

# Patients treated for uric acid stones reoccur more often and within a shorter interval compared to patients treated for calcium stones

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## Abstract

**Introduction:** We aimed to investigate the association between stone composition and recurrence rate in a well-characterized group of patients.

**Methods:** From our prospectively assembled database of 1328 patients undergoing ureteroscopy and percutaneous nephrolithotomy (PCNL) between 2010 and 2015, we identified 457 patients who met the inclusion criteria: a minimum of two years' followup, stone-free status following surgery, normal anatomy, and Fourier transform infrared (FT-IR) stone analysis results. Stone recurrence was identified by kidney-ureter-bladder (KUB) or an ultrasound (US). All symptomatic events were recorded. Kaplan-Meier and Cox proportional hazard regression methods were used to assess the differences in recurrence rates and associated risk factors.

**Results:** Calcium oxalate (CaOx), uric acid (UA), and struvite stones were found in 298 (65.2%), 99 (21.7%), and 28 (6.1%) patients, respectively. During a median followup of 38 months (interquartile range [IQR] 31–48), stone recurred in 111 (24%) patients. One-year stone-free rates (SFRs) stratified by composition were: CaOx 98%, UA 91.9%, calcium phosphate 90%, struvite 88%, and, cystine 83%; the two-year SFRs were 92.6%, 82.7%, 80%, 73%, and 75%, respectively. On multivariate Cox regression analysis, UA composition, the absence of medical preventive therapy, and preoperative stone burden were associated with a shorter time to recurrence. Secondary intervention for recurrent, symptomatic stones was required in 11 (11.1%) and 22 (7.4%) of patients with UA and CaOx stones, respectively ( $p=0.02$ ).

**Conclusions:** UA stone-formers are more likely to have a recurrence and to undergo surgical intervention in comparison to CaOx stone-formers, regardless of medical preventive treatment. These differences are more prominent during the first year of followup and should be incorporated into the patient's followup protocol.

## Introduction

Nephrolithiasis is a common, recurrent disease. The lifetime risk of stone formation in an individual is estimated at 5–10%, and the risk for recurrence is reported to be as high as 50% at five years and 80–90% at 10 years.<sup>1,2</sup> Routine followup and medical prevention have been shown to decrease stone recurrence.<sup>3</sup> To balance between the medical yield and the economic burden of metabolic workup and treatment, major urological associations recommend that first-time stone-formers who have uric acid (UA), brushite, and infection stones, or certain medical conditions, should undergo extensive evaluation. However, followup protocols after surgical stone removal are uniform despite the substantial differences in the pathogenesis, risk factors, and medical management of the various stone types.<sup>4,5</sup>

UA stones are the second most common stone composition in Israel, following calcium oxalate (CaOx), stones, found in 21.4% in patients 60 years and older and reaching 29% in specific populations.<sup>6,7</sup> This unique distribution of stone compositions allowed us to study the impact of stone type, particularly UA, on stone recurrence, in order to evaluate whether a uniform followup protocol is appropriate for all stones types.

## Methods

After obtaining approval from the institutional ethic committee, we reviewed our retrospective database of patients who underwent percutaneous nephrolithotomy (PCNL) or ureteroscopy (URS) for the treatment of kidney stones at our center between January 2010 and January 2015. We included patients aged 18 years and older who were found to be stone-free bilaterally at the first postoperative visit, with two years or longer of followup, and had stone analysis results available. Stone-free status was defined as no residual stones

Patients with anatomical abnormalities, urinary diversion, medullary sponge kidney, hyperparathyroidism, renal

tubular acidosis, and enteric hyperoxaluria, were excluded from the study. Initial postoperative assessment of residual stones was performed in the first postoperative clinic visit, usually one month after the procedure, and comprised a combination of kidney-ureter-bladder (KUB) and an ultrasound for radio-opaque stones, and non-contrast computed tomography (NCCT) for radiolucent stones. Followup imaging studies using KUB and ultrasound for radio-opaque and radiolucent stones, respectively, were done at six months and yearly thereafter. Imaging studies were also performed following any symptomatic event. Stones were analyzed using infra-red spectrometry (Fourier transform infrared [FT-IR]; Bruker Alpha-T spectrometer), and the composition was determined by the predominant component comprising >50% of the stone. The study's primary outcome was radiological stone recurrence, defined as any new identifiable stone in a patient who was stone-free. The study's secondary outcomes were symptomatic events and the need for surgical re-intervention.

