

# Is medical dissolution treatment for uric acid stones more cost-effective than surgical treatment? A novel, solo practice, retrospective cost-analysis of medical vs. surgical therapy

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## Abstract

**Introduction:** Effective medical dissolution therapy (MDT) for uric acid stones is more cost-effective than surgical treatment; however, treatment failure may be associated with increased cost. We aimed to study the cost-effectiveness of MDT for uric acid stones vs. surgical management.

**Methods:** We performed a retrospective study within our institution of all patients receiving MDT for uric acid stones from 2008–2019. All patients had a known history of uric acid stones, urine pH  $\leq 5.5$ , and  $<500$  Hounsfield units on preoperative computed tomography (CT). The cost of treatment in the dissolution group was compared to the cost of primary surgical treatment in a theoretical matched cohort. Cost was estimated using local Medicare reimbursement scales. Statistical analysis was performed with SPSS Statistics.

**Results:** A total of 28 patients were identified, of which 18 were included in the study. Complete and partial dissolution occurred in six (33%) and four (22%) patients, respectively. Five (28%) patients developed symptoms and underwent ureteral stent placement. Ureteroscopy and percutaneous nephrolithotomy (PCNL) were each performed in three (17%) patients in whom dissolution treatment was not effective on followup CT. Following dissolution trial, six (33%) patients had residual stone burden requiring surgical intervention. The average cost of treatment, including surgeries, was \$14 604 in the dissolution group vs. \$17 680 in the surgical cohort. The average cost to achieve stone-free status in patients with complete, partial, or no response to dissolution were \$1675, \$10 124, and \$21 584, respectively, while primary surgical treatment for the same patients would cost \$15 037, \$10 901, and \$20 511, respectively.

**Conclusions:** Successful MDT is highly cost-effective. Incomplete response to dissolution can stem from several reasons and contributes to higher costs and likely decreased quality of life.

## KEY MESSAGES

- Existing literature suggests medical dissolution for stones may not be as widely used or as effective among providers.
- While stone dissolution can be financially beneficial for patients when successful, incomplete response can stem from multifocal etiologies and contribute to additional costs and morbidity.
- Urologists should not only be familiar with but also keenly aware of hurdles with medical dissolution therapy in order to improve patient compliance and ultimately reduce treatment cost and morbidity.

## Introduction

Urolithiasis is a costly and common disease, with a high recurrence rate and an increasing incidence, affecting approximately 8% of the U.S. population. It is associated with tremendous direct and indirect costs, projected to be \$4.1 billion in 2030.<sup>1</sup> The economic aspects of kidney stone treatment have been extensively studied, and cost-conscious methods for treating kidney stones are highly desirable. Although most stones, once formed, are only able to be eliminated through spontaneous passage or surgical removal, uric acid stones can and have illustrated promising, albeit limited, results to medical therapy and dissolution.<sup>2</sup> Existing literature and published guidelines have found that medical dissolution can be achieved by manipulating the urine pH with oral alkalinizing agents so that urine pH is between 7.2 and 6.5, achieving chemolitholysis, and between 6.5 and 6.8 for prophylaxis.<sup>3,4</sup> Within the U.S., uric acid kidney stones comprise upwards of 14% of all kidney stones and that rate is as high as 28% in other countries.<sup>5,6</sup> Their preva-

lence is highest among patients with diabetes mellitus, obesity, and components of metabolic syndrome and is likely to increase as these conditions become increasingly prevalent.<sup>7</sup>

Multiple case reports and series have documented the feasibility of uric acid stone dissolution.<sup>8</sup> Contemporary studies, however, illustrate the proportion of uric acid stones treated surgically is similar, if not greater than all kidney stones, suggesting that medical dissolution may not be as effective or used at all.<sup>9</sup> While medical dissolution therapy (MDT) may be appealing as a non-surgical therapy, the success rate, complications, and direct cost of this treatment have not been previously described. We aimed to study the direct cost of MDT of uric acid stones vs. surgical management. Additionally, we reviewed the success of MDT and the rates of necessary surgical intervention following failed or partial dissolution therapy.

