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

Amihay Nevo[1], Mitchell R. Humphreys[2], Michael Callegari[1], Mira Keddis[3], Jonathan P. Moore[2], Saif Salih[2], Karen L. Stern[2]
[1]University Hospitals Cleveland Medical Center – Urology Institute, Cleveland, OH, United States; [2]Department of Urology, Mayo Clinic, Arizona, AZ, United States; [3]Department of Nephrology, Mayo Clinic, Arizona, AZ, United States

Cite as: Nevo A, Humphreys MR, Callegari M, et al. 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. *Can Urol Assoc J* 2022 August 30; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.7833

Published online August 30, 2022

Corresponding author: Dr. Amihay Nevo, Urology Institute, University Hospitals - Cleveland Medical Center, Cleveland, OH, United States; amihay.nevo@uhhospitals.org

***

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 ≤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.

KEY MESSAGES

- Existing literature suggests medical dissolution 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 financial and morbidity costs.
- Urologists should not only be familiar with but also keenly aware of hurdles with medical dissolution therapy in order to attempt to improve patient compliance and ultimately reduce treatment cost and patient morbidity

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.

INTRODUCTION

Urolithiasis is a costly and common disease, with a high recurrence rate and an increasing incidence, affecting approximately 8% of the population in the United States (US). It is associated with tremendous direct and indirect costs, projected to be $4.1 billion in 2030.[1] The economic aspects of kidney stone treatment have been extensively studied, and cost consciencous 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.[2] Existing literature and published guidelines have found that medical dissolution can be achieved by manipulating the urine pH with oral alkalizing agents so that urine pH is between 7.2 and 6.5, achieving chemolitholysis and between 6.5 and 6.8 for prophylaxis.[3,4] Within the US uric acid kidney stones comprise upwards of 14 % of all kidney stones in the US and as high as 28% in other countries.[5,6] Their prevalence is highest amongst patients with diabetes mellitus, obesity, and components of metabolic syndrome and are likely to increase as these conditions become increasingly prevalent. are.[7]

Multiple case reports and series have documented the feasibility of uric acid stone dissolution.[8] 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 utilized at all.[9] While medical dissolution therapy (MDT) may be appealing as a nonsurgical 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 versus 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 (Hfu) attenuation and urinary pH ≤ 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.[10] Only calculi > 5mm were included. All patients were treated with at least 45 mEq of potassium citrate daily for a period of 60 days minimum. All patients reported taking the medication as prescribed, and underwent noncontrast 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 utilized. CPT code 50432 (Placement of nephrostomy catheter, percutaneous, including all intraoperative radiologic 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 nonneoplasm 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 1-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. Categorical variables were described as number and percent. All statistical analyses were 2 sided and performed with SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY). A P value <.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 4 (22%) and 12 (67%) patients, respectively. Median BMI was 30 kg/m2 (IQR 28-38). Stones were found in the upper calyx, middle calyx, lower calyx, and renal pelvis in 2, 4, 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 or higher in 12 (67%) patients and 6.5 or higher in 8 (44%) patients.

