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Practical Approach to Metabolic Evaluation and Treatment of the Recurrent Stone Patient

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ABSTRACT

Although significant progress has been made during the last 3 decades in the minimally invasive surgical management of stone disease, the medical prevention of urolithiasis still remains challenging as much less progress has been achieved during the same time period. The purpose of this article is to provide the practicing urologist with practical guidelines for the metabolic evaluation and management of the recurrent stone patient. The recommendations are based on the latest available information regarding the pathogenesis, medical treatment options, and decision-making rationale when managing these challenging patients.

INTRODUCTION

Kidney stones affect approximately 15% of men and 7% of women in the United States, at an estimated cost of more than $2 billion per year.[1] Recent epidemiologic data suggest an increasing prevalence and incidence of kidney stones.[2] Modern lifestyle, obesity, and changing dietary habits are some of the factors that have been attributed to this increase in incidence.

The last 3 decades have seen significant advances in the surgical management of stone disease. Minimally invasive techniques including ureteroscopy, extracorporeal shock wave lithotripsy (SWL), and percutaneous nephrostolithotomy (PNL) have essentially replaced open stone surgery for the management of stone disease today. This has resulted, in part, in tempered interest in medical management for urinary calculi. Although most of these procedures are performed on an outpatient basis or during a short hospital stay, they have the potential for morbidity and long-term side effects. Additionally, repeat surgical treatment of recurrent stones in these patients is associated with increased financial burden. The prevention of stone formation by medical therapy has been shown to be cost-effective and is thus a logical extension of care.[3]

This article addresses patients who are at high risk of recurrent stone formation and provides guidelines for medical management.

EVALUATION OF A FIRST-TIME STONE FORMER

First-time stone formers have been estimated to have a 50% risk of recurrence within the subsequent 10 years. In a northern European population, a prospective evaluation noted an overall rate of recurrence of 53% within 8 years.[4]

The decision to investigate a first-time stone former remains controversial. Even though up to 50% of patients with a stone will have recurrence, more than 50% of all recurrent calcium stone formers have only 1 recurrence during their lives and only 10% of recurrent stone formers have more than 3 recurrences.[5] Although the remission rate of medical prophylaxis in calcium stone formers is 80%, recent data suggest that medical prevention in patients who form stones less frequently than once every 3 years may not be cost-effective.[6]

However, formation of a kidney stone may be the harbinger of a more severe underlying systemic disorder like renal tubular acidosis or hyperparathyroidism. All first-time stone formers should at least have a simplified evaluation (Table 1) to rule out any severe underlying systemic disorders that may cause recurrent calculi and extrarenal complications. A careful medical history is an important part of the evaluation as it may disclose any underlying dietary habits, medical conditions, and medications that contributed to the stone

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Table 1. Simplified Evaluation of Low-risk First-time Stone Formers

History
Predisposing medical conditions (as in Table 2)
Medications
Dietary history (fluid, calcium, oxalate, and purine intake)
Family history of stone disease
Occupational history (excessive fluid loss)
Blood Screen
Basic metabolic panel
Calcium
Parathyroid hormone
Uric acid
Urine
Urinalysis
Urine culture
Radiography
KUB (Kidney, ureter, and bladder)
Computed tomography (CT) scan or intravenous pyelography
Stone analysis

disease. A multichannel blood screen, including measurement of serum calcium, uric acid, and parathyroid hormone, should be obtained.

