Non-Calcium Renal Stones:
Diagnosis and Prophylaxis

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Urinary stone prevalence is estimated at 3%, affects up to 12% of the population and recurrence rates approach 55%. Renal deterioration is more likely from recurrent compared to solitary stone episodes. For most patients, the number and frequency of recurrent stones may be diminished effectively with dietary or pharmacologic therapy. Although the majority of stones are calcium oxalate or calcium phosphate, up to 25% of stones are composed of uric acid, struvite (magnesium ammonium phosphate), or cystine. In this article, the evaluation and management of metabolic stone disease and uric acid, struvite and cystine stones are addressed.

Derek's case

Derek is a 47-year-old diabetic male with a history of multiple uric acid stones. Metabolic testing showed a normal serum uric acid and renal function and 24 hour urine showed:

- Volume 1.7 liters
- pH 5.0
- Calcium 5.2 (normal),
- Sodium 225 mmol (high)
- Oxalate 340 umol (normal)
- Uric acid 4 mmol (normal)
- Citrate 1.1 mmol (low normal)

He was advised to increase his water intake, reduce his sodium intake and was given potassium citrate 20 mequiv b.i.d. On follow-up, his 24 hour urine showed:

- Volume 2.1 liters
- pH 6.0
- Sodium 170 mmol
- Citrate 3.4 mmol

He has not formed any new stones with 2 years follow-up.

For another case, look to page 98.

Uric acid stones

Metabolic evaluation

Certain elements of history raise the risk of recurrent uric acid stone disease:

- History of prior or recurrent stones
- Gout (15% to 20% of patients with gout have uric acid stones)
- Diabetes mellitus (increases both urine uric acid excretion and acidic urine which decreases uric acid solubility)
- Renal tubular acidosis (especially distal renal tubular acidosis)
- Metabolic syndrome
- Inflammatory bowel disease (decreases urine volume, increases metabolic acidosis)
- Obesity (associated with hyperuricosuria, hypocitraturia, and low urinary pH)
- Certain drugs (carbonic anhydrase inhibitors [topiramate], NSAIDs and probenecid [hyperuricosuric effect])

Table 1
Metabolic tests for uric acid stone formers

- Stone composition analysis
- Serum electrolytes, BUN, creatinine, calcium, phosphate, uric acid
- 24 hour urine for total volume, pH, uric acid, sodium, sulfate, citrate, calcium, oxalate, phosphate

BUN: Blood urea nitrogen

The typical metabolic laboratory evaluation includes (Table 1):

- Stone composition analysis
- 24 hour urine for urinary risk factors for uric acid stones
- Serum studies for risk factors for uric acid stones
- Dietary history

Common metabolic factors are shown in Table 2. Low urine volume increases urinary supersaturation. Citrate is excreted in urine and some citrate is metabolized to bicarbonate, so it alkalinizes the urine. Uric acid is more soluble at pH 6 compared to pH 5. Most uric acid stone formers have normal urinary uric acid excretion, but fail to mount a post-prandial alkaline tide. These gouty diathesis patients maintain a low urine pH. In contrast, hyperuricosuria is unusual. It may be caused by large dietary intake of purines. Dietary history is instructive and 24 hour urine shows urinary sulfate and uric acid are both elevated, usually associated with low pH. Some disease states may also be associated with hyperuricosuria, such as lymphoma or leukemia patients when they receive chemotherapy. The sudden lysis of millions of cells releases a large quantity of purines that may precipitate in the renal tubules.

Management

Low urine volume is reduced by instructing patients to increase fluid intake. Patients should be instructed to drink enough water to maintain their urine clear, or for (female) patients that cannot gauge their urine colour, drink at least eight glasses (240 ml each) of water daily. The types of fluids that are beneficial for uric acid stone patients include:

- Water is ideal (minimum 2 L q.d.)
- Tea and coffee intake associated with

Table 2
Metabolic patterns for uric acid stones

Stone risk	Test results	Relevant history
Dehydration	Low urine output (< 2 L q.d)	Inquire about fluid intake and fluid types
Acidic urine	Low urine pH	Inquire about purine intake, diabetes
Hypocitraturia	Low or low-normal urine citrate	Look for metabolic acidosis, renal tubular acidosis
Hypernatriuria	Increased urine sodium	Inquire about dietary sodium and salt intake
Hyperuricosuria	Increased urine uric acid, normal or increased serum uric acid	Inquire about gout, dietary intake for purine intake
Hyperuricemia	Increased serum uric acid, normal or increased urine uric acid	Inquire about gout

modest risk reduction

- Beer and wine intake associated with moderate risk reduction (discretion advised)
- Orange juice increases urine citrate and pH, both factors are beneficial for uric acid stone formers. However, the large amount of orange juice required poses a sugar load, which may be problematic, particularly for diabetics

