Medical Management of Urolithiasis

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Last Updated:

Tuesday, February 7, 2023

1. Introduction

Medical management of kidney stones involves the initiation of dietary measures and in some cases medications to reduce the risk of stone recurrence in **recurrent**, **high-risk first-time**, or **interested stone formers**. The basis for recommendations may be empiric or based on stone composition and/or underlying pathophysiologic risk factors. Often medical management is guided by the results of 24-hour urine analyses evaluating for kidney stone forming risk factors.

1.1 Key words

nephrolithiasis, calcium oxalate, potassium citrate, thiazide, allopurinol, uric acid stones, cystine stones

1.2 Brief Method for Assessing 24-hour Urine Collection

If a 24-hour urine collection is to be used to guide the therapy as noted below, it is recommended to analyze the results of these collections in a standard and stepwise fashion. While various methods for assessment are utilized,a single “correct” method for evaluation does not exist; the stepwise explanation that follows is simply used to ensure all pieces of a standard 24-hour urine collection are examined.

Initially, creatinine values should be evaluated to ensure a reasonable and complete collection. Additionally, cystinuria should be ruled out before assessing the remainder of the collection results. If stone supersaturations or relative risks are reported, it can be helpful to compare these risk factors to the stone type of the patient, if known. At this point, the overall volume can be assessed, as well as urinary calcium and oxalate (as these may explain calcium oxalate risk). Urinary calcium can be affected by urinary sodium and chloride loads, so these are often helpful to assess at this time to better understand possible causes of elevated urinary calcium and if certain treatment modalities will be beneficial. Urinary citrate will help to delineate if hypocitraturia may be an associated cause of nephrolithiasis in this patient. Additionally, urinary pH may point towards both possible stone type (if this is unknown) and cause of stone formation (e.g. renal tubular acidosis). Urinary uric acid values are also important for understanding possible causes of calcium and uric acid stone formation. Regarding other dietary information that can be gleaned from a urine collection, a low urinary magnesium has been associated with stone risk and should be assessed and possibly corrected. Urinary potassium may be a useful method for assessing adherence to potassium-based nephrolithiasis medications. Lastly, if measurements of protein intake are available, these can be assessed to explain causes of low urinary pH (e.g. impacts on ammoniagenesis vs gastrointestinal alkali loss) or elevated uric acid. Importantly, if additional collections are available, a comparison of different collections (with or without treatment) can be helpful to assess stability or improvements over time.

2. Calcium Oxalate/Calcium Phosphate Stones

2.1 Diet Therapy

The benefit of dietary therapy in preventing stone recurrence has long been recognized. However, few dietary measures have been subjected to prospective, randomized clinical trials (RCTs). **High fluid intake** (**enough to achieve a urine volume of >2 L daily**) **has been shown in a randomized trial to reduce the likelihood of stone recurrence**.[2] **The AUA guidelines for the Medical Management of Kidney Stones recommends that all stone formers should be instructed to increase their fluid intake for a goal urine output > 2.5 L daily**[3] (“**Medical Management of Kidney Stones (2019)**”)[3] Other dietary measures have been investigated in small metabolic studies, large cohort studies or multi-component dietary trials and their risk/benefit ratio is derived indirectly. Although the effect of dietary calcium on stone formation has not been evaluated independently in RCTs, there is evidence from epidemiological studies[4-6,7] and a randomized trial that strict dietary calcium restriction should be avoided and **patients should be counseled to consume the recommended daily allowance of calcium** (1000 mg daily for women < 50 years and men <70 years, 1200 mg daily for women >50 years and men >70 years)[3,8,9] **Higher sodium intake enhances urinary calcium excretion**, and limitation of sodium intake to ≤100 mEq daily is recommended for hypercalciuric stone formers.[8,10]

