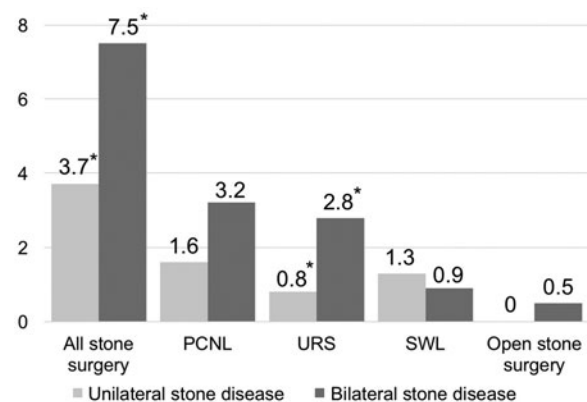


FIG. 1. The mean number of surgical interventions for unilateral and bilateral stone disease. The mean number of lifetime stone surgeries was significantly higher in the bilateral stone formers (7.5 vs 3.7 sessions, $p < 0.05$). PCNL was the most common procedure performed for stone removal, following URS. The mean number of ureteroscopic procedures was also significantly higher in the bilateral stone group (2.8 vs 0.8 sessions, $p < 0.05$). *Statistically significant difference. PCNL=percutaneous nephrolithotomy; SWL = shockwave lithotripsy; URS=ureteroscopy.

TABLE 2. RENAL FUNCTIONAL OUTCOMES AND MEDICATION REGIMENS IN BILATERAL VERSUS UNILATERAL CYSTINE STONE FORMERS

Parameters	Overall (n = 42)	Bilateral stone disease (n = 28)	Unilateral stone disease (n = 14)	p
GFR at the first visit (mL/min), median [IQR]	85 [65.5 to 98.5]	84 [64 to 97]	88 [67 to 101]	0.56
GFR at the last visit (mL/min), median [IQR]	86 [60 to 101]	81.5 [59 to 96]	95 [71 to 102]	0.28
Change in GFR (current—initial, mL/min), median [IQR]	-2 [-14.5 to +10]	-3 [-17 to +11]	-1 [-11 to +9]	0.64
Current use of potassium citrate, n (%)	36 (85.7)	26 (92.9)	10 (71.4)	0.16
Current use of thiol compound, n (%)	11 (26.2)	6 (21.4)	5 (35.7)	0.46
Current use of D-penicillamine, n (%)	2 (4.8)	2 (7.1)	0	N/A

GFR = glomerular filtration rate.

transporters is equal in each kidney, this has not been definitively proven. Are some other lithogenic factors present that may influence stone predominance in one particular kidney? One attractive hypothesis is a potential discrepancy of renal blood flow in each kidney, which may result in differences in glomerular filtration, fluid concentrations, cystine supersaturation, and subsequent risk of stone formation. Some have suggested that sleep patterns may be linked to stone laterality in other forms of nephrolithiasis. We have shown that the side of stone was identical to the dependent sleep side in 76% of 110 consecutive patients with unilateral calcium-based stones ($p < 0.05$). It has been postulated that routinely sleeping on one side may cause subtle alterations to renal hemodynamics or urinary stasis that promote stone formation.^{8,9}

In reviewing imaging studies from unilateral stone formers, there was no clear evidence that urinary stasis as caused by anatomic or functional abnormalities such as infundibular stenosis, ureteropelvic junction obstruction, impaired ureteral peristalsis, or neuropathic bladder was present as risk factors for stone formation. It is important to point out that most—but not all—patients with cystinuria form stones. Because cystinurics are often diagnosed after symptomatic stone episodes, it remains unclear how many nonstone-forming cystinurics there are in the general population.⁵ It remains possible that the actual prevalence of cystinuria is underreported. Perhaps those who form stones carry additional unknown environmental, genetic, or metabolic risk factors.