To identify predictors for recurrence, we collected data on age, gender, preoperative cumulative stone size, type of surgery (PCNL/URS), and data on medical preventive treatment (MPT), obtained from an outpatient electronic system, which is automatically populated upon medication purchase. This system is very reliable in recording purchased medications, as the same health management organization (HMO) operates our hospitals, clinics, and pharmacies. All patient data, including drugs prescribed and dispensed, are entered into the HMO's centralized database. Preparations used in Israel for urine alkalinization include Uralyt-U and Alkasolve; both

contain potassium sodium citrate. Allopurinol is used for hyperuricosuria and hydrochlorothiazide or chlorthalidone for hypercalciuria.

## Statistical analysis

Continuous variables are described as the median and interquartile range (IQR). Categorical variables are described as the number and percent. T-test or Mann Whitney U-test and Chi-squared or Fisher's exact tests were used to comparing continuous and nominal variables, respectively. Recurrence probability was calculated by the Kaplan-Meier method, with statistical differences evaluated by the log-rank test. Univariate Cox proportional hazard model was used to correlate time to stone recurrence with potential prognostic indicators. For all analyses stratified by stone composition, CaOx was used as a reference. All statistical analyses were two-sided. Data were analyzed with SPSS® Statistics, version 21.0, with  $p < 0.05$  considered statistically significant.

## Outcome measures and results

From a total of 1328 patients who were operated during the study period, 457 (34.4%) patients met the inclusion criteria. The median age of the study cohort was 53 years (Q1=37, Q3=64), and 317 (69.4%) patients were male. PCNL and URS were performed in 112 (24.5%) and 345 (75.5%) patients for a median stone size of 25 mm (Q1=18, Q3=35) and 10 mm (Q1=7, Q3=17), respectively. Stone composition was CaOx, UA, calcium phosphate (CP), struvite, and cystine

**Table 1. Clinical characteristics of patients stratified by stone composition**

	Total (457)	CaOx (298)	UA (99)	CP (20)	Struvite (28)	Cystine (12)
Median age in years (IQR)	53 (37, 64)	51 (38, 62)	60 (51, 70)	41 (31, 50)	59 (40, 73)	16 (11, 28)
Male gender (%)	317(69.2%)	225 (75%)	65 (65.7%)	9 (45%)	11 (39.337%)	7 (58.3%)
Median BMI (IQR)	26.8 (25.3, 28.6)	26.5 (24.3, 29.2)	29.2 (27.4, 31.2)	26.2 (23.2, 29.1)	27.6 (23.6, 30.1)	24.3 (22.1, 26)
Median preoperative stone size in mm (IQR)	12 (8,20)	10 (7,18)	14 (10,22)	17 (11,30)	20 (16,26)	21 (15,40)
PCNL (%)	104 (22.8%)	50 (16.8%)	30 (30.3%)	8 (40%)	10 (35.7%)	6 (50%)
Medical prevention treatment (%)	140 (36%)	61 (20.5%)	58 (58.6%)	4 (20%)		8 (66.7%)
Alkasole/Uralyt-U (%)	75 (16.4%)	21 (7%)	40 (40%)	4 (20%)	2 (7.1%)	8 (67%)
Hydrochlorothiazide/ chlorthalidone (%)	42 (9.2%)	32 (10.7%)	0	0	5 (17.9%)	0
Allopurinol (%)	29 (6.3%)	12 (4%)	0	0	2 (7.1%)	4 (33%)
Median followup in months (IQR)	37 (20)	37 (32, 47)	60 (31, 59)	41 (31, 63)	59 (31, 45)	16 (26, 45)
Median recurrence time in months						14
1-year SFR	97.4%	98%	91.9%	90%	88%	83%
2-year SFR	95.2%	92.6%	82.7%	80%	73%	75%
3-year SFR	77.7%	85.1%	72.9%	73%	68%	51%
Symptomatic recurrence (%)	69 (15.1%)	40 (13.4%)	20 (20.2%)	3 (15%)	3 (10.7%)	3 (25%)
Repeat surgical treatment (%)	43 (9.4%)	22 (7.4%)	11 (11.1%)	3 (15%)	3 (10.7%)	4 (33.3%)
Median recurrent stone size (IQR)	7 (5, 9)	5 (6, 8)	8 (6, 9)	8 (6, 9)	9 (6, 10)	15 (5, 18)