Proper identification of stone composition is fundamental in the risk evaluation. This is best done with either roentgen crystallography or infrared spectroscopy; it is recommended that all patients have at least 1 stone analyzed. Patients with uric acid, cystine, and infection stones have a high incidence of recurrent stone formation. The presence of uric acid or cystine suggests gouty diathesis or cystinuria, respectively. The finding of struvite, carbonate apatite, and magnesium ammonium phosphate suggests lithiasis of infection origin. Calcium stones are less useful diagnostically as they may occur in several conditions, including hypercalciuria, hyperuricosuria, enteric hyperoxaluria, hypocitraturia, and low urine volume.[7] However, it may be important to know if the calcium stone was mixed. A predominance of a hydroxyapatite component suggests renal tubular acidosis or primary hyperparathyroidism. There is also evidence to suggest that calcium oxalate stones with significant calcium phosphate or calcium oxalate dihydrate content have a higher recurrence rate than pure calcium oxalate monohydrate stones.[8]

An indirect approach for analysis using radiologic information and urinalysis can be applied. Radiologic evaluation can also rule out any anatomic abnormality associated with recurrent stone formation. Uric acid stones are radiolucent on KUB (kidney, ureter, and bladder) and radiopaque on computed tomography (CT) scan. Other stones such as ammonium urate, sodium urate, xanthine, and 2,8-hydroxyadenine have similar properties. Further clues in support of the uric acid diagnosis are a high serum level of urate, low urine pH, and the appearance of uric acid crystals in the urine. Struvite and cystine stones have a much lower radiographic density than calcium stones. Struvite stones are usually accompanied by a history of infection with urease producing bacteria and have a staghorn and multilayered morphology. The microscopic demonstration of coffin-like crystals is diagnostic for struvite. Cystine stones are associated with a positive nitroprusside test and flat hexagonal crystals on a urinalysis.

EVALUATION OF A HIGH-RISK OR RECURRENT STONE FORMER

A more extensive evaluation is warranted in individuals with recurrent nephrolithiasis as well as in patients at an increased risk for further stone formation (Table 2). This extensive evaluation was first described by Pak et al in 1980 and later modified by Levy et al in 1995.[9,10] The evaluation is completed in 2 outpatient visits (Table 3). It is preferable that patients discontinue any medication that may interfere with calcium, uric acid, or oxalate metabolism both before and during the evaluation. These include vitamins C and D, calcium supplements, antacids, diuretics, and acetazolamide.

The first visit includes all the testing done in the simplified evaluation as mentioned above, along with 2 24-hour urine specimens on a random diet. On the second visit, the patient brings in a third sample of 24-hour urine on a restricted diet (400 mg calcium and 100 mEq sodium/day). This dietary restriction is imposed to standardize the diagnostic tests, to better assess the cause of hypercalciuria, and to prepare for the "fast and calcium load" test. This test is performed on the morning of the second visit to identify the cause of hypercalciuria (absorptive versus resorptive versus renal leak). After overnight hydration with 600 ml of water, patients empty the bladder completely, discard this urine and drink 600 mL of distilled water. All urine produced during the next 2 hours is collected (fasting urine). A 1g oral calcium load is administered and urine is again collected over the next 4 hours (post-load urine). Both fasting and post-load samples are then assayed for calcium and creatinine.

This extensive evaluation can be time consuming, difficult, and expensive, since it requires multiple office visits and diet adherence. We do not routinely perform a calcium-loading test to differentiate between absorptive and renal leak hypercalciuria as the treatment of both

is similar. However, if the physician plans to prescribe a calcium-binding agent (sodium cellulose phosphate, orthophosphate), it may be beneficial to perform the test. Several authors have suggested more simplified protocols that do not include the calcium fast and loading tests and can be performed in 1 office visit. Some have recommended the collection of 2 separate 24-hour urine specimens, while others have advocated 1 24-hour random urine sample.[11] However, the adequacy of a single 24-hour urine evaluation has been challenged.[12]

THE 24-HOUR URINE EVALUATION

The urinary parameters typically assayed in the 24-hour urine evaluation include calcium, oxalate, citrate, total volume, sodium, magnesium, phosphate, potassium, pH, uric acid, and cystine. The normal values are shown in Table 4. Commercially available systems provide collection containers with chemical preservatives (obviating iced storage and refrigerated transport), and extrapolate 24-hour cumulative data from the submission of a small aliquot of the entire collection. The physician receives a report that provides a numeric and graphic display of the test results. Results display 24-hour excretion of urinary constituents along with supersaturation values for common urinary crystals. Urine supersaturation values have been shown to correlate well with the stone analysis and treatment outcomes.[13]