Consumption of foods high in oxalate (beets, nuts, spinach, potatoes, tea, chocolate) can increase urinary oxalate and raise urinary

saturation of calcium oxalate; consequently, oxalate-containing foods should be consumed in moderation[9]. **Calcium intake modulates urinary oxalate excretion by binding oxalate in the intestine**; as such, dietary calcium restriction leads to increased urinary oxalate and should be avoided[10]. **Animal protein** (**red meat**, **fish**, **poultry**, **pork**) **confers an acid load that can reduce urinary citrate excretion and also provides a purine load that increases urinary uric acid**, both of which increase stone risk. On the other hand, **fruits and vegetables provide alkali**, which enhances urinary citrate excretion and increases urinary inhibitory activity.[9] Additionally, a recent cohort study suggests that increases in urine volume, citrate, and GI alkali absorption, as well as a decrease in dietary acid load, allow for an clinically meaningful increase in urine pH[11]. The AUA guidelines recommend limited dietary animal protein for all stone formers and increasing intake of fruits and vegetables for patients with calcium stones[3]. In an attempt to augment typical dietary changes, a number of studies have evaluated the benefit of various citrate and/or alkali-containing beverages, including lemonade, orange juice, and certain carbonated beverages, with some success[12,13,14]. Importantly, while these liquids enable an increase in fluid intake, they may also contain a large amount of sugar, which should be factored into their utility.

Of note, there are numerous over-the-counter supplements that attempt to provide similar urinary alkalinization; research is currently ongoing to better understand the possible therapeutic benefit of these non-prescription treatment options[15,16]. These supplements include everything from non-prescription potassium citrate formulations (BulkSupplements, NOW Potassium Citrate) and other alkalinizing agents (Litholyte®, a mixture of potassium citrate, magnesium citrate, and sodium bicarbonate) to combination treatments that blend citrate with vitamin B6 and magnesium (e.g. TheraLithXR®, StoneStop™, KSPTabs, Kidney C.O.P.®, Lithobalance™, and Moonstone Stone Stopper). In addition to these alkalinization-focused supplements, there are other homeopathic treatments for stone prevention including products containing *Phyllanthus niruri* (Chanca Piedra), a plant used for stone prevention in various cultures; additional studies are required to support the use of this in urolithiasis.

While a number of studies and reviews have looked at the effects of other trace minerals (e.g. iron, copper, zinc, manganese, magnesium), the overall results are mixed. While magnesium supplementation has not been shown to decrease stone formation risk, zinc appears to have both positive and negative associations across different studies[17,18,19]. A recent study suggests higher copper levels may be associated with stone episodes, while manganese may be protective[17].

2.2 Pharmacologic Therapy

A number of medications have been demonstrated to reduce the likelihood of stone recurrence in recurrent stone formers by promoting a more favorable urinary milieu[9].

2.2.1 Thiazides

Rationale: Thiazide diuretics promote net calcium reabsorption directly in the distal renal tubule and indirectly by way of extracellular volume depletion in the proximal renal tubule.

Outcomes: A number of RCTs have shown a benefit of thiazide diuretics in reducing rates of stone recurrence in calcium stone formers[20,21]. **Thiazide diuretics reduce urinary calcium through action directly on the distal renal tubule and indirectly at the proximal renal tubule**. Although the benefit of therapy is not limited to hypercalciuric stone formers, as some of the trials applied the drugs to recurrent stone formers regardless of metabolic background, **its use has primarily been directed at hypercalciuric calcium stone formers**[21,22]. The AUA guidelines for the Medical Management of Kidney Stones recommend initiation of thiazides for patients with elevated 24 hour urine calcium and recurrent calcium stones[3]. The use of hydrochlorothiazide, chlorthalidone and indapamide (a thiazide-like diuretic) have been shown to reduce rates of stone recurrence in RCTs (**Table 1**). Additionally, treatment with thiazides has been shown to improve health-related quality of life.[23]

Adverse Effects: Thiazide use may be accompanied by **hypokalemia**, **hyperglycemia**, **hyperuricemia**, **dyslipidemia** and **hypocitraturia**, and therefore monitoring of these levels is indicated.[24] Long term use of thiazides solely for the prevention of kidney stones has not been found to increase the risk of developing diabetes mellitus[25]. To prevent thiazide-induced hypokalemia and hypocitraturia, potassium supplementation is recommended. Potassium citrate has the advantage of enhancing urinary citrate and further reducing the risk of stone formation.