During a median dissolution time of 97 days (IQR 71-151), 5 (28%) patients developed progres7sive renal colic and underwent ureteral stent placement followed by dissolution attempt. Of these five patients, comptete and partial dissolution occurred in one and two patients, respectively (Figure 1). Overall, complete dissolution occurred in 6 (33%) patients, eliminating the need for PCNLs or URS. Partial dissolution occurred in 4 (22%) patients, however all 4 patients still required surgical intervention as would have been recommended prior to MDT (figure 1). At the end of the dissolution trial, 8 (44%) patients with unchanged residual stone burden warranting surgical intervention remained (3 PCNLs and 5 ureteroscopies) (Figure 1). Five of eight patients with stones larger than 2 cm, and three of ten patients with stones smaller than 2cm, 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 IV 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 $1,161, 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 $1,675, $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.[11,12] 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 nephrolithaisis by comparing the cost of MDT and primary surgical intervention. We found that when dissolution was achieved, the cost was approximately 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.[13] Uric acid has two dissociation constants. Only the first, at pH of 5.5, is physiologically relevant. Supersaturation occurs when the pH is lower than 5.5, and at a pH of 6.5 and higher, the majority of uric acid is in the form of soluble anionic urate.[14] 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 underutilized or not effective in some cases, or both.[9] Possible explanations include surgeon's 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 adherence 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 mainreasons for discontinuation.[15] Dauw et al. reported that only 13.4% of patients were adherent to Citrate monotheraphy.[16] Improvements in surveillance strategies for patients on medical therapy could also aid in adherence and ultimate treatment outcomes, such as implementing tools to more readily assess urinary pH and adjust medical therapy as necessary.[17] It is imperative to convey the importance of treatment to the patient. Short follow-up 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 percent of the patients evaluated ultimately achieved complete dissolution. Patients who subsequently underwent surgical intervention were found to have a small component of calcium oxalate withint heir final stone composition.[18] 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.[19] 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 at only 88% currently.[20] 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 alters its 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.[21] Similarly, ammonium acid urate, a rare composition in industrial countries, but endemic in developing areas, is not dissolvable in physiologic pH.[22] Mixed uric acid/calcium oxalate stones are more common than pure uric acid stones. They have similar 24-hours urinary parameters and imaging characteristics to pure uric acid stones, and are clearly not amenable to complete dissolution.[23]

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 medial therapy to our study. Despite this, complete dissolution was achieved in only a third of the patient and did not result in a cost benefit for the remaining.

This study has several limitations. First, the average mEq of potassium citrate prescribed in this study was 55 milliequivalents. Published literature has alluded to a higher dose being necessary for dissolution with the highest reported rates of MDT near 67%.[12] Gridley et al. used dosages of 60-90 milliequivalents of potassium citrate daily which is a higher dose than rom our practice.[19] Our lower success rate is likely due to the lower dosage utilized 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 unreasaonble to continue therapy as long as they remain asymptomatic, without obstruction and diligent with the course of medical therapy.

Limitations from this study stem from the retrospective design and small number of patient power. 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 remised in mentioning the limited generalizability that may exist with our findings, both domestically as well as 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 follow-up 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 or other individual patient features could make MDT inappropriate and at which time should be addressed surgically when necessary.

CONCLUSIONS

Uric acid stone dissolution is highly cost consciencous therapy when complete stone dissolution is able to be achieved. Incomplete response to dissolution can stem from 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.