Using a 24-hour urine evaluation, patients with nephrolithiasis can be classified into 12 categories reflecting specific physiologic derangements (Table 5). However, 3% of all patients undergoing a full metabolic evaluation will demonstrate no abnormalities.[10] The potential reasons for having an error in 24-hour urine evaluation include error in collection technique, changes in the patient's diet, failure of specimen to accurately represent a "typical" day, and bacterial contamination.

Risk Factors for Recurrent Stone Disease

Multiple risk factors have been associated with recurrent nephrolithiasis. They are summarized in Table 2. Identifying a familial incidence of stones is useful. Geographic and occupational factors, medical conditions, and drugs are associated with recurrent stones. Certain stone types are also associated with recurrence. Anatomic factors associated with stasis are associated with recurrent stones as well.

Table 2. Risk Factors for Recurrent Nephrolithiasis

Demographic Factors
Male gender
Children
Family history of stone disease
Obesity
Geographic factors: residence in stone belt
Genetic Disorders
Cystinuria
Primary hyperoxaluria
Renal tubular acidosis
Xanthinuria
Stone Type
Uric acid stones
Cystine stones
Infection stones
Brushite stones
Bilateral stones
Staghorn calculi
Multiple stones
Recurrent calculi
Anatomic Factors
Medullary sponge kidney
Solitary kidney
Polycystic kidney disease
Nephrocalcinosis
UPJ (ureteropelvic junction) obstruction
Horseshoe kidney
Caliceal diverticulum
Hydronephrosis
Medical Diseases
Gastrointestinal disease (colitis, crohn's disease, malabsorption)
Hyperparathyroidism
Hyperthyroidism
Immobilization
Sarcoidosis
Osteoporosis
Gout
Medication-induced stones (indinavir, acetazolamide, triamterene, topiramate, ephedrine)

CONSERVATIVE MEASURES FOR PREVENTION OF RECURRENT NEPHROLITHIASIS

General recommendations should be made for all patients, regardless of the underlying cause of the stone disease and metabolic abnormality. After a few months of conservative management, patients should be re-evaluated. If the metabolic abnormalities have been corrected, conservative therapy can be continued. However, if the metabolic abnormalities persist, a more selective medical therapy should be instituted.

Fluid Intake

Low urinary volume is the most common abnormality (50% combined occurrence) seen on evaluation of

Table 3. Extensive Evaluation of High-risk, First-time, or Recurrent Stone Formers

	Blood				Urine							
	SMA	PTH	Calcium	Uric Acid	Calcium	Creatinine	Volume	Oxalate	Citrate	Volume	Oxalate	Cystine
Visit 1	X	X	X	X	X	X	X	X	X	X	X	X
Visit 2		X	X	X	X	X	X	X	X	X	X	
Fast					X	X						
Load					X	X						

SMA = Spinal muscular atrophy, PTH = Parathyroid hormone

Table 4. Normal Concentration of Urinary Constituents in 24-hour Urine Specimen

Urinary Constituent	24-hour Urinary Concentration
Calcium	<250 mg
Oxalate	<45 mg
Citrate	>320 mg
Magnesium	>60 mg
Phosphate	<1100 mg
Uric acid	<700 mg
Cystine	<250 mg
Urine volume	>2000 ml
pH	5.5-7.0