BMI: body mass index; CaOx: calcium oxalate; CP: calcium phosphate; IQR: interquartile range; PCNL: percutaneous nephrolithotomy; SFR: stone-free rate; UA: uric acid.

**Table 2. Univariate multivariate analysis of risk factors for stone recurrence**

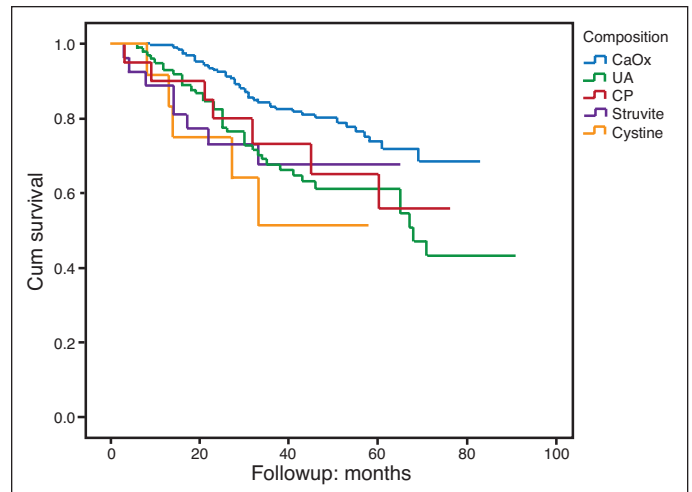
Covariate	Univariate Cox regression analysis		Multivariate Cox regression analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age	1 (0.99–1.02)	0.48		
Gender	0.92 (0.76–1.12)	0.44		
BMI	1.1 (0.62–1.33)	0.6		
Type of procedure	1.33 (0.89–2)	0.17		
Stone composition				
Calcium oxalate	1			
Uric acid	2.1 (1.41–3.2)	0.001	1.61 (1.02–2.53)	0.04
Calcium phosphate	1.83 (0.83–4.02)	0.13	1.53 (0.68–3.42)	0.3
Struvite	2.1 (1–4.4)	0.05	1.62 (0.73–3.6)	0.23
Cystine	3.07 (1.23–7.7)	0.016	1.43 (0.47–4.4)	0.53
Preoperative stone size	1.02 (1.01–1.03)	0.001	1.013 (1–1.03)	0.055
Medical prevention	0.53 (0.37–0.77)	0.001	0.81 (0.61–0.91)	0.048

BMI: body mass index; CI: confidence interval; HR: hazard ratio.

in 298 (65.2%), 99 (21.7%), 20 (4.4%), 28 (6.1%), and 12 (2.6%) patients, respectively. MPT was used by 149 (32.6%) patients, including 20% of CaOx stones-formers, and 58% of UA stones-formers. Clinical characteristics of patients stratified by stone composition are depicted in Table 1.

