Kidney Stones: Diagnostic and Treatment Strategies

ABSTRACT: In patients with stone disease, multiple risk factors are often present, including high concentrations of crystalloids that exceed supersaturation, lack of inhibitors of stone formation, or excess promoter substances. You can best determine the type of stone by retrieving and analyzing it. If the stone cannot be recovered, consider clinical features, urinalysis results, and radiologic findings. The first line of treatment for any stone former is high fluid intake to increase urine volume. Thiazides are indicated in calcium stone formers with hypercalciuria, hypertension, or osteoporosis, but they may be beneficial in the absence of these conditions. Metabolic syndrome is associated with nephrolithiasis, and diabetes may be a factor in the development of uric acid stones. The long-term treatment goal is to prevent future stone formation and growth of existing stones. Prevention is preferable to repeated urological procedures, even though the latter are less invasive than open surgery.

Key words: kidney stones, nephrolithiasis

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Nephrolithiasis is a common problem in primary care practice. The lifetime risk is about 10% to 15% in the developed world, and the incidence is three times greater in men than in women. The relapse rate is 50% in 5 to 10 years and 75% in 20 years. Patients who have recurrent stones are at increased risk for future recurrence.

The tendency of nephrolithiasis to recur underscores the importance of prevention, which requires an understanding of the pathophysiology and risk factors associated with stone formation. These are described in this article; in addition, we provide an overview of treatment options.

CLINICAL FEATURES: RENAL COLIC

The most common clinical consequence of nephrolithiasis is stone passage with acute renal colic. Flank pain radiating to the groin, building to a maximum in half an hour and extreme in severity, is typical. Renal failure is unusual; it is associated with bilateral obstruction, staghorn stones, or some causes of nephrocalcinosis.

Gross or microscopic hematuria, dysuria or frequency, nausea, vomiting, and occasionally ileus can accompany stone passage. Stone passage occurs spontaneously in at least 90% of cases, usually within a day or two. The likelihood that ureteral stones will pass depends on the size and location of the stone. Stones that are smaller (less than 5 mm) and more distal are more likely to pass without intervention. Larger stones (more than 7 mm) are unlikely to pass.

Renal colic results not from the direct effect of the stone on adjacent urothelium but from stretching of the renal capsule due to obstruction. Both nonsteroidal anti-inflammatory drugs (NSAIDs), particularly ketorolac, and opiates have been used to relieve the pain of acute renal colic. NSAIDs have the potential advantage of decreasing urine output (because of afferent arteriolar constriction) and diminishing back pressure.

The patient should be adequately hydrated, but forcing fluids may worsen pain without facilitating stone passage; stones are passed by ureteral contractions and may pass even in anuric patients. If stone passage is delayed but expected (the stone is smaller than 5 mm), you may be able to facilitate stone passage with agents that diminish ureteral edema or spasm, including calcium channel blockers and alpha-adrenergic receptor agonists; tamsulosin may be more effective than nifedipine. If pain cannot be controlled by oral medications or if the patient is vomiting, parenteral analgesics and hospitalization may be required. Patients should be instructed to strain their urine for several days and bring in for analysis any stone that is retrieved.

DIAGNOSIS: RADILOGICAL IMAGING

In patients with suspected renal colic, non-contrast-enhanced helical CT is the modality of choice because...
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Table 1 – Radiologic procedures for the evaluation of kidney stones

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>KUB</td>
<td>Readily available; inexpensive; limited radiation; useful to follow stone growth</td>
<td>Limited sensitivity</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Readily available; no radiation exposure (eg, procedure of choice during pregnancy); high sensitivity for urinary obstruction; detects radiolucent stones</td>
<td>Moderately expensive; poor sensitivity for small stones</td>
</tr>
<tr>
<td>IVP</td>
<td>Useful in planning therapy and diagnosis of obstructing stones</td>
<td>Intravenous contrast required; misses nonobstructing stones; moderate x-ray exposure</td>
</tr>
<tr>
<td>CT scan</td>
<td>New gold standard; no intravenous contrast needed; high sensitivity and specificity; detects radiolucent stones; detects other causes of flank or abdominal pain</td>
<td>Expensive; moderate x-ray exposure</td>
</tr>
</tbody>
</table>

KUB, plain abdominal radiograph; IVP, intravenous pyelogram.