patients with nephrolithiasis.[10] Low urine volume can result from environmental factors such as inadequate fluid intake and dehydration, and also from malabsorptive bowel disorders that result in excessive fecal fluid losses. A consistently high fluid intake is the most effective means of reducing urinary supersaturation,[9] and failure to increase urine output is 1 of 3 strong predictors of relapse observed in a dedicated stone clinic.[14] A daily urine output >2 L is targeted. This can be accomplished by drinking more than 2.5 L/day, distributed throughout the day. At least 8-10 ounces of fluid should be ingested at bedtime, because urinary concentration usually occurs during sleep. A larger amount of fluids must be consumed if there is excessive sweating, diarrhea, or vomiting, and in patients whose urinary risk factors cannot be satisfactorily controlled with targeted nutrition therapy and/or pharmacologic therapy. In these patients, higher urine output—exceeding the 2 L/day cutoff—is necessary to maintain suitably low urinary supersaturation in the face of a high concentration of crystal promoters. Similarly, patients on medications known to increase risk for urinary stones should be advised to aim for a higher urine output.

Although water hardness can alter urinary parameters, it appears to have little effect on clinical outcomes. Carbonated water has been shown to protect against recurrent stone formation.[15] Epidemiologic studies have demonstrated that people who consumed high volumes of water, caffeinated or decaffeinated coffee, tea, beer, and wine have a decreased risk of nephrolithiasis.[16] In those with suboptimal dietary calcium intakes, consumption of caffeinated beverages should be limited to offset the modest hypercalciuric effect of caffeine.[17]

Animal Protein and Acid-base Balance of Diet

Dietary protein of animal origin provides an acid load to the body; increases urinary calcium, oxalate, and uric acid excretion; reduces citrate excretion and urinary pH; and increases probability of stone formation, even in normal subjects.[18-19] Animal protein restriction has been shown to decrease urinary calcium, phosphate, uric acid, and oxalate excretion.[20] Strategies to accomplish a reduction in animal protein intake include reduced portion sizes as well as reduced frequency of intake throughout the week.

In all stone-forming patients, we recommend a diet rich in fruits and vegetables (>5 servings/day). The potassium content of these foods will counteract the high acid load of the typical Western diet. Additionally, fruits and vegetables provide other nutrients and compounds that are associated with reduced stone risk,[21] including magnesium, phytate, fiber, citric acid, and many non-nutrient antioxidants.

Oxalate

Reduced oxalate intake is recommended for patients with hyperoxaluria. Foods known to cause a high urinary excretion of oxalate include tea (both green and black), nuts, chocolate and cocoa, spinach, beets, rhubarb, and soybeans and soy foods (eg, tofu).[22-23] Dietary fat intake should be reduced since fat may enhance oxalate absorption.[24] Vitamin C supplementation should be restricted to <1000 mg/day, if at all, as it is metabolized to oxalate.[25] Other nutritional supplements, such as cranberry tablets[26] and supplements containing concentrated plant derivatives may confer a high oxalate load and should be avoided. Recently, a study in calcium oxalate stone formers revealed that a subset developed hyperoxaluria as a result of a high meat intake.[27] The role of meat intake in the development of hyperoxaluria

Table 5. Classification of Patients Based on 24-hour Urine Evaluation

	Ca	P	PTH	Ca Fasting	Ca Load	Ca Restricted	UA	Ox	Cit	pH	Mg
Absorptive hypercalciuria type 1	N	N	N	N	↑	↑	N	N	N	N	N
Absorptive hypercalciuria type 2	N	N	N	N	↑	N	N	N	N	N	N
Renal hypercalciuria	N	N	↑	↑	↑	↑	N	N	N	N	N
Primary hyperparathyroidism	↑	↓	↑	↑	↑	↑	N	N	N	N	N
Unclassified hypercalciuria	N	N/↓	N	↑	↑	↑	N	N	N	N	N
Hyperuricosuria	N	N	N	N	N	N	↑	N	N	N	N
Enteric hyperoxaluria	N/↓	N/↓	N/↓	↓	↓	↓	↓	↑	↓	N	N
Hypocitraturia	N	N	N	N	N	N	N	N	↓	N	N
Renal tubular acidosis	N	N	N/↑	↑	N	N/↑	N	N	↓	N/↑	N
Hypomagnesiuria	N	N	N	N	N	N	N/↓	N	↓	N	↓
Gouty diathesis	N	N	N	N	N	N	N/↑	N	N/↓	↓	N
Infection lithiasis	N	N	N	N	N	N	N	N	↓	↑	N

Ca = Calcium, P = Phosphorus, PTH = Parathyroid hormone, UA = Urinalysis, Ox = Oxalate, Cit = Citrate, Mg = Magnesium.
N = Norrmal, ↑ = Increased, ↓ = Decreased.

warrants further attention.