During a median followup of 38 months (Q1=31, Q3=48), 111 (24.2%) patients developed stone recurrence, with a median time of 25 months. The median time to stone recurrence was reached only in patients with cystine stones (14 months). One-year stone-free rates (SFRs) stratified by composition were: CaOx 98%, UA 91.9%, CP 90%, struvite 88%, and cystine 83%, and the two-years SFRs were 92.6%, 82.7%, 80%, 73%, and 75%, respectively.

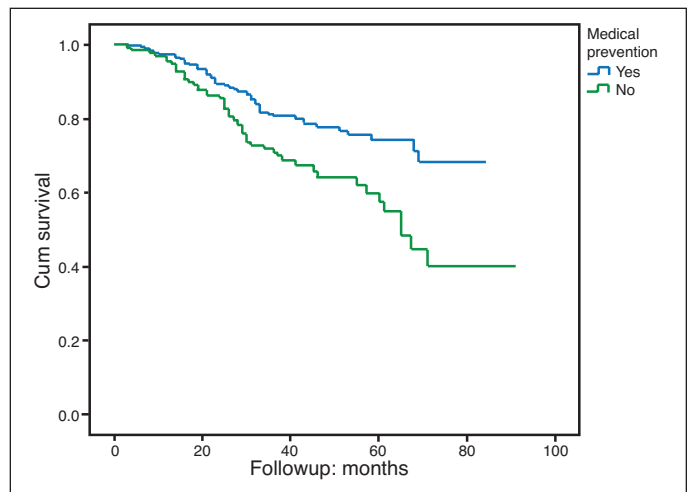
On univariate Cox regression analysis, UA (hazard ratio [HR] 2.1, 95% confidence interval [CI] 1.41–3.2, p=0.001), struvite (HR 2.1, 95% CI 1–4.4, p=0.05), and cystine (HR 3.07, 95% CI 1.23–7.7, p=0.016) stones, as well as preoperative stone size (HR 1.02, 95% CI 1.01–1.03, p=0.001) and MPT (HR 0.53, 95% CI 0.37–0.77, p=0.001) were associated with stone recurrence, while age (HR 1, 95% CI 0.99–1.02, p=0.48), gender (HR 0.92, 95% CI 0.76–1.12, p=0.44), body mass index (BMI) (HR 1.1, 95% CI 0.62–1.33, p=0.6), and type of surgery (HR 1.33, 95% CI 0.89–2, p=0.17) were not. On multivariate Cox regression analysis adjusted for stone composition, MPT, and stone size, UA composition (HR 1.61, 95% CI 1.02–2.53, p=0.04) and MPT (HR 0.81, 95% CI 0.61–0.91, p=0.048) remained independent predictors for stone recurrence, while stone size (HR 1.013, 95% CI 1–1.03, p=0.055) was marginally associated with stone recurrence. Table 2 presents univariate and multivariate Cox regression analysis of different variables. Figs. 1A and 1B



**Fig. 1A.** Kaplan-Meier curves for stone recurrence stratified by stone composition. CaOx: calcium oxalate; CP: calcium phosphate. UA: uric acid.

show the Kaplan-Meier curves for stone recurrence stratified by stone composition and MPT status.

Symptomatic recurrence occurred in 69 (15.1%) patients, including three (25%) patients with cystine stones, 20 (20.2%) patients with UA stones, three (15%) patients with CP stones, 40 (13.4%) patients with CaOx stones, and three (10.7%) patients with struvite stones (p=0.001). Surgical intervention was required in 43 (9.4%) patients: four patients (33.3%) had cystine stones, three patients (15%) had CP stones, three patients (10.7%) had struvite stones, 11 (11.1%) patients had UA stones, and, 22 patients (7.4%) had CaOx stones (p between UA and CaOx=0.02). Median sizes of the recurrent stones were 5 mm (Q1=6, Q3=8), 8 mm (Q1=6, Q3=9), 8 mm (Q1=6, Q3=9), 9 mm (Q1=6, Q3=10), and 15 mm (Q1=5, Q3=18), for CaOx, UA, CP, struvite, and cystine stones, respectively. Recurrent struvite stones were significantly larger than CaOx stones (p=0.02).