Three endourological techniques are currently available (Table 2):
- Percutaneous nephrostolithotomy (PNL).
- Rigid and flexible ureteroscopy (URS).
- Extracorporeal shock wave lithotripsy (ESWL).

These newer approaches have all but eliminated the need for open surgical procedures.

Shock wave lithotripsy employs high-energy shock waves produced by an electrical discharge in a fluid medium. It is the treatment of choice for uncomplicated small stones (less than 2 cm) in the upper urinary tract. ESWL requires that the distal
urinary tract be free of obstruction so that fragmented material can pass. Stents can be placed in patients in whom a large stone burden increases the risk of obstruction by pulverized material (Steinstrasse). ESWL is contraindicated in pregnant patients and in those with an obstruction or an aortic or renal artery aneurysm. In pregnant women, an obstructed stone can be managed with a retrograde stent until after delivery, when ESWL can be safely performed.

PNL is preferred when stones are large (more than 2 cm in diameter) or fill much of the collecting system (staghorn calculi), when anatomic abnormalities inhibit passage of pulverized material, or when stones are resistant to fracture with shock waves (cystine stones). Transurethral ureteroscopy can be used to remove small stones (less than 5 mm) with a basket or to pulverize larger stones (more than 5 mm) with direct contact fragmentation devices (eg, holmium laser lithotripsy). This technique is best suited for mid- and distal ureteral stones.

**PATHOPHYSIOLOGY OF STONE FORMATION**

Calcium stone formation begins with formation of calcium phosphate deposits (Randall plaques) on the external urothelial surface of the papilla. Hence, calcium oxalate stones typically have a small component of calcium phosphate (apatite or brushite). If small particles were not anchored to these plaques, they would simply wash into the urine. Stone formation requires that crystalloids be present in supersaturating concentrations; but even when this condition is met, stone formation may not occur in the presence of adequate concentrations of inhibitors, including citrate, magnesium, and macromolecules. On the other hand, some substances, such as uric acid and alkaline urine pH, act as promoters to facilitate stone formation at a given level of supersaturation.

Urinary saturation approximates the ratio of the concentration product (eg, of calcium oxalate) to its solubility in urine. At values greater than 1 (supersaturation), crystal formation is favored; values below 1 do not support stone formation and some crystals (uric acid, cystine) may even dissolve. Stone formation correlates with supersaturation values, and measuring supersaturation may be helpful, for example, in monitoring calcium phosphorus supersaturation in patients with stones who are receiving alkali therapy. Commercial laboratories offer urinary metabolic profiles that also include urinary saturation of calcium oxalate, calcium phosphate, and uric acid (see the Box).

**CLASSIFICATION OF KIDNEY STONES**

The most common types of kidney stones are listed in Table 3.

**CALCIUM OXALATE STONES**

Etiology. Calcium oxalate stone formation is favored by:

- High concentrations of crystalloids,
as occurs in hypercalciuria, hyperoxaluria, and low urine volume.

• Low concentrations of inhibitors, as in hypocitraturia.

• High concentrations of promoter substances, as in hyperuricosuria.

Low urine volume. Low urine volume increases crystalloid concentration and favors stone formation in all types of nephrolithiasis. Low urine volume may be due to hot climate or occupation, diarrheal disease or ileostomy, urological disease (incontinence or frequency) with tendency to limit fluid intake, or low intake due to social and cultural factors.

Hypercalciuria. In approximately 5% of patients with hypercalciuria, a specific cause is present, most commonly primary hyperparathyroidism but occasionally distal renal tubular acidosis (RTA), sarcoidosis, hyperthyroidism, vitamin A or D intoxication, excessive calcium ingestion, or prolonged immobilization. The remaining 95% of calcium stones are idiopathic.