## Methods

Institutional review was performed and completed for our retrospective review. All patients who treated with MDT for presumed uric acid stones within our institution between 2008 and 2019 were evaluated. Patients with a known history of uric acid stones (previous stone analysis available), cross-sectional abdominal imaging demonstrating calculi with <500 Hounsfield units (HU), attenuation, and urinary pH  $\leq 5.5$  were included. These parameters have been shown to have a sensitivity, specificity, and positive predictive value (PPV) to predict uric acid calculi amenable for MDT at 86%, 98%, and 80%, respectively.<sup>10</sup> Only calculi >5 mm were included. All patients were treated with at least 45 mEq of potassium citrate daily for a minimum period of 60 days. All patients reported taking the medication as prescribed, and underwent non-contrast computed tomography (CT) before and after initiating medical therapy. Patients who underwent a surgical intervention after initiating dissolution were included only if their stone composition was uric acid.

Demographics, medical history, CT findings (stone location, size, number, and attenuation), duration of treatment, and urinary pH during treatment were recorded. The primary outcome was the average cost of treatment for complete removal of the stone. Our secondary outcome was degree of stone dissolution categorized as complete, partial (>30% decrease in stone size), or none. For cost-analysis, if partial or no dissolution was achieved, we assessed the remaining stone burden to determine whether surgery was indicated. The cost of treatment in the dissolution group was compared to the cost of primary surgical treatment in a theoretical matched cohort. Calculations were based on a theoretical matched cohort of patients with uric acid stones who did not try MDT and pursued immediate surgical treatment.

The cost of treatment was estimated using local Medicare reimbursement scales based on 2019 coding instruction

from both the Diagnosis Related Group (DRG) and Current Procedural Terminology (CPT) codes for inpatient and outpatient procedures, respectively (Table 1). For percutaneous nephrolithotomy (PCNL), CPT codes 50081 (PCNL for >2 cm stone burden) or 50080 (PCNL for <2 cm stone burden) were used. CPT code 50432 (placement of nephrostomy catheter, percutaneous, including all intraoperative radiological studies) was billed as part of operating room procedure in primary PCNL, or as part of radiology procedure if nephrostomy tube was placed urgently by interventional radiology. CPT codes 52332 and 52356 were used for ureteral stent placement and ureteroscopy (URS) and stent placement, respectively. DRG code 661 (kidney and ureter procedure for non-neoplasm without major complication or morbidity) was used for inpatient care for patients undergoing PCNL. Because anesthesia reimbursements depend on the type of procedure, its length, and patient comorbidities, we generated an estimated Medicare anesthesia cost based on average length of procedures within our institution. The cost of outpatient imaging and procedures were estimated using local Medicare reimbursement for outpatient cystoscopy/ureteral stent removal (52310) and nephrostogram (50394/74425). CT scans were routinely performed before and after PCNL, before URS, and before and during dissolution therapy, depending on the change in stone size and clinician clinical discretion. Medication cost was based on the average retail price (\$226 for a one-month supply of potassium citrate 15 meq three times daily) adjusted for the duration of treatment.

Continuous variables were described as median and interquartile range (IQR). Categorical variables were described as number and percent. All statistical analyses were two-sided and performed with SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, U.S.). A p-value <0.05 was considered statistically significant.

## Results

A total of 28 patients received MDT between 2008 and 2019, of which 18 met inclusion criteria. Median age was 66 years (IQR 56–72) and 13 (72%) were male. Diabetes and hypertension were present in four (22%) and 12 (67%) patients, respectively. Median body mass index (BMI) was 30 kg/m<sup>2</sup> (IQR 28–38). Stones were found in the upper calyx, middle calyx, lower calyx, and renal pelvis in two, four, 12, and 12 patients, respectively. The median cumulative stone size was 19 mm (IQR 11–36), with a median stone density of 450 HU (IQR 387–485). Treatment urinary pH was 6.0 or higher in 12 (67%) patients and 6.5 or higher in eight (44%) patients.