**Fig. 1B.** Kaplan-Meier curves for stone recurrence stratified by medical preventive treatment status.

In a subgroup analysis of patients with recurrent stones, re-treatment was associated with younger age (44 years vs. 55 years,  $p < 0.01$ ), larger recurrent stone size (9.5 mm vs. 7.5 mm,  $p = 0.05$ ), and symptomatic recurrence (49.2% vs. 17.3%,  $p < 0.01$ ), but not with gender ( $p = 0.9$ ) or stone composition ( $p = 0.24$ ), in comparison to patients that were not treated for recurrent stones.

## Discussion

In the present study, we evaluated the impact of stone composition on recurrence rates. The time to recurrence of UA stones was shorter than that of CaOx stones, and patients with recurrent UA stones were more likely to undergo surgical intervention. Additionally, larger preoperative stone size and the absence of preventive medical treatment were also associated with stone recurrence.

Several studies evaluated risk factors for stone recurrence after surgical treatment. Lee et al developed a stone recurrence predictive score, comprising eight clinical variables; family history, number of stones, and gouty arthritis were all associated with stone recurrence.<sup>8</sup> Kamihira et al found that stone burden and postoperative pyuria are associated with earlier recurrence among 903 patients undergoing extracorporeal shock wave lithotripsy (ESWL), while Strauss et al identified hypercalciuria and shorter interval between previous stone episodes as risk factors for recurrence among 522 patients receiving MPT.<sup>9,10</sup>

These studies and others focused on CaOx stone-formers, comprising the majority of stone-formers. In the Western world, UA stones — found in up to 40% of the patients in other areas — have hardly been studied.<sup>11</sup> The high prevalence of UA stones in our area, reaching 29% in some populations, allowed us to investigate the impact of stone composition on stone recurrence.<sup>7</sup>

Median recurrence time was shorter for UA stones compared with CaOx stones (23 vs. 28 months), and SFR was substantially lower after the first year of followup, during which UA stones were four times likelier to reoccur in comparison to CaOx stones (SFR 98% vs. 92%). Likewise, the SFRs at two-year followup were 92.6% for CaOx stones, 82.7% for UA stones, and 80%, 73%, and 75% for CP, struvite, and cystine stones, respectively. Median recurrence time and the Kaplan-Meier curves of CP, struvite, and cystine stones suggest that their recurrence rates are even higher. However, the limited number of patients in the last three stone compositions precluded any definite conclusion regarding their recurrence rates. Clues to the impact of stone composition on stone recurrence are scarce.

Nakamoto et al performed a retrospective study of the recurrence pattern in 145 patients who underwent endourological intervention. UA and calcium stones recurred in 33% and 17% of the patients, respectively. However, their

cohort was composed of a mixed population of patients who underwent ESWL, URS, and PCNL, and only three patients in this cohort had UA stones.<sup>12</sup> Rule et al used a large database of 2239 first-time stone-formers from Olmsted County, Minnesota, to design the ROKS nomogram for the prediction of stone recurrence. Ten-year recurrence varied from 12% to 56%. They found that UA composition, as well as younger age, male sex, white race, family history of nephrolithiasis, and the presence of non-obstructing stones were all associated with increased risk for recurrence. Their study, however, was designed to predict symptomatic rather than radiographic stone recurrence. As such, imaging surveillance was not available. Additionally, stone composition was available for only 50% of the patients, and only 4% of the cohort had UA stone composition. Lastly, 30.4% of the patients had another non-obstructing kidney stone, which was found to be the most predominant predictor for symptomatic recurrence.<sup>13</sup>

More recently, Daudon et al studied the association between stone composition and recurrence rate by identifying recurrent stones in a database of 38 274 stones; 51% of patients with UA stones and 38–43% of patients with CaOx stones had recurrent stone episodes. Clinical data, however, was not available for this study.<sup>14</sup> As we aimed to study the impact of stone composition on stone recurrence, we included only patients who were stone-free after PCNL or URS, had stone composition analysis, and had at least two years of imaging followup. Using these strict criteria, we provide the largest data to date to address this issue.