Table 1: Urolithiasis Pharmacotherapy

Agent	Trade Names	MOA	Pathophysiologic Effect	Typical Dose	Adverse Effects
Thiazides/thiazide-like diuretics (hydrochlorothiazide, chlorthalidone, indapamide)	Microzide/ Hydrodiuril; Thalitone; Lozol	↑'s calcium reabsorption in distal renal tubule (direct mxn) and through extracellular volume depletion in the proximal tubule (indirect mxn)	↓ in urinary calcium	HCTZ 25 mg BID; chlorthalidone 25-50 mg q day; indapamide 1.25-2.5 mg q day	Hypokalemia, hyperglycemia, dyslipidemia, hyperuricemia
Potassium citrate	Urocit K	Binds to ionized calcium; inhibits calcium oxalate and calcium phosphate crystallization	↓ in urinary ionized calcium; ↑ in urinary citrate and pH	15-20 mEq BID	GI symptoms (nausea, heartburn, loose stools)
Allopurinol	Zyloprim	Inhibits xanthine oxidase	↓ in serum and urinary uric acid	300 mg q day	Elevation in liver enzymes, rash (Stevens-Johnson syndrome)
Acetohydroxamic acid	Lithostat	Inhibits urease	↓ in urine pH and urinary urea	250 mg TID	Nausea, headache, tremor, anemia, GI symptoms, DVT
Alpha mercaptopropionyl glycine	Thiola	Disulfide exchange	↓ in urinary cystine	Titrate to effect and absence of side effects	Hematologic abnormalities (anemia, pancytopenia), proteinuria, loss of taste, anemia, rash

2.2.2 Potassium Citrate and Alkalinizing agents

Rationale: Potassium citrate therapy provides an alkali load that promotes citraturia. Increased urinary citrate increases urinary inhibitory activity by complexing urinary calcium, thereby reducing ionized calcium, and by inhibiting calcium oxalate and calcium phosphate crystal formation.[20,21,26] In dRTA patients **treatment with potassium citrate therapy corrects the metabolic acidosis**, **thereby normalizing serum potassium**, **increasing urinary citrate and reducing the rate of stone formation**.[25,26,27] Some patients with type I RTA and hypercalciuria additionally benefit from a thiazide diuretic to reduce urinary calcium if hypercalciuria fails to resolve with correction of the underlying metabolic acidosis. In addition to potassium citrate, alternative alkalinizing agents have been looked at in terms of efficacy for impacting 24 hour urine parameters. Both potassium bicarbonate and sodium bicarbonate demonstrated similar improvements in urinary pH and urinary citrate in patients with hypocitraturia or low urine pH.[28] For patients with renal insufficiency or for those who cannot tolerate or afford potassium citrate, these medications are viable alternatives. As noted above in Section 2.1, multiple over-the-counter supplements are available for patients who cannot tolerate standard urinary alkalinization options, although additional studies are needed to assess equivalence to prescription treatment.