References

1. Antonelli, J.A., 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.* European urology, 2014. **66**(4): p. 724-729.
2. Kamphuis, G.M., van Hattum, J.W., de Bie, P., et al. "Method of Alkalization and Monitoring of Urinary Ph for Prevention of Recurrent Uric Acid Urolithiasis: A Systematic Review." *Translational Andrology and Urology*, vol. 8, no. S4, 2019, https://doi.org/10.21037/tau.2019.05.01.
3 "EAU Guidelines on Urolithiasis - Metabolic Evaluation and Recurrence Prevention." *Uroweb*, European Association of Urology, https://uroweb.org/guidelines/urolithiasis/chapter/metabolic-evaluation-and-recurrence-prevention.
4. De Coninck, Vincent, et al. "Evaluation of a Portable Urinary Ph Meter and Reagent Strips." *Journal of Endourology*, vol. 32, no. 7, 2018, pp. 647–652., https://doi.org/10.1089/end.2018.0202.
5 Rafique, M., et al., *Chemical Composition of Upper Renal Tract Calculi in Mutan.* Journal-Pakistan Medical Association, 2000. **50**(5): p. 145-147.
6 Sakhaee, K., *Uric acid metabolism and uric acid stones*, in *Urinary tract stone disease*. 2010, Springer. p. 185-193.
7 Daudon, M., et al., *Type 2 diabetes increases the risk for uric acid stones.* Journal of the American Society of Nephrology, 2006. **17**(7): p. 2026-2033.
8 Pak, C.Y., K. Sakhaee, and C. Fuller, *Successful management of uric acid nephrolithiasis with potassium citrate.* Kidney international, 1986. **30**(3): p. 422-428.
9 Rizvi, S.A.H., et al., *Surgical outcomes of percutaneous nephrolithotomy in 3402 patients and results of stone analysis in 1559 patients.* BJU international, 2017. **120**(5): p. 702-709.
10 Spettel, S., et al., *Using Hounsfield unit measurement and urine parameters to predict uric acid stones.* Urology, 2013. **82**(1): p. 22-26.
11 Tsaturyan A, Bokova E, Bosshard P, et al. Oral chemolysis is an effective, non-invasive therapy for urinary stones suspected of uric acid content. Urolithiasis. 2020 Dec;48(6):501-507. doi: 10.1007/s00240-020-01204-8. Epub 2020 Aug 7. PMID: 32770255; PMCID: PMC7666279.
12 Gridley C.M., Sourial M.W., Lehman A., et al. Medical dissolution therapy for the treatment of uric acid nephrolithiasis. World J Urol. 2019 Nov;37(11):2509-2515. doi: 10.1007/s00345-019-02688-9. Epub 2019 Feb 27. PMID: 30810833.
13 Freid, R.M. and A.D. Smith, *Chemolysis of urinary calculi.* Smith's Textbook of Endourology. Hamilton, ON: BC Decker Inc, 2007: p. 149-158.
14 Finlayson, B. and A. Smith, *Stability of first dissociable proton of uric acid.* Journal of Chemical and Engineering Data, 1974. **19**(1): p. 94-97.
15 Golomb, D., et al., *Long-term adherence to medications in secondary prevention of urinary tract stones.* Journal of endourology, 2019. **33**(6): p. 469-474.
16 Dauw, C.A., et al., *Factors associated with preventive pharmacological therapy adherence among patients with kidney stones.* Urology, 2016. **93**: p. 45-49.

17 Kamphuis GM, van Hattum JW, van Dongen-Lases EC, et al. Introduction of a Standardized Approach of Electronic Urinary pH Monitoring to Assist Alkalization Therapy: A Uric Acid Urolithiasis Patient's Perspective. J Endourol. 2021 Oct;35(10):1563-1570. doi: 10.1089/end.2020.0621. Epub 2021 Sep 1. PMID: 34210175.
18 Maneesh, S., et al., *Results of urinary dissolution therapy for radiolucent calculi.* International braz j urol, 2013. **39**(1): p. 103-107.
19 Nakada, S.Y., et al., *Determination of stone composition by noncontrast spiral computed tomography in the clinical setting.* Urology, 2000. **55**(6): p. 816-819.
20 Primak, A.N., et al., *Noninvasive differentiation of uric acid versus non–uric acid kidney stones using dual-energy CT.* Academic radiology, 2007. **14**(12): p. 1441-1447.
21 Iwata, H., et al., *Solubility of uric acid and supersaturation of monosodium urate: why is uric acid so highly soluble in urine?* The Journal of urology, 1989. **142**(4): p. 1095-1098.
22 SOBLE, J.J., B.D. HAMILTON, and S.B. STREEM, *Ammonium acid urate calculi: a reevaluation of risk factors.* The Journal of urology, 1999. **161**(3): p. 869-873.
23 Reichard, C., et al., *100% uric acid stone formers: what makes them different?* Urology, 2015. **85**(2): p. 296-298.