The types of fluid that increase the risk of uric acid stone formation include:

- Grapefruit juice, lowers urine pH
- Cranberry juice, lowers urine pH
- Soft drinks (high sodium content increases monosodium urate formation)
- Lemonade likely is detrimental (it may be beneficial for calcium stones). The citrate effect comes in the form of H+ citrate, so that the added H+ load decreases urine pH

Hypocitraturia is treated with potassium citrate. Even in the absence of hypocitraturia, potassium citrate therapy is effective for uric acid stone formers as the renal metabolism of citrate to bicarbonate will increase urine pH (Derek's case). Hyperuricosuria increases risk for calcium oxalate and uric acid stones. Gout coexists in 20% of patients and should be treated with allopurinol. However, 80% of uric acid stone patients do not have gout but rather have gouty diathesis (low urine pH). For patients with large dietary intake of purines, counselling should focus on reduction of dietary sodium and purines. For lymphoma or leukemia patients undergoing chemotherapy, most regimens incorporate copious IV fluids, diuresis and urinary alkalinization.

Follow-up of uric acid stone patients includes serial imaging studies with either renal ultrasound or CT scan. Pure uric acid stones are radiolucent on plain radiographs, whereas uric acid stones appear on ultrasonography or CT scan. Pure uric acid stones may also be treated with oral dissolution therapy using alkali therapy (potassium citrate or bicarbonate).

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Miguel's Case

Miguel is a 62-year-old retired high school teacher, who says he has passed at least 125 cystine stones over the past 45 years. He presented with a 3.2 cm left renal stone requiring percutaneous nephrolithotomy. Stone composition analysis showed cystine. His 24 hour urine volume was 2.2 L and his cystine levels were >1,200 mg q.d. He was instructed to increase his water intake, potassium citrate and started on α-mercaptopropionylglycine (tiopronin) 300 mg q.d., titrated eventually up to 900 mg q.d.

On follow-up, his urine volume was > 3.5 liters per day and cystine levels were 274 mg per day. He has not formed any new stones with 3 years follow-up.

Struvite stones

Struvite stones are caused by urinary infections with urease producing organisms, the most common pathogen being *Proteus mirabilis* and less common pathogens being *Klebsiella*, *Pseudomonas* or *Enterobacter* (*E. Coli* does not produce urease.) Urease hydrolyzes each mole of (soluble) urea into two moles of (relatively insoluble) ammonium (NH_4^+), a process that requires free two H^+ to produce two NH_4^+ (from each mole of urea), yielding two OH^- from water, making urine more alkaline. Phosphate precipitates at alkaline pH, compounding the problem by yielding magnesium ammonium phosphate. The bacteria remain within the stone (where antibiotics penetrate poorly) and continue to produce urease and cleave urea, so this process may accelerate and form large, staghorn stones. Stone prophylaxis here requires complete surgical clearance of the struvite stone and appropriate antibiotics to eradicate the pathogen. No metabolic studies are required. Patients should be followed with urine cultures to verify that their urine remains free of urease-producing pathogens and also followed with serial imaging studies to verify they remain stone-free.

Cystine stones

Cystinuria is a homozygous recessive disease of renal tubular transport of cystine, producing excess urinary cystine. Cystine stones account for 1% of all stone formers. However, cystinurics tend to form recurrent stones and often form their first of many stones during teenage years. Cystine is a dibasic amino acid (cysteine-S-S-cysteine). There are no known inhibitors of cystine. Cystine is more soluble at a pH of nine and higher compared to lower pH, but it is practically impossible to achieve this high urine pH by oral alkali (and not without risk of calcium phosphate stone formation). Stone composition analysis demonstrates cystine which virtually cinches the diagnosis of cystinuria. Confirmation of cystinuria is obtained by qualitative or quantitative measure of 24 hour urine cystine.

Effective prophylaxis includes:

- increased fluid intake,
- potassium citrate and
- use of thiol medications that break the cysteine-cysteine disulfide bond to form a thiol-sulfhydryl exchange with cystine, producing a more soluble drug-cysteine complex.

These medications are titrated to reduce urine citrate to < 250 mg q.d. (Miguel's case):

- α-mercaptopropionylglycine (α-MPG, or tiopronin) is the preferred therapy
- D-penicillamine, 50% discontinuation rate due to side effects Dx

For references, please contatct **diagnosis@sta.ca**.