Patients in whom hyperoxaluria cannot be controlled with dietary oxalate restriction and those with enteric hyperoxaluria should be managed by optimizing calcium intake. This can be done by ensuring they meet the adequate intake (AI) for calcium (between 1000-1200 mg/day for adults) and that it is distributed throughout the day with meals. Calcium acts by binding with oxalate in the gastrointestinal tract, forming an insoluble complex.

Calcium

In 1 prospective study, dietary calcium was inversely associated with the risk of kidney stones.[28] However, similar results were not seen with calcium supplementation.[29] Thus, a normal calcium intake from foods may be continued per the AI in almost all stone forming patients. A severe calcium restriction may increase oxalate absorption, thereby raising the supersaturation of calcium oxalate.[28-29] Calcium supplementation should be considered mainly in those whose dietary calcium is suboptimal and in enteric hyperoxaluria.[30]

Sodium

Dietary sodium has been shown to increase urinary calcium and pH and decrease citrate excretion. In a prospective, randomized study, Borghi and colleagues demonstrated that patients on a low-animal protein (52 g/day), low-sodium (1150 mg/day), and moderate-calcium (1200 mg/day) diet had a 50% reduction in stone events compared to those on a low-calcium (400 mg/day) diet.[31] Sodium intake should be restricted in all stone formers to <200 mEq (4600 mg)/day and even less in those with hypercalciuria. The Estimated Safe and Adequate Daily Dietary Intake range for sodium, determined to meet the needs of most healthy adults, is 1100-3300 mg/day. We believe in aggressive nutrition counseling to identify foods contributing most to sodium intake as sodium added to foods, either during cooking or at the table, accounts for far less than half of total sodium intake among Americans.[32] As sodium counteracts the ability of thiazide to control hypercalciuria, patients on this therapy especially should be counseled about sodium restriction.

Dietary Citrate

Specific fruits and fruit juices are rich sources of citric acid. The juice of lemons and limes are most concentrated with citric acid. Other fruit juices like orange, grapefruit, apple, and black currant juice contain appreciable citric acid as well and may also increase urinary citrate by providing an alkali load. However, orange, grapefruit, and black currant juice also raise urinary oxalate,[33-34] potentially offsetting the crystal inhibitory effect of the citric acid. Moreover, fruit juices generally provide ample carbohydrate and kilocalories, excessive intake of which should be avoided to maintain appropriate weight. In all patients forming calcium stones, we consider "lemonade therapy," consisting of 4 ozs/day of lemon or lime juice—either squeezed from the fresh fruit or in their concentrated forms—providing about 6 g of citric acid.[35] Alternatively, 32 ozs/day of a low-sugar, low-calorie lemonade or limeade product provides a similar amount of citric acid and has the added benefit of adding to total fluid intake, enhancing urine volume and reducing urinary supersaturation of crystalloids. This therapy does not replace the need for the alkali load delivered by ample fruits and vegetables.

Obesity

Obesity is an independent risk factor for urinary calculi, especially in women.[36] Obese patients are known to have

increased urinary excretion of sodium, calcium, sulfate, phosphate, oxalate, uric acid, and cystine, and also likely to have a more acidic urine, which may explain the increased incidence of uric acid calculi. Although obese patients should be advised to lose weight, certain weight-reduction diets should be avoided, particularly those such as the Atkins diet (which is low-carbohydrate, high-protein, and high-fat), which delivers a marked acid load to the kidney, further increasing the risk for stone formation and bone loss.[37]

SELECTIVE MEDICAL THERAPY FOR RECURRENT NEPHROLITHIASIS

If physiochemical aberrations are seen on the 24-hour urine evaluation, selective medical therapy can be instituted to correct these disturbances and prevent future stone formation. The commonly used medications, their indications, doses, and side effects are listed in Table 6.