Why would UA stones recur faster than CaOx stones? The intuitive thinking is that in the absence of an anchoring mechanism on which a stone can gradually accumulate, a substantial lithogenic force is required to promote crystallization during the short transition time of a free-floating particle. However, our understanding of the pathogenesis of UA stone formation is still evolving. The traditional hypothesis of “simple” crystallization of supersaturated minerals gave its way to a complicated interaction between the crystals and the renal parenchyma in the form of “Randall’s plaques” and the intramedullary collecting ducts plugging. These extensively studied lesions were considered precursors for calcium stones formation, since they were not found in kidneys of UA stones-formers.<sup>15,16</sup> Recent evidence, however, challenge this concept as well.

Evan et al obtained papillary biopsies from stone-formers who have an ileostomy. All seven patients, including four patients with UA stones, had intra-tubular apatite deposits. Interestingly, only in UA stone-formers, there was no stone attached to the plaque.<sup>17</sup> Viers et al compared the endoscopic and histological appearance of papillary biopsies obtained from UA and CaOx stone-formers. Among patients with UA stones, 100% had endoscopic plaques and 57% had endoscopic plugs, significantly more than CaOx stone-formers or

controls. They also noted greater interstitial inflammation in biopsies obtained from CaOx stone.<sup>18</sup> These studies suggest that similarly to CaOx stones, tissue factors may play a role in the pathogenesis of UA stones.

This study is novel in providing evidence for the association between stone composition and recurrence rate, an association that is clinically and economically valuable. Because of the tremendous cost of kidney stone treatment and prevention, cost-effective followup protocols are desirable. In the present study, the one-year stone recurrence was four times higher in UA stone-formers. Shorter followup intervals in these patients may improve care and decrease the cost of care. Further cost-effectiveness studies are needed to shed light on this question.

### Limitations

This study has several limitations. The electronic computerized system has the advantage of live followup after medicines that were prescribed for the patients, as well as after medicines that were issued. However, there is no reliable way to follow the patient's compliance. Indeed, studies examining patient's adherence to chronic pharmacological therapy found the one-year adherence of men with lower urinary tract symptoms was only 29%.<sup>19</sup> Additionally, we did not account for dietary habits and comorbidities in this study, as it is clear that UA and CaOx stone-formers are different in that regard.

### Conclusions

UA stones-former are more likely to have recurrence and to undergo surgical intervention in comparison to CaOx stones-formers, regardless of MPT. These differences are more prominent during the first year of followup and should be incorporated into the patient's followup protocol.