In the current analysis, cystinurics developed their first stone episode at a young age, with a median age of onset at 18.5 years and 75% of patients experiencing stones by the age of 30 years. These results parallel previous longitudinal studies of cystinuric patients that have demonstrated a strong predisposition to develop symptomatic stone disease during the first three decades of life.^{2,3,10}

The median age of disease onset and presenting symptoms was not significantly different between unilateral and bilateral stone formers. Our analyses demonstrated that, overall, cystinurics underwent an average of 6.2 procedures from the time of diagnosis through the follow-up period. Similarly, Varda and colleagues reported a pediatric cystinuria series of 23 patients with long-term follow-up indicating a median surgery number of 6 with a median number of 1.0 surgery per year.¹⁰ Smaller series from Korea and Japan, however, have demonstrated a much lower average surgical burden; 2.7 surgeries per lifetime during a mean follow-up period of 5 years in 14 patients,¹¹ and <0.2 stone events yearly from a

study in 31 patients with a mean follow-up period of 7.5 years.¹² The relatively lower surgery or stone event number from these Asian studies may be explained by differences in disease severity, urologic practice patterns, and definitions of stone-related surgery.¹² Certainly, the differences in daily cystine excretion among various races may contribute to variable results in differing racial cohorts.¹³ While Caucasians are more likely than other races to be diagnosed with cystinuria, the overall effect of geographic location and race on cystinuria remain poorly elucidated.

In the current study, bilateral stone formers required significantly more sessions of lifetime surgery than unilateral stone formers. Although median duration of cystinuria was higher in the bilateral stone group, this finding still held true with subgroup analysis matched for duration of disease. Bilateral stone formers were also more likely to have Staghorn stones. Yet, overall renal function was well preserved over the course of treatment in all patients, with a median GFR of 85 mL/min at the conclusion of this study. Median change in GFR from the initial presentation was almost nonperceivable at an absolute value of 2 mL/min. Renal function was well preserved in both bilateral and unilateral stone formers (Table 2). No patients in our study progressed to end-stage renal disease (ESRD) or required renal replacement therapy. The long-term renal preservation seen in this contemporary series of cystinurics is encouraging, but should be interpreted with caution. Previous work has warned that adults with cystinuria are at heightened risk for the development of reduced GFR and the development of chronic kidney disease (CKD). In fact, large population-based studies have indicated that all stone formers, not just cystinurics, are at a heightened risk of CKD.¹⁴ Given the refractory nature of cystinuria marked by frequent bouts of intermittent renal obstruction and repetitive need for procedures, it stands to reason that cystinurics are at risk for renal functional decline over time. Worcester et al. previously reported that 52 adult cystinuric patients had significantly reduced creatinine clearance (63.2 mL/min) compared with 3215 noncystinuric patients (111.1 mL/min).¹⁵ A larger analysis of a French cystinuric cohort ($n = 442$) demonstrated that 26.8% of patients had impaired renal function as indicated by a GFR <60 mL/min per 1.73 m² and 1.1% had progressed to ESRD.¹⁶ Another contemporary study by Assimos et al.¹⁷ reported a mean serum creatinine level of 1.13 mg/dL in 85 cystinuric patients. Not surprisingly, they found that a history of open surgical stone removal procedures and/or nephrectomy was correlated with significant decline in renal function. In their cohort, cystinurics were significantly

more likely (14.1%) to undergo nephrectomy compared with calcium oxalate stone formers (2.9%).¹⁷ Of note, in our study, although cystine stones are considered resistant to SWL, this modality appeared to be utilized as a primary treatment outside of UCSF, in line with previous published findings.¹⁸ Judicious use of invasive surgery and more widespread adoption of minimally invasive stone extraction techniques may be helping to preserve long-term renal function in cystinuric patients. Furthermore, optimizing hydration habits, medication regimens, and medication compliance can help to decrease the frequency of surgical interventions. Poorly compliant cystinuric patients have been found to require a fourfold average increase in surgical interventions compared with medically compliant cystinuric stone formers.¹⁹