Idiopathic hypercalciuria (IH) is identified in up to 50% of calcium stone formers. The serum calcium level is almost always normal. Hypercalciuria is defined as daily excretion of more than 300 mg in men or 250 mg in women or 4 mg/kg in either sex or in children. The etiology of idiopathic hypercalciuria involves one or more of the following events: enhanced intestinal calcium absorption, reduced renal tubular absorption, increased calcium mobilization from bone, and renal phosphate leak. Some have classified hypercalciuria according to mechanism, but in most cases there are multiple mechanisms and such classification is not required. For example, a substantial proportion of patients with IH have elevated circulating 1,25 dihydroxyvitamin D or a putative increase in vitamin D receptors, either of which could account for abnormalities of bone, intestinal, and renal calcium metabolism.

Several dietary factors exacerbate IH, including salt, protein, and refined carbohydrates. The most important is dietary sodium, which increases renal calcium excretion. Proximal tubular sodium reabsorption is reduced, as is the reabsorption of moieties handled in parallel with sodium, such as calcium. Another factor is dietary protein. Dietary animal protein exacerbates calciuria because it is an acid load and thereby inhibits renal tubular calcium absorption.

Hyperuricosuria. The usual upper limits of daily urine uric acid excretion, 800 mg (men) and 750 mg (women), are exceeded more often by calcium stone formers than by healthy persons. Hyperuricosuria contributes to calcium stones by enhancing calcium oxalate precipitation. Hyperuricosuria is almost invariably due to dietary purine excess and can be ameliorated by a low-purine (which is also low-protein) diet. However, only allopurinol (300 mg/d) has been shown to reduce calcium stone formation in patients with hyperuricosuric, normocalciuric calcium stone formation.

Hypocitraturia. Citrate inhibits stone formation, and hypocitraturia is present in about 10% to 40% of calcium stone formers. Citrate complexes calcium in a soluble form and prevents precipitation of calcium oxalate. Hypocitraturia is defined as daily excretion of more than 300 mg in men or 250 mg in women or 4 mg/kg in either sex or in children. The etiology of hypocitraturia involves one or more of the following events: enhanced intestinal calcium absorption, reduced renal tubular absorption, increased calcium mobilization from bone, and renal phosphate leak. Some have classified hypocitraturia according to mechanism, but in most cases there are multiple mechanisms and such classification is not required. For example, a substantial proportion of patients with IH have elevated circulating 1,25 dihydroxyvitamin D or a putative increase in vitamin D receptors, either of which could account for abnormalities of bone, intestinal, and renal calcium metabolism.
such as acidosis or hypokalemia, or, if hypocitraturia is idiopathic, induction of a mild metabolic alkalosis to increase urine citrate excretion.

**Hyperoxaluria.** Hyperoxaluria can cause calcium oxalate stones by increasing urinary saturation of calcium oxalate. Oxalate is an end product of metabolism that forms a poorly soluble complex with calcium. Normal excretion is 15 to 40 mg daily, with the bulk derived from endogenous synthesis. Hyperoxaluria may be result from increased synthesis, as in congenital enzyme deficiencies (primary hyperoxaluria types 1 and 2), which are associated with severe oxaluria (over 100 mg/d). It is controversial whether high-dose vitamin C increases oxalate synthesis in vivo, since vitamin C is excreted unchanged in the urine and breaks down to oxalate in vitro. Increased intestinal oxalate absorption can be due to a high-oxalate diet, intestinal malabsorption (enteric hyperoxaluria), or calcium restriction in patients with idiopathic hypercalciuria.

Enteric hyperoxaluria occurs particularly in Crohn’s disease and ileal bypass surgery; an intact colon is required. Increased luminal free fatty acids may promote oxalate hyperabsorption by binding to calcium, which otherwise would form poorly absorbed complexes with oxalate, and by increasing the permeability of colonic epithelium to oxalate. Treatment includes a low-oxalate and low-fat diet. Calcium carbonate supplements, 1.3 g three times a day with meals, and cholestyramine bind oxalate in the intestinal lumen. Because of malabsorption, there is no risk of hypercalciuria. A new treatment is provision of oxalate-metabolizing bacterial cultures (*Oxalobacter*).