During a median dissolution time of 97 days (IQR 71–151), five (28%) patients developed progressive renal colic and underwent ureteral stent placement followed by dissolution

**Table 1. Calculation of average cost of dissolution vs. surgical treatment based on Medicare reimbursement scale**

				Dissolution		Primary surgical treatment	
Reimbursement type	DRG or CPT	Reimbursement (\$)		Number	Total reimbursement (\$)	Number	Total reimbursement (\$)
		Hospital	surgeon				
PCNL >2 cm	50081	7651	1332	5	44 915	9	80 847
Access	50432	1740	216		9780		17 604
Cystoscopy + stent insertion	52332	2927	162		15 445		27 801
Admission	661	6554			32 770		58 986
Anesthesia		2940			14 700		26460
Total					117 610		211 698
PCNL <2 cm	50080	7651	906	2	17 114	2	17 114
Access	50432	1740	216		3912		3912
Cystoscopy + stent insertion	52332	2927	162		6178		6178
Admission	661	6554			13 108		13 108
Anesthesia		2940			5880		5880
Total					46 192		46 192
Ureteroscopy, laser lithotripsy, stent insertion	52356	4021	434	5	22 275	7	31 185
Anesthesia		2240			11 200		15 680
Total					33 475		46 865
Cystoscopy + stent insertion	52332	2927	162	5	15 445		
Anesthesia		1200			6000		
Total					21 445		
CT abdomen non-contrast	74150	465		50	23 250	29	13 485
Cost of medications				2775 days	20 908		
TOTAL \$					262 880		318 240
Average cost per patient					14 604		17 680

CPT: current procedural terminology; CT: computed tomography; DRG: diagnosis-related group; PCNL: percutaneous nephrolithotomy.

attempt. Of these five patients, complete and partial dissolution occurred in one and two patients, respectively (Figure 1). Overall, complete dissolution occurred in six (33%) patients, eliminating the need for PCNL or URS. Partial dissolution occurred in four (22%) patients; however, all four patients still required surgical intervention as would have been recommended prior to MDT (Figure 1). At the end of the dissolution trial, eight (44%) patients with unchanged residual stone burden warranting surgical intervention remained (three PCNL and five URS) (Figure 1). Five of eight patients with stones >2 cm, and three of 10 patients with stones <2 cm failed dissolution therapy ( $p=0.36$ ). Subjective reported data regarding patient adherence were not included for analysis.

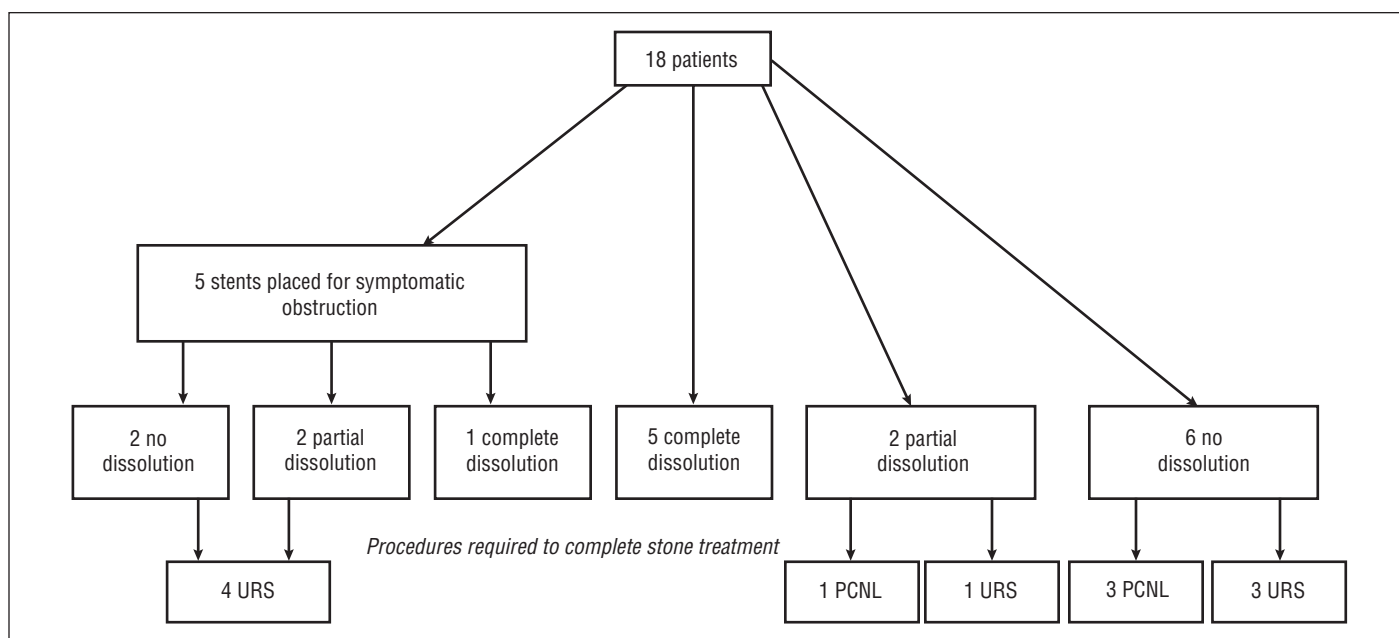
Overall, 50 CT scans were performed for the diagnosis, followup, and postoperative evaluation of residual stones in the dissolution group (average of 2.77 exams per patient); 29 CT scans were performed in the surgical group. These were mostly non-contrast exams, but also two dual-energy exams, and two exams with intravenous contrast.