Cystine is poorly soluble at physiological urine pH values <7.0, with stone formation occurring especially when cystine excretion exceeds 250 mg/L.⁵ As a result, medical prophylaxis with hydration and urine alkalinization are usually offered as a first-line therapy unless contraindicated.³ If these interventions fail to prevent cystine stone recurrence, the next step in the treatment algorithm is the addition of a chelating agent, such as thiol compound (tiopronin) or D-penicillamine in an attempt to decrease cystine excretion below 250 mg/L.²⁰ In the current cohort, the majority of patients received potassium citrate to alkalinize their urine and ~25% of patients were on combination therapy with tiopronin + potassium citrate. Less than 5% of patients were receiving D-penicillamine. Stone laterality did not specifically correlate with medication regimens.

Some limitations should be recognized in this analysis. The retrospective nature of the data acquisition was susceptible to incomplete and inaccurate retrieval of some data points (such as presenting symptoms and details of all procedures performed before referral to our institution) and hence the results presented must be interpreted cautiously. While a diagnosis of cystinuria was confirmed by stone analysis for all patients at our institution, history of nephrolithiasis in other family members was collected from chart review of patient-reported information, thus lacking confirmation that family members with a history of stone disease were cystinurics. Laterality of stone disease, which was the primary determinant in this study, was concluded from the review of imaging studies, radiology reports, and clinic notes. Additionally, only one-third of patients in our cohort were receiving thiol therapy or D-penicillamine, and neither medication compliance nor adequacy of dosing was assessed. It is therefore possible that the extent of a patient's stone burden may have been affected by nontherapeutic levels of cystine-binding medication. We believe this effect was likely minimal given that there were equivalent number of patients in each laterality group taking cystine-binding medications. With a limited follow-up duration of 8.8 years and cystinuria duration of 17.5 years, it is also possible that some of the unilateral stone formers will ultimately form stone on the other kidney, and our limited follow-up period does not truly represent the life-long natural history of cystine stone formation. With an ongoing prospective data registry, including all stone patients at our institution,²¹ we expect to observe patients in this cohort closely, along with future cystine stone patients as well as stone formers of all types. This registry effort will help verify the natural history and clinical outcomes from this rare genetic disease in a more meaningful manner and over time will be able to generalize findings related to laterality to different types of kidney

stones. Overall, our study examines the natural history of laterality in cystinuria and highlights an area for future research— if an intervention can be designed to prevent unilateral stone formers from converting to bilateral stone formers, disease morbidity may be reduced.

Conclusions

Approximately two-third of cystine stone patients within our cohort form stone bilaterally during their lifetimes and require a significantly greater number of surgical stone interventions compared with unilateral stone formers. The etiology of unilateral vs bilateral stone formation in cystinuric patients remains unclear, but may relate to intrinsic renal and environmental factors.

Despite the need for significantly more lifetime surgical procedures, bilateral cystinurics were found to have median GFRs comparable to unilateral stone formers, indicating excellent intermediate-term renal preservation in both groups.

Acknowledgments

Funding support was provided by the NIH NIDDK K12-DK-07-006: Multidisciplinary K12 Urologic Research Career Development Program (T.C.) and NIH P20-DK100863 (T.C.).

Author Disclosure Statement

No competing financial interests exist.