**Competing interests:** The authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed

### References

1. Antonelli JA, Maalouf NM, Pearle MS, et al. Use of the National Health and Nutrition Examination Survey to calculate the impact of obesity and diabetes on cost and prevalence of urolithiasis in 2030. *Eur Urol* 2014;66:724-9. <https://doi.org/10.1016/j.eururo.2014.06.036>
2. Stamatelou KK, Francis ME, Jones CA, et al. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. *Kidney Int* 2003;63:1817-23. <https://doi.org/10.1046/j.1523-1755.2003.00917.x>
3. Uribarri J, Oh MS, Carroll HJ. The first kidney stone. *Ann Intern Med* 1989;111:1006-9. <https://doi.org/10.7326/0003-4819-111-12-1006>
4. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. *J Urol* 2014;192:316-24. <https://doi.org/10.1016/j.juro.2014.05.006>
5. Skolarikos A, Straub M, Knoll T, et al. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. *Eur Urol* 2015;67:750-63. <https://doi.org/10.1016/j.eururo.2014.10.029>
6. Usman KD, Golan S, Abidin T, et al. Urinary stone composition in Israel: Current status and variation with age and sex — a bicenter study. *J Endourol* 2013;27:1539-42. <https://doi.org/10.1089/end.2013.0236>
7. Zaidman JL, Pinto N. Studies on urolithiasis in Israel. *J Urol* 1976;115:626-7. [https://doi.org/10.1016/S0022-5347\(17\)59313-1](https://doi.org/10.1016/S0022-5347(17)59313-1)
8. Lee YH, Huang WC, Lu CM, et al. Stone recurrence predictive score (SRPS) for patients with calcium oxalate stones. *J Urol* 2003;170:404-7. <https://doi.org/10.1097/01.ju.0000072365.22948.30>
9. Kamihira O, Ono Y, Katoh N, et al. Long-term stone recurrence rate after extracorporeal shock wave lithotripsy. *J Urol* 1996;156:1267-71. [https://doi.org/10.1016/S0022-5347\(01\)65566-6](https://doi.org/10.1016/S0022-5347(01)65566-6)
10. Strauss AL, Coe FL, Deutsch L, et al. Factors that predict relapse of calcium nephrolithiasis during treatment: A prospective study. *Am J Med* 1982;72:17-24. [https://doi.org/10.1016/0002-9343\(82\)90566-6](https://doi.org/10.1016/0002-9343(82)90566-6)
11. Moran ME, Abrahams HM, Burday DE, et al. Utility of oral dissolution therapy in the management of referred patients with secondarily treated uric acid stones. *Urology* 2002;59:206-10. [https://doi.org/10.1016/S0090-4295\(01\)01499-6](https://doi.org/10.1016/S0090-4295(01)01499-6)
12. Nakamoto T, Sagami K, Yamasaki A, et al. Long-term results of endourologic treatment of urinary calculi: Investigation of risk factors for recurrence or regrowth. *J Endourol* 1993;7:297-301. <https://doi.org/10.1089/end.1993.7.297>
13. Rule AD, Lieske JC, Li X, Melton LJ, et al. The ROKS nomogram for predicting a second symptomatic stone episode. *J Am Soc Nephrol* 2014;25:2878-86. <https://doi.org/10.1681/ASN.2013091011>
14. Daudon M, Jungers P, Bazin D, et al. Recurrence rates of urinary calculi according to stone composition and morphology. *Urolithiasis* 2018;46:459-470. <https://doi.org/10.1007/s00240-018-1043-0>
15. Evan A, Lingeman J, Coe FL, et al. Randall's plaque: Pathogenesis and role in calcium oxalate nephrolithiasis. *Kidney Int* 2006;69:1313-8. <https://doi.org/10.1038/sj.ki.5000238>
16. Evan AP, Lingeman JE, Coe FL, et al. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. *J Clin Invest* 2003;111:607-16. <https://doi.org/10.1172/JCI17038>
17. Evan AP, Lingeman JE, Coe FL, et al. Intra-tubular deposits, urine and stone composition are divergent in patients with ileostomy. *Kidney Int* 2009;76:1081-8. <https://doi.org/10.1038/ki.2009.321>
18. Viers BR, Lieske JC, Vrtiska TJ, et al. Endoscopic and histologic findings in a cohort of uric acid and calcium oxalate stone formers. *Urology* 2015;85:771-6. <https://doi.org/10.1016/j.urol.2014.12.036>
19. Cindolo L, Pirozzi L, Fanizza C, et al. Drug adherence and clinical outcomes for patients under pharmacological therapy for lower urinary tract symptoms related to benign prostatic hyperplasia: Population-based cohort study. *Eur Urol* 2015;68:418-25. <https://doi.org/10.1016/j.eururo.2014.11.006>

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