## Cost-analysis

The average cost of treatment, including surgeries performed to complete treatment, was \$14 604 for MDT vs. \$17 680 in the surgical cohort. The average cost of medical treatment alone was \$1161, comprising 8% of the overall cost. The average cost of treatment to achieve a stone-free status in patients with complete, partial, or no response to MDT was \$1675, \$10 124, and \$21 584, respectively, while index surgical treatment cost \$15 037, \$10 901, and \$20 511, respectively.

## Discussion

Multiple reports have demonstrated the feasibility and attractiveness of MDT for treatment of uric acid stones through urine alkalization.<sup>11,12</sup> Due to increasing financial and social pressure to provide value-based treatment, financial cost can and is a primary consideration when considering any therapy. In this study, we evaluated the cost burden of treatment methods for uric acid nephrolithiasis by comparing the cost of MDT and primary surgical intervention. We found that when dissolution was achieved, the cost was approxi-



**Figure 1.** Flow diagram of patient selection and ultimate outcome and treatment. PCNL: percutaneous nephrolithotomy; URS: ureteroscopy.

mately 10% of that of primary surgical treatment; however, this occurred in only one-third of patients. In the remaining patients with partial or no response to MDT, the average cost of treatment was similar to primary surgical treatment, and in cases where dissolution therapy did not work at all, treatment costs were higher when combining both medical and surgical therapies.

While uric acid concentration plays a role in stone formation, solubility is the primary factor and ultimately determined by urine pH. Normal ranges between 200 mg/l to 1200 mg/l leading to urinary pH of 5.35 and 6.5, respectively.<sup>13</sup> Uric acid has two dissociation constants. Only the first, at pH of 5.5, is physiologically relevant. Supersaturation occurs when the pH is <5.5, and at a pH of ≥6.5, the majority of uric acid is in the form of soluble anionic urate.<sup>14</sup> As such, dissolution should be easily achieved with adequate alkalization. While there are numerous reports on successful stone dissolution, the success rate of this treatment has not been reported. Recent literature shows that the percentage of patients with uric acid stones undergoing surgical treatment is proportional to their percentage among stone-formers, suggesting that dissolution is either underused or not effective in some cases, or both.<sup>9</sup> Possible explanations include surgeon preference, poor adherence to medical treatment, and inaccurate diagnosis based on imaging studies and clinical findings to predict uric acid stone composition. In addition, poor treatment response necessitating ultimate surgical management also contributes to the high surgical rate of uric acid stones.

The most important hurdle in achieving dissolution, and potentially avoiding an invasive procedure, is poor adher-

ence to medical treatment. Golomb et al found that adherence to alkalization treatment was only 42%. The number of pills and adverse drug effects, most commonly gastrointestinal upset, abdominal pain, and diarrhea, were the main reasons for discontinuation.<sup>15</sup> Dauw et al reported that only 13.4% of patients were adherent to citrate monotherapy.<sup>16</sup> Improvements in surveillance strategies for patients on medical therapy — such as implementing tools to more readily assess urinary pH and adjust medical therapy as necessary — could also aid in adherence and ultimate treatment outcomes.<sup>17</sup> It is imperative to convey the importance of treatment to the patient. Short followup intervals to assess the patients' adherence and to adjust the treatment accordingly can improve outcomes and reduce the cost of ineffective treatment.