**CALCIUM PHOSPHATE STONES**

Calcium phosphate (apatite or brushite) is often a minor component of calcium oxalate stones, but sometimes comprises more than 50% of stone material. Risk factors for predominant calcium phosphate stones are hypercalciuria and alkaline urine pH. Most commonly these stones are idiopathic, but such stones should increase suspicion for conditions that predispose to alkaline urine, including distal RTA and hyperparathyroidism or alkali treatment (eg, with potassium citrate).

Distal RTA is associated with hypercalciuria, hypocitraturia, and alkaline urine pH. Hypercalciuria is an early finding and tends to normalize with relatively small decrements of renal function. Hypocitraturia is profound (typically less than 100 mg/d). Hypocitraturia is corrected by alkali treatment; large amounts are required in distal RTA (1 to 3 mEq/kg/d). Urine citrate excretion increases with successful alkali therapy and is a guide to the adequacy of alkali treatment. However, correction of hypocitraturia must be balanced against increasing urine alkalinity, which increases stone risk. Measurement of supersaturation of urine with regard to calcium phosphate may assist in dosing of alkali in this difficult situation.

**URIC ACID STONES**

Uric acid stones result most commonly from persistently acid urine pH (80%) and, less often, from hyperuricosuria (20%). Uric acid is predominantly in the poorly soluble acid form at pH 5 and predominantly in the soluble urate form at pH 7; alkalinization effectively reduces uric acid concentration by over 90%. Excessive urinary uric acid is due, with rare exceptions, to dietary purine overconsumption. Persistently acid urine, caused by deficient renal ammoniagenesis, is a feature of gout and of idiopathic uric acid stones as well as diabetes mellitus and metabolic syndrome. Diabetic stone form-
ers have a 30% to 40% rate of uric acid stones compared with the 5% to 8% rate of uric acid nephrolithiasis in the general stone-forming population. We closely investigate idiopathic uric acid stone formers for diabetes and metabolic syndrome and sometimes detect previously undiagnosed cases. Chronic diarrheal disease (eg, inflammatory bowel disease) also causes uric acid stones because of persistently acid urine due to loss of alkali equivalents in the stool.

The goals of treatment of uric acid stones are the regression of preformed stones and the prevention of new ones. The available therapeutic tools include fluids, diet, alkali, and allopurinol. Urinary alkalinization is the best treatment for most patients with uric acid stones; it is more effective than allopurinol, which generally reduces uric acid excretion by about half. The target urine pH is 6 to 7 and can be monitored by 24-hour urine collection or, more conveniently, by self-testing with nitrazine indicator paper. Higher urine pH should be avoided because of the risk of calcium phosphate stones. Unlike calcium stones, uric acid stones dissolve during alkali therapy (if they are not secondarily calcified). A pure uric acid stone of 1 cm in diameter can dissolve within a week if urine pH is maintained at 7. Potassium citrate is preferred because sodium salts can increase excretion of sodium hydrogen urate, which may contribute to stone formation. Allopurinol can be added or substituted if urinary uric acid is excessive (over 800 to 1000 mg daily).

**INFECTION STONES**

Infection stones are composed of magnesium ammonium phosphate (struvite) and calcium phosphate (apatite or brushite). Infection stone is the most severe form of nephrolithiasis: it can cause progressive renal failure, urosepsis or perinephric abscess, intractable urinary tract infection, pain, and bleeding. Staghorn formation (stones extending from one calyx to another) is common (Figure 1).

Infection stones form only when the urinary tract is infected by a urea-splitting bacterium, usually a *Proteus* or *Providencia* species. The bacterial enzyme urease catalyzes the production of ammonia from urea. This makes the urine more alkaline, which favors precipitation of struvite and calcium phosphate. Anatomic abnormality of the urinary tract, including neurogenic bladder, chronic bladder catheterization and other instrumentation of the urinary tract, and prior stones of other types, as well as ileal loop urinary diversion, predispose to urease-positive urinary tract infection. Metabolic evaluation for underlying stone diathesis of other types should be undertaken in patients with infection stones.

The preferred treatment of infection stones is removal by endourological techniques. Large staghorns typically require combined PNL followed by ESWL, often followed by repeated PNL. Residual fragments are a nidus for intractable infection and recurrent stone formation. Antibiotic suppression is sometimes given for a 4-month course, but sterilization of the urine occurs in only 20% of cases; antibiotic suppression may be required indefinitely.