Outcomes: **Potassium citrate therapy has been shown to reduce the rate of recurrent calcium stone formation in hypocitraturic stone formers**[20,21,22,26] and may additionally be beneficial in unselected stone formers.[3] Additionally, treatment with potassium citrate has been shown to improve health-related quality of life.[23]

Adverse Effects: The most common adverse effects associated with potassium citrate therapy are gastrointestinal (nausea, vomiting, abdominal pain) which occur in 3-17% of patients; taking the medication with a meal may avert these effects. Additionally, potassium levels need to be monitored in patients with CKD to avoid possible hyperkalemia. Due to difficulties with drug tolerance and affordability, some over-the-counter dietary supplements are becoming more commonly recommended as an alternative to potassium citrate.[29] Sodium bicarbonate administration can increase blood pressure and decrease bone mineral retention. Importantly for kidney stone patients, it has a hypercalciuric effect that can be counterproductive.[30]

2.2.3 Allopurinol

Rationale: Allopurinol is a xanthine oxidase inhibitor that reduces serum and urinary uric acid. Administration of allopurinol is **reserved for recurrent**, **hyperuricosuric**, **calcium oxalate stone formers** who are unable to reduce urinary uric acid through dietary means (lowering animal protein intake).[22]

Outcomes: Allopurinol has been shown in a single RCT to reduce stone recurrence rates specifically in **hyperuricosuric**, **recurrent**, **calcium oxalate** stone formers.[31]

Adverse Effects: Allopurinol is well tolerated. However, liver enzymes should be monitored during treatment because of the potential for elevation of serum transaminases. **Allopurinol has been associated with the occurrence of Stevens-Johnson syndrome**.

2.2.4 Corticosteroids

Rationale: Sarcoidosis is associated with hypercalcemia, hypercalciuria and calcium stones.

Outcomes: Administration of corticosteroids suppresses the production of 1,25 di-hydroxy vitamin D by the granuloma and reduces serum and urinary calcium.

Adverse Effects: Chronic corticosteroid use may be associated with osteoporosis, weight gain, ulcers, gastrointestinal bleeding, insomnia, hyperglycemia and aseptic necrosis of the hip, depending on the dose and duration of use.

2.2.5 Combination Therapy in Special Circumstances

Hyperoxaluria deserves special mention because of the need for combination therapy in some cases. Although dietary hyperoxaluria may be adequately managed with dietary oxalate restriction and normal calcium intake, **enteric hyperoxaluria requires liberal calcium intake and in some cases calcium supplementation** (**taken with meals to reduce intestinal oxalate absorption**), **potassium citrate as well as oxalate and fat restriction**. A liquid formulation of potassium citrate is recommended in patients with bowel disease or in those with bowel resection, as extended release tablets are ineffective in the setting of rapid intestinal transit associated with chronic diarrhea.[22]

Patients with **primary hyperoxaluria (PH)** may benefit from administration of **pyridoxine** (**vitamin B6**), as pyridoxine is a co-factor in the process that diverts the conversion of glyoxalate away from oxalate.[22] Despite suggestions for pyridoxine use in patients with hyperoxaluria due to other causes, a large cohort study showed no difference in rates of incident stones in individuals without PH.[32] Another potential treatment for PH is altering the gut biome with the oxalate-metabolizing bacterium *Oxalobacter formigenes*, but results of clinical trials have been disappointing.[33] **Potassium citrate** therapy is additionally used to lower urinary saturation of calcium oxalate in patients with primary hyperoxaluria.

2.2.6 Novel Therapies

Hyperoxaluria has become a novel pharmacologic target through a number of different prescription and over-the-counter oral treatments. Through utilization of RNA interference, a novel pharmacologic treatment lumasiran (given subcutaneously) has been shown to reduce oxalate excretion in patients with PH Type 1 and is currently FDA approved[34]. By utilizing enzymes derived from Oxalobacter, oral administration has been shown to decrease plasma and urine oxalate levels, although trials are still ongoing[35].

2.2.7 Surgery

Patients diagnosed with **primary hyperparathyroidism** due to a **parathyroid adenoma** are best served with **parathyroidectomy**. Imaging studies consisting of a thyroid ultrasound and nuclear scan can localize the involved parathyroid gland and facilitate directed parathyroidectomy.