Absorptive Hypercalciuria

No medical treatment is capable of correcting the basic abnormality of absorptive hypercalciuria type 1. Due to their cost-effectiveness and lower incidence of side effects, thiazides may be utilized as first-line therapy. Appropriate dietary restriction of calcium and oxalate, combined with thiazide and potassium citrate, can decrease the stone formation rate from 2.94 to 0.05 per year.[38] However, thiazides may have limited long-term effectiveness in this condition.[39] About 30%-35% of patients on thiazides will experience side effects, most of which are mild in nature. Although sodium cellulose phosphate can reduce the stone events by 78%,[40] it is associated with an extremely high rate of gastrointestinal distress. Its use should be restricted only to patients with severe absorptive hypercalciuria type 1 who are resistant to or intolerant of thiazide therapy.

Patients on this medication should be on a low-oxalate diet and supplemented with magnesium since magnesium depletion can occur due to the binding of magnesium and secondary hyperoxaluria can occur due to the binding of divalent cations in the intestinal tract.[40] Orthophosphates have been shown to inhibit 1,25-dihydroxyvitamin D synthesis,[41] decrease urinary calcium, and increase urinary citrate and phosphate.[42] However, there is no convincing evidence that this treatment restores normal intestinal calcium absorption in absorptive hypercalciuria type 1. It may be specifically indicated in absorptive hypercalciuria type 3 (vitamin D dependent). We do not routinely use sodium cellulose phosphate or orthophosphates for management of absorptive hypercalciuria in our metabolic stone clinic.

Patients with absorptive hypercalciuria type 2 can be managed conservatively with a normal calcium intake, high fiber diet, and high fluid intake. No specific drug treatment may be necessary since the physiologic defect is not as severe as in absorptive hypercalciuria type 1.

Renal Hypercalciuria

Thiazide diuretics are the treatment of choice for renal hypercalciuria as they correct the renal leak of calcium by augmenting calcium reabsorption in the distal tubule. With prolonged therapy, they cause extracellular volume depletion, which leads to stimulation of proximal tubular reabsorption of calcium. Long-term efficacy has been reported.[39] To avoid hypokalemia, patients on thiazides should be either supplemented with potassium citrate or started on a potassium-sparing diuretic like amiloride.

Resorptive Hypercalciuria

Resorptive hypercalciuria is an infrequent abnormality commonly associated with primary hyperparathyroidism. Primary hyperparathyroidism is the most common cause of hypercalcemia in an outpatient setting, and is associated with nephrolithiasis in <5% of affected individuals.[43] However, the diagnosis should be suspected in patients with nephrolithiasis and serum calcium levels >10.1 mg/dL. An assay for intact PTH can help distinguish patients with hyperparathyroidism from those with other causes of hypercalcemia. Parathyroidectomy is the treatment of choice for patients with primary hyperparathyroidism and nephrolithiasis.

Hyperuricosuric Calcium Oxalate Nephrolithiasis

Patients with hyperuricosuric calcium oxalate nephrolithiasis have monosodium urate-induced calcium oxalate crystallization. Hyperuricosuria associated with dietary purine overindulgence (purine gluttony) may be treated with dietary purine restriction. Patients with refractory disease can be treated with allopurinol or by urinary alkalanization with potassium citrate. In a double-blinded, prospective, randomized, controlled trial, allopurinol was shown to have a stone formation rate of 0.12 per patient per year compared to 0.26 in the placebo group.[44] Similarly, in another study, potassium citrate decreased stone formation from 1.55 to 0.38 per patient-year during a mean treatment period of 2.35 years.[45] Potassium citrate may be particularly useful in patients with mild to moderate hyperuricosuria (<800 mg/day), especially if hypocitraturia is also present.