**CYSTINE STONES**

These stones develop in patients with cystinuria, an autosomal recessive disorder of proximal tubular amino acid transport. The diagnosis of cystine stones is typically made
from stone analysis; other factors that should raise suspicion include young age at presentation, mildly radiopaque stones, family history, and characteristic hexagonal crystals in the urinary sediment (Figure 2).

Drinking large amounts of fluid remains the mainstay of therapy. The solubility of cystine is 1 mM/L (250 mg/L). In patients with relatively low levels of cystinuria, high urine volume (4 L/d) may be sufficient to reduce the concentration of cystine below this threshold. Potassium citrate may be a useful adjunct because urine pH above 7.5 increases cystine solubility. Those with more severe cystinuria or in whom high urine volume cannot be achieved require penicillamine, tiopronin, or captopril, which react with cystine to form a soluble mixed cystine disulfide. These agents may achieve stone dissolution. Unfortunately, penicillamine and tiopronin have significant side effects, including dysgeusia, fever and myalgias, marrow depression, and nephrotic syndrome.

**EVALUATION OF THE PATIENT WITH KIDNEY STONES**

A complete history and metabolic evaluation are needed to optimize preventive measures in patients with nephrolithiasis.

**History.** While calcium stones remain the most common type in children, stone formation in a child should prompt a search for cystinuria or distal RTA. Stone onset in an older woman may reflect primary hyperparathyroidism. Chronic or recurrent urinary tract infection or neurogenic bladder (or both) suggest struvite stones. Be alert to a history of associated medical conditions such as primary hyperparathyroidism, sarcoidosis, gout, intestinal surgery, or inflammatory bowel disease. Ask about neck irradiation during childhood, which may have caused primary hyperparathyroidism. Heavy exercise, excessive sun exposure, and work in a hot environment may reduce urine output.

Find out what medications your patient has taken. Certain medications can predispose to stone formation, such as indinavir, sulfadiazine, acetazolamide, triamterene, and vitamins A and D. The importance of high-dose vitamin C is uncertain. Dietary history should include calcium intake: low calcium intake predisposes to oxaluria. Popular high-protein, weight-reducing diets predispose to stones by multiple mechanisms, including hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria.

**Metabolic evaluation.** We recommend a limited evaluation of calcium oxalate stones after a first episode and a full evaluation with recurrent episodes (Box). At least two 24-hour urine collections should be obtained while the patient maintains his or her usual diet and physical activity. A panel of tests, including saturation measurements, may be available from commercial laboratories (see the Box). We suggest waiting several months after the initial stone episode.

We obtain urine urea nitrogen in order to estimate protein intake and urine creatinine to assess completeness of urine collection. The normal rate of urinary creatinine excretion in patients under the age of 50 is 15 to 25 mg/kg lean body weight in men and 10 to 15 mg/kg lean body weight in women. Values substantially different from these values suggest over- or undercollection. If stone composition is unknown, qualitative or quantitative assessment of cystine excretion is advisable. Medications that could interfere with urinary determinations (eg, NSAIDs, diuretics, calcium supplements, antacids) should be avoided if possible.

**PREVENTION AND TREATMENT**

**Dietary treatment.** The first key point in therapy for any stone former is high fluid intake (Tables 4 and 5). We recommend a target of 80 oz daily to achieve urine output of 2 L. A systematic regimen is essential, either two 8-oz glasses of fluid every 4 hours while awake or a large-volume (1 quart) container twice a day plus fluids with meals. In general, patients do best drinking plain water, diet soda, or dilute apple juice. Wine and beer and, to a lesser extent, coffee and tea have been associated with decreased stone risk.