References

1. Rutchik SD, Resnick MI. *Cystine calculi*. Diagnosis and management. *Urol Clin North Am* 1997;24:163–171.
2. Dahlberg PJ, van den Berg, Kurtz SB, Wilson DM, Smith LH. Clinical features and management of cystinuria. *Mayo Clin Proc* 1977;52:533–542.
3. Purohit RS, Stoller ML. Laterality of symptomatic cystine calculi. *Urology* 2003;62:421–424.
4. Rosenberg LE, Downing S, Durant JL, Segal S. Cystinuria: Biochemical evidence for three genetically distinct diseases. *J Clin Invest* 1966;45:365–371.
5. Knoll T, Zollner A, Wendt-Nordahl G, Michel MS, Alken P. Cystinuria in childhood and adolescence: Recommendations for diagnosis, treatment, and follow-up. *Pediatr Nephrol* 2005; 20:19–24.
6. Seyedzadeh A, Momtaz HE, Moradi MR, Moradi A. Pediatric cystine calculi in west of Iran: A study of 22 cases. *Urol J* 2006;3:134–137; discussion 8.
7. Ketata S, Ketata H, Sahnoun A, Haj Slimen M, Fakhfakh H, Bahloul A, Mhiri, MN. Laterality of symptomatic recurrent calcium nephrolithiasis. *Afr J Urol* 2008;14:143–146.
8. Shekarriz B, Lu HF, Stoller ML. Correlation of unilateral urolithiasis with sleep posture. *J Urol* 2001;165:1085–1087.
9. Ziaee SA, Moradi A, Fateh M, Moghaddam SM. Sleep posture and unilateral renal stone formation. *Scand J Urol Nephrol* 2008;42:551–554.
10. Varda BK, Johnson EK, Johnson KL, Rosoklija I, Baum MA, Nelson CP. Imaging and surgical utilization for pediatric cystinuria patients: A single-institution cohort study. *J Pediatr Urol* 2016;12:106.e1–106.e7.
11. Shim M, Park HK. Multimodal treatments of cystine stones: An observational, retrospective single-center analysis of 14 cases. *Korean J Urol* 2014;55:515–519.

12. Akakura K, Egoshi K, Ueda T, Nozumi K, Kotake T, Masai M, et al. The long-term outcome of cystinuria in Japan. *Urol Int* 1998;61:86–89.
13. Chow GK, Strem SB. Medical treatment of cystinuria: Results of contemporary clinical practice. *J Urol* 1996;156:1576–1578.
14. Rule AD, Bergstralh EJ, Melton LJ, 3rd, Li X, Weaver AL, Lieske JC. Kidney stones and the risk for chronic kidney disease. *Clin J Am Soc Nephrol* 2009;4:804–811.
15. Worcester EM, Coe FL, Evan AP, Parks JH. Reduced renal function and benefits of treatment in cystinuria vs other forms of nephrolithiasis. *BJU Int* 2006;97:1285–1290.
16. Prot-Bertoye C, Lebbah S, Daudon M, Tostivint I, Bataille P, Bridoux F, et al. CKD and its risk factors among patients with cystinuria. *Clin J Am Soc Nephrol* 2015;10:842–851.
17. Assimos DG, Leslie SW, Ng C, Strem SB, Hart LJ. The impact of cystinuria on renal function. *J Urol* 2002;168:27–30.
18. Thomas K, Wong K, Withington J, Bultitude M, Doherty A. Cystinuria—a urologist’s perspective. *Nat Rev Urol* 2014;11:270–277.
19. Pareek G, Steele TH, Nakada SY. Urological intervention in patients with cystinuria is decreased with medical compliance. *J Urol* 2005;174:2250–2252, discussion 2.
20. Thiola Full Prescribing Information. Available at: www.thiolahcp.com/sites/default/files/2016-12/thiola-prescribing-information.pdf (Accessed May, 2017).
21. Chang HC, Tzou DT, Usawachintachit M, Duty BD, Hsi RS, Harper JD, et al. Rationale and design of the registry

for stones of the kidney and ureter (ReSKU): A prospective observational registry to study the natural history of urolithiasis patients. *J Endourol* 2016;30:1332–1338.

Address correspondence to:

Thomas Chi, MD
Department of Urology
University of California, San Francisco
400 Parnassus Avenue
Suite A610 Box 0330
San Francisco, CA 94143

E-mail: tom.chi@ucsf.edu

Abbreviations Used

BMI = body mass index
 CKD = chronic kidney disease
 ESRD = end-stage renal disease
 GFR = glomerular filtration rate
 IQR = interquartile range
 PCNL = percutaneous nephrolithotomy
 SWL = shockwave lithotripsy
 UCSF = University of California, San Francisco
 URS = ureteroscopy
 UTI = urinary tract infection