Enteric Hyperoxaluria

Oral administration of large amounts of calcium or magnesium, taken with meals, should be recommended

Table 6. Common Medications Used for Medical Management of Urinary Calculi

Medication	Indications	Mechanism of Action	Dose	Side-effects
Thiazide diuretics Hydrochlorothiazide Chlorthalidone Indapamide	Hypercalciuria (all causes)	Stimulates calcium resorption in the distal nephron, prolonged therapy results in volume depletion and proximal tubular resorption of calcium	25 mg bid 25-50 mg daily 2.5 mg daily	Potassium wasting, muscle cramps, hyperuricosuria, intracellular acidosis, hypocitraturia, umasking of hyperparathyroidism, sexual dysfunction
Sodium cellulose phosphate	Severe absorptive hypercalciuria	Binds intestinal calcium and inhibits absorption	10-15 g/day divided with meals	Gastrointestinal distress, hyperoxaluria, hypomagnesemia, parathyroid hormone stimulation
Orthophosphate	Absorptive hypercalciuria	Inhibits vitamin D synthesis, impairs renal tubular reabsorption of calcium, binds calcium in the GI tract, increase urinary pyrophosphate	0.5 g tid	Similar to sodium cellulose phosphate, soft tissue calcification, brushite stone formation
Potassium citrate	Thiazide therapy, hypocitraturia, hyperuricosuria, gouty diathesis, cystinuria, enteric hyperoxaluria	Increases urinary citrate and pH, decreases urinary calcium. Corrects metabolic acidosis and supplements potassium	20 mEq bid-tid	Gastrointestinal upset, hyperkalemia
Allopurinol	Hyperuricosuria, gouty diathesis	Inhibits xanthine oxidase which converts xanthine to uric acid, thus decreasing serum and urine uric acid levels	300 mg daily	Rash, myalgia
Magnesium	Hypomagnesuria, adjunct to sodium cellulose phospate	Increases urinary magnesium and citrate, decreases urinary oxalate	0.5-1.0 g tid	Diarrhea
D-Penicillamine	Refractory cystinuria	Chelates cystine	250 mg daily (titrate to effect)	Nephrotic syndrome, dermatitis, pancytopenia
α-mercaptopropionyl glycine	Cystinuria	Chelates cystine	100 mg bid (titrate to effect)	Rash, asthenia, GI distress, rheumatologic complaints, mental status changes
Captopril	Cystinuria	Chelates cystine	25 mg bid-tid	Rash, cough, hypotension
Acetohydroxamic acid	Infection stones	Inhibits urease and reduces the urine saturation of struvite	250 mg bid-tid	Thromboembolism, tremor, headache, palpitations, GI distress, loss of taste, rash, alopecia, anemia, edema, abdominal pain

Bid=2 times per day; Tid=3 times per day; GI=gastrointestinal.

to prevent oxalate absorption from foods.[30] However, the concurrent rise in urinary calcium may occasionally obviate the beneficial effect of this therapy. Calcium citrate may be the optimum salt as it may raise urinary citrate excretion and urine pH.[46] Cholestyramine may be used as well because it binds bile salts in the bowel lumen, thereby decreasing the irritation of the colonic mucosa and the subsequent hyperabsorption of oxalate.[47] Magnesium gluconate should be given to patients with hypomagnesuria from chronic malabsorption because it is better tolerated than other magnesium products. Potassium citrate may correct the hypokalemia and metabolic acidosis associated with severe enteric hyperoxaluria. The liquid form of this medication should be used because it is better absorbed than the slow-release, wax matrix pills. A high fluid intake and an antidiarrheal agent may be necessary to ensure adequate urine volume. Dietary modifications include decreasing dietary fat and oxalate intake.