Even with complete adherence to treatment, stone dissolution is not guaranteed, as imaging findings are not always predictive of stone composition. Maneesh et al studied the success rate of oral dissolution for radiolucent stones. Only 20% of the patients evaluated ultimately achieved complete dissolution. Patients who subsequently underwent surgical intervention were found to have a small component of calcium oxalate within their final stone composition.<sup>18</sup> CT scanners are available worldwide and have a better ability to differentiate uric acid from calcium-based stones, but overlap still exists between calcium and uric acid stones.<sup>19</sup> Even dual-energy CT, which has been shown to be extremely accurate in identifying various stone compositions, is limited in the evaluation of small stones, with sensitivity to detect uric acid stones currently at only 88%.<sup>20</sup> Moreover, this technology is not available in the majority of non-academic centers.



In some cases, uric acid stones contain a small percentage of secondary composition that alter their solubility. Sodium urate is a rare finding and never appears as a primary component. It can result from over-alkalization with sodium bicarbonate, which creates a hard shell of sodium urate that is impossible to dissolve.<sup>21</sup> Similarly, ammonium acid urate, a rare composition in industrial countries but endemic in developing areas, is not dissolvable in physiological pH.<sup>22</sup> Mixed uric acid/calcium oxalate stones are more common than pure uric acid stones. They have similar 24-hour urinary parameters and imaging characteristics to pure uric acid stones, and are clearly not amenable to complete dissolution.<sup>23</sup>

In the current study, we used strict criteria to evaluate the cost of MDT. We only evaluated patients with known or suspected uric acid stones (via cross-sectional imaging or urine studies) who remained compliant with medical therapy to our study. Despite this, complete dissolution was achieved in only a third of the patients and did not result in a cost benefit for the remaining.

## Limitations

This study has several limitations. First, the average mEq of potassium citrate prescribed in this study was 55 mEq. Published literature has alluded to a higher dose being necessary for dissolution, with the highest reported rates of MDT near 67%.<sup>12</sup> Gridley et al used dosages of 60–90 mEq of potassium citrate daily, which is a higher dose than our practice.<sup>12</sup> Our lower success rate is likely due to the lower dosage used by our patients. Additionally, 28% of the patients required surgical intervention in the form of stent placement, which ultimately directs them towards surgical over continued MDT for stone resolution. In patients who do achieve partial dissolution and stone reduction, it would not be unreasonable to continue therapy as long as they remain asymptomatic, without obstruction, and diligent to the course of medical therapy.

Limitations from this study stem from the retrospective design and the small number of patients. Additionally, within all cost analyses, a wide variation in cost of treatment may alter trends and outcomes. Lastly, being a single-center, retrospective review, we would be remiss in mentioning the limited generalizability that may exist with our findings, both domestically and internationally. Despite these limitations, we feel that this study provides a novel perspective towards the success rate and associated cost of dissolution treatment for uric acid stones and provides an interesting and necessary launchpad for future research.

Ultimately from this analysis, it would seem reasonable to initiate MDT for patients with presumed uric acid stones who do not present with acute obstruction or illness. As with any therapy, thorough discussions regarding the risks-benefits

and alternatives is imperative when discussing stone treatment with patients. Providing an initial course of MDT with close followup to evaluate adherence and stone alteration could lead to stone resolution without surgical intervention — a potential financial, social, and medical benefit for patients interested in avoiding immediate surgical intervention. Stone characteristics, location, and other individual patient features could make MDT inappropriate, at which time, surgery may be necessary.

## Conclusions

Uric acid stone dissolution is a highly cost-effective therapy when complete stone dissolution is able to be achieved. Incomplete response to dissolution can be due to several reasons and can contribute to higher costs and morbidity risk. Urologists should not only be familiar with MDT but, more importantly, the hurdles of MDT in order to attempt to improve patient compliance and ultimately reduce treatment cost and patient morbidity.

**Competing interests:** The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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