**Hypercalciuria.** Calcium restriction should not be instituted. Stone risk decreased progressively in one large study with increasing calcium servings from 0 to 5 daily. The

| Table 5 – Uric acid stones: urinary risk factors and treatment |
|---|---|---|
| **Risk factor** | **Causes** | **Treatment** |
| Low urine volume | Exercise, sweating, low fluid intake, bowel disease | Scheduled fluid intake: 16 oz q 4 hr while awake |
| Acid urine | Gout, chronic diarrheal state, metabolic syndrome or diabetes mellitus, idiopathic | Alkali (potassium citrate), dietary protein restriction |
| Hyperuricosuria | Excessive purine ingestion | Dietary purine restriction, allopurinol |
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**CLINICAL HIGHLIGHTS**

- Increase urine volume in all stone formers.
- In patients with stone disease, multiple risk factors are often present, including high concentrations of crystalloids that exceed supersaturation, lack of inhibitors of stone formation, or excess promoter substances.
- You can best determine the type of stone by retrieving and analyzing it. When we cannot recover a stone, we rely on clinical features, urinalysis, and radiologic findings.
- Thiazides are indicated in calcium stone formers with hypercalciuria, hypertension, or osteoporosis, but they may be beneficial in the absence of these conditions.
- Metabolic syndrome is associated with nephrolithiasis, and diabetes may be a factor in the development of uric acid stones.
- Your long-term treatment goal is to prevent future stone formation and growth of existing stones. Prevention is preferable to repeated urological procedures, even though the latter are less invasive than open surgery.

**Thiazide diuretics.** Thiazides are indicated in stone formers with hypercalciuria, hypertension, or osteoporosis. The usual starting dose of hydrochlorothiazide is 12.5 to 25 mg/d; chlorothalidone is recommended by some because of its longer half-life. Thiazides work by two mechanisms: first, by causing volume depletion and thereby increasing proximal tubular calcium absorption; second, by stimulating calcium reabsorption directly in the early distal convoluted tubule.

A low-salt diet is essential in order that extracellular fluid volume contraction be maintained. Hypokalemia must be avoided because it can cause hypocitraturia, a risk factor for stone pathogenesis. Therefore, we check serum potassium levels after initiating a thiazide and, if hypokalemia develops, potassium supplements (preferably as citrate) or amiloride can be administered. Thiazides have been of value in normocalciuric as well as hypercalciuric patients in controlled prospective trials.

**Potassium citrate.** Potassium citrate is indicated in hypocitraturia or in mixed calcium and uric acid stones, but controlled trials show efficacy regardless of the underlying metabolic abnormality. The target urine citrate is over 400 mg daily. Any alkali will raise urine citrate levels. We prefer potassium citrate 10 to 20 mEq three times daily with meals. Sodium citrate and sodium bicarbonate are less desirable because their sodium content tends to increase calciuria. Potassium citrate therapy is generally well tolerated, but 15% of patients experience significant gastrointestinal side effects, such as dyspepsia and diarrhea. A risk of potassium citrate is calcium phosphate stone formation due to alkaline urine pH. Potassium citrate should not be used in patients with hypercalciuria unless it is effectively treated. Monitoring urine calcium phosphate saturation may help in dosing of potassium citrate.

Regardless of the type of treatment you choose, you must obtain urine samples intermittently to monitor therapy, preferably within 2 months of a change of regimen. You can thus ensure that your patient is following your instructions about fluid intake and diet as well as medication.

**FOR MORE INFORMATION:**

mechanism of this paradoxical effect is probably hyperoxaluria during a low-calcium diet. Refined carbohydrates and possibly alcohol are calcicuric, and high dietary fiber intake is hypocalcicuric. An appropriate diet in patients with hypercalciuria includes moderate sodium (3 g/d), moderate protein (1 g/kg/d), and adequate calcium (3 servings per day). This diet was shown to be superior to a low-calcium diet in a prospective trial.

**Hyperoxaluria.** High oxalate-containing foods include black tea, beets, colas, spinach and other dark green leafy vegetables, rhubarb, nuts and seeds, chocolate, and meat. A low-oxalate diet has not been shown to reduce stone formation. Maintaining adequate dietary calcium will help to reduce oxalate absorption.

**Hypocitraturia.** Low-salt or low-protein diets increase urine citrate excretion, as do lemon juice and lemonade (2 L/d).

**Drug treatment.** If there is growth of existing stones or formation of new stones despite high fluid intake and dietary modification, or if metabolic activity of stone disease is marked, drug treatment is indicated.