Hypocitraturic Calcium Oxalate Nephrolithiasis

Hypocitraturia is a common metabolic abnormality seen in 50% of patients with nephrolithiasis.[10] Hypocitraturia from distal renal tubular acidosis can be managed with potassium citrate therapy, which is capable of correcting the metabolic acidosis and hypokalemia and restoring normal urinary citrate levels in larger doses (up to 120 mEq/day). Potassium citrate can also be utilized for treatment of hypocitraturia due to chronic diarrheal states, thiazide therapy, and idiopathic hypocitraturia. Citrate supplementation with lemonade[35] and orange juice[33] has also been shown to increase urinary citrate excretion.

Hypomagnesiuric Calcium Nephrolithiasis

Hypomagnesiuric calcium nephrolithiasis is characterized by low urinary magnesium level, hypocitraturia, and low urine volume. Management includes increasing urinary magnesium levels with a magnesium salt and correction of the hypocitraturia with potassium citrate. Magnesium oxide and magnesium hydroxide are the mostly commonly used form of magnesium. Both are poorly absorbed and produce only a slight decrease in urinary oxalate and a modest increase in urinary magnesium. Urinary calcium and citrate levels are increased during magnesium oxide supplementation,[48] and thus urine saturation of calcium oxalate is not significantly lowered.

Older studies have shown that magnesium therapy is associated with decreased stone recurrence. Ettinger reported a double-blinded, randomized trial of potassium-magnesium citrate versus placebo and showed that 12.9% versus 63.6%, respectively, developed calculi.[49] However, this product is currently not available for use in the United States.

Gouty Diathesis

The most common metabolic abnormality in patients with uric-acid stones is not hyperuricosuria, but increased urinary acidity followed by low urinary volume. These patients should be managed with hydration and potassium citrate at a dose sufficient to maintain urine pH of approximately 6.5. Attempts at alkalinization to a pH higher than 7.0 should be avoided because it is associated with an increased risk of calcium phosphate stone formation. If the urinary uric acid excretion is persistently elevated or hyperuricemia exists, allopurinol (300 mg/day) should be added. Allopurinol is also preferred in patients with marked hyperuricosuria (>1000 mg/day).

Cystinuria

The goal of treatment of cystinuria is to keep the urine concentration of cystine below its solubility limit (200 to 300 mg/L). This can be done initially by increasing the urine volume by high fluid intake. Dietary manipulation with a low-methionine diet is rarely successful; however, dietary sodium should be restricted since it can lead to increased urinary cystine excretion.[50] Solubility of cystine can be increased to 400 mg/L by alkalinizing the urine with potassium citrate to a pH of 7.0. Further alkalinization up to the pKa of cystine (8.3) can be difficult and risky. Failure of these conservative measures requires therapy with chelating agents, which have a sulfhydryl group that forms a disulfide bond with cystine (cysteine). Due to better tolerability, α-mercaptopropionylglycine is preferred over D-penicillamine. Captopril can be used as well; however, there are no long-term clinical trials demonstrating its effectiveness.

Infection Stones

Complete surgical removal of all infected stone material is essential for the prevention of recurrent struvite stone formation. Long-standing effective control of infection can be achieved by preventing bladder infections, achieving adequate urine drainage, and appropriate use of suppressive antibiotics. Although acetohydroxamic acid can effectively inhibit urease, its use should be reserved for patients who are not candidates for surgery because of the risk of serious side effects.

SUMMARY

All urolithiasis patients should undergo a basic evalua-

tion in order to rule out treatable systemic causes. All recurrent stone formers should have a more extensive metabolic evaluation based on 24-hour urine samples. A significant number of patients may be able to normalize their urinary risk factors using conservative, nonspecific preventive measures. Selective medical therapy tailored to the individual patient's metabolic evaluation is effective in preventing new stone formation. However, continued compliance of patients and a commitment by the physician to provide long-term follow-up and care are vital.

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