3. Uric Acid Stones

3.1 Diet Therapy

There are no RCTs assessing the effect of dietary or pharmacologic therapy for the treatment of patients with uric acid stones. Most patients with uric acid stones have normal urinary uric acid; consequently, restriction of dietary animal protein intake is limited to those patients with hyperuricosuria. High fluid intake is recommended for uric acid stone formers, as in all stone formers, to reduce urinary saturation of urinary uric acid[36]. Of note, as metabolic syndrome is a common cause of uric acid stones, general dietary and lifestyle modifications may lessen the magnitude of metabolic syndrome and subsequently the resultant uric acid stone risk.

3.2 Pharmacologic Therapy

3.2.1 Potassium Citrate

Rationale: The most common pathophysiologic abnormality in idiopathic uric acid stone formers is low urine pH (<5.5). At low pH, most uric acid exits in a poorly soluble, undissociated form. **Increasing urine pH to 6.0-6.5 results in conversion of most uric acid into the more soluble, urate salt**.[36,37] Administration of alkali, most commonly as potassium citrate (30-60 mEq daily in divided doses), increases urine pH and reduces the risk of uric acid stone formation as well as potentially accomplishing dissolution of existing uric acid stones. Of note, obese patients may require more frequent dose adjustments (increases) when treated with potassium citrate for low urine pH[34]. For patients who are unable to tolerate potassium citrate or who have hyperkalemia or kidney disease, the use of sodium alkali (sodium bicarbonate or sodium citrate/citric acid) can be used.

Outcomes: Although no published trials have demonstrated reduced uric acid stone recurrence rates with the use of potassium citrate therapy, its efficacy is widely accepted based on its mechanism of action as well as widespread clinical experience[3].

Adverse Effects: The most common adverse effects associated with potassium citrate therapy are gastrointestinal (nausea, vomiting, abdominal pain), which occur in 3-17% of patients; taking the mediation with a meal may avert these effects.

3.2.2 Allopurinol

Rationale: When urine pH is ≥6.0, total uric acid concentration must exceed 1000 mg/L to exceed solubility limits. As such, **the use of uric acid lowering drugs is rarely necessary in the treatment of idiopathic uric acid nephrolithiasis**.[36] However, patients with increased cell turnover, from myeloproliferative disorders or hemolytic anemia, or those with monogenic enzymatic disorders of uric acid metabolism such as **Lesch-Nyhan Syndrome** or **phosphoribosylpyrophosphate synthase overactivity**, demonstrate significantly increased rates of uric acid production and subsequent hyperuricemia and hyperuricosuria. For these patients, administration of a xanthine oxidase inhibitor, **allopurinol** or alternatively **feboxostat** can lower urinary uric acid, although efficacy of these drugs in preventing stone formation has not been evaluated in clinical trials.

Adverse Effects: Allopurinol and febuxostat are generally well tolerated. However, liver enzymes should be monitored during treatment because of the potential for elevation of serum transaminases. **Although rash is a potential side effect of both drugs**, **allopurinol has been associated with the occurrence of Stevens-Johnson syndrome**.

4. Struvite Stones

4.1 Diet Therapy

Dietary measures, namely low calcium and low phosphorus intake, advocated for the management of stuvite stones, have met with limited success, and there is no high level evidence to support these measures[39]. High fluid intake, as recommended for other stone types, has the potential to lower urinary saturation of magnesium ammonium phosphate and reduce the likelihood of struvite stone formation, although there are no trials to validate this approach.

4.2 Pharmacologic Therapy

Rationale: Urease inhibitors prevent urealysis, thereby preventing the increased production of ammonium and alkaline urine that is

associated with urease-producing bacteria.

Outcomes: **Acetohydroxaminic acid** is an irreversible urease inhibitor that has been shown in RCTs to reduce urine pH and ammonia levels and to result in stone dissolution.[8,39]

Adverse Effects: A high side effect profile resulted in the need for cessation or dose reduction of the medication in a high percentage of patients (22-62%) in these trials.[21,39] Side effects include headaches (30%), nausea, tremors, gastrointestinal symptoms (20-25%), anemia (15%), hair loss, and superficial thrombophlebitis or DVT.