Figure and Tables

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

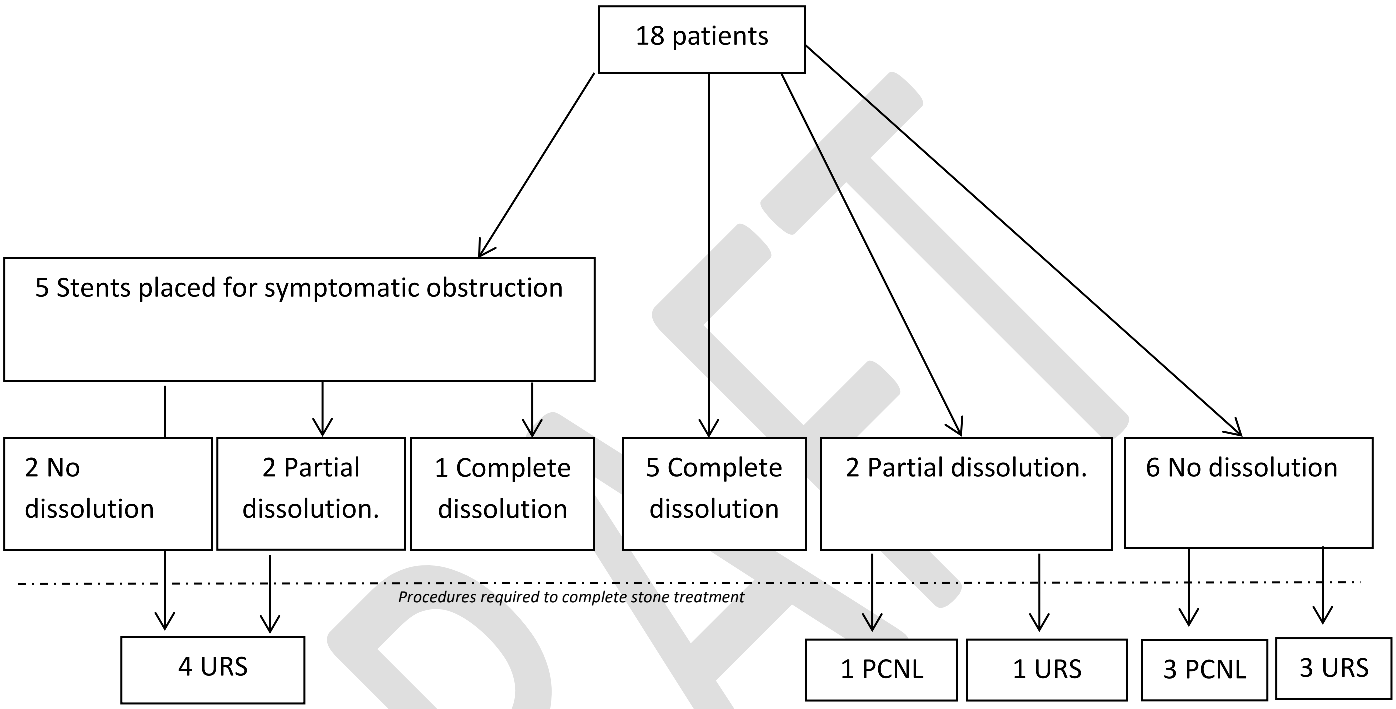

Table 1. Calculation of average cost of dissolution vs surgical treatment based on Medicare reimbursement scale

				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	44915	9	80847
Access	50432	1740	216		9780		17604
Cystoscopy + stent insertion	52332	2927	162		15445		27801
Admission	661	6554			32770		58986
Anesthesia		2940			14700		26460
Total					**117610**		**211698**
PCNL <2 cm	50080	7651	906	2	17114	2	17114
Access	50432	1740	216		3912		3912
Cystoscopy + stent insertion	52332	2927	162		6178		6178
Admission	661	6554			13108		13108
Anesthesia		2940			5880		5880
Total					**46192**		**46192**
Ureteroscopy, laser lithotripsy, stent insertion	52356	4021	434	5	22275	7	31185
Anesthesia		2240			11200		15680
Total					**33475**		**46865**
Cystoscopy + stent insertion	52332	2927	162	5	15445		
Anesthesia		1200			6000		
Total					**21445**		
CT abdomen non-contrast	74150	465		50	**23250**	29	**13485**
Cost of medications				2775 days	**20908**		
TOTAL $					**262880**		**318240**
Average cost per patient					**14604**		**17680**

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