5. Cystine Stones

5.1 Diet Therapy

Rationale: The goal of treatment in patients with cystinuria is to increase cystine solubility and decrease cystine concentration. Maintaining a high fluid intake will lower cystine concentration and reduce the likelihood of stone formation. **The limit of solubility of cystine is approximately 250 mg/L**, and for patients with mild cystinuria, increasing urine volume may be sufficient to prevent cystine stone formation (a fluid intake that produces a urine volume of >3 L daily is recommended). **Lower sodium intake has been shown to reduce cystine excretion**, thereby decreasing cystine concentration.[21,40] Likewise, avoidance of a high animal protein intake limits cystine substrate (methionine) and prevents low urine pH associated with the acid load.[24]

5.2 Pharmacologic Therapy

5.2.1 Potassium Citrate

Rationale: Cystine solubility is highly dependent on urine pH and significantly increases above pH 7.5. Although most cystinurics have relatively high urine pH, **increasing pH to 7-7.5 can reduce cystine solubility and risk of cystine stone formation**.[3]

Outcomes: The use of potassium citrate will raise urine pH and increase cystine solubility.[20,36,37] No clinical trials have assessed the isolated effect of potassium citrate therapy on cystine stone recurrence rates.

Adverse Effects: The most common adverse effects associated with potassium citrate therapy are gastrointestinal (nausea, vomiting, abdominal pain) which occur in 3-17% of patients; taking the mediation with a meal may avert these effects.

5.2.2 Cystine-Binding Thiol Drug

Rationale: For patients in whom high fluid intake and urinary alkalinization is insufficient to control cystine stone formation, the addition of a cystine-binding thiol drug (**alpha mercaptopropionyl glycine or tiopronin**) **promotes a disulfide exchange that converts the poorly soluble cystine-dimer into the more soluble cysteine monomer-thiol complex**.[3,21,40,41] The drug is titrated to reduce cystine concentration and urinary cystine supersaturation.

Outcomes: No randomized trials have evaluated the efficacy of tiopronin in reducing recurrence rates for cystine stones. However, case control studies have demonstrated a 78-94% reduction in stone formation rates in recurrent cystine stone formers.[41]

Adverse Effects: Side effects include gastrointestinal effects (17%), fatigue, rash, loss of taste (4%), renal complications including proteinuria (5%) and hematologic effects (4%). Monitoring of blood and urine for complete blood count, liver enzymes and 24-hour urinary protein or urine protein-to-creatinine ratio should accompany the initiation of therapy and any dosage escalations.

6. Patient Follow-Up

Stone formers managed with diet and drug therapy should be periodically monitored with imaging studies to identify stone growth or recurrence and with 24-hour urine analyses of stone risk factors to monitor response to therapy. The frequency of imaging and urine collections should be tailored to the aggressiveness of the disease, but generally should be assessed within 6 months of initiation of therapy. If medications are prescribed, appropriate monitoring of blood tests is required to assess for potential adverse effects.

7. Podcasts

NIDDK Urologic Diseases In America Report - Urinary Stone Disease

AUAUniversity Podcast Series: Episode No. 111: Urolithiasis: Metabolic Evaluation and Medical Management

AUA2021 John K. Lattimer Lecture-Kidney Stones: Is Prevention possible? (Jan 12, 2022)

Webinar: Surgical & Medical Management of Stones Guidelines Update: A Case-Based Approach (2020)

8. Other Links

AUA Position Statement on Opioids

Rationale and Strategies for Reducing Urologic Post-Operative Opioid Prescribing (2021)

UrologyHealth.org Pain Management Fact Sheet

Opioid Stewardship in Urology: Quality Improvement Summit 2018

Presentations

Medical Stone Disease Management Presentation 1

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