CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will distinguish the various types of urine stones and enumerate measures to prevent their recurrence

PHILLIP M. HALL, MD
Department of Nephrology, Glickman Urological and Kidney Institute, Cleveland Clinic

Nephrolithiasis: Treatment, causes, and prevention

■ ABSTRACT

Factors that promote stone formation include low daily urine volumes; saturation of the urine with calcium, oxalate, calcium phosphate, uric acid, or cystine; acidic urine; and bacterial infection. The author identifies the mechanisms of stone formation and outlines management aimed at preventing recurrences.

■ KEY POINTS

During an acute stone event, medical management focuses on pain control. Hydration and certain drugs may help the stone to pass.

Most stones are composed of calcium oxalate or calcium phosphate. Less common are uric acid, magnesium ammonium phosphate, and cystine stones.

To prevent stones from recurring, patients who have had any type of stone should maintain an adequate fluid intake to keep the urine dilute.

Paradoxically, calcium restriction is not warranted for patients who have had calcium stones, and may even be harmful.

Alkalinization of the urine may help prevent recurrent uric acid stones and cystine stones.

K IDNEY STONES ARE NOT all the same, and neither are their causes (**TABLE 1**), treatment, and prevention. This paper reviews the diagnostic approach and pathophysiologic mechanisms for nephrolithiasis in order to provide a rationale for preventive management.

■ COMMON AND ON THE INCREASE

Nephrolithiasis is common, with a lifetime prevalence of 10% in men and 5% in women.[1,2] Studies have shown that the prevalence is increasing in the United States. In the second National Health and Nutrition Examination Survey (1988–1994), the prevalence in adults ages 20 to 74 was greater than in the 1976–1980 survey (5.2% vs 3.2%).[3] The increase was observed in whites but not in African Americans or Mexican Americans, was greater in men than in women, and was greater with age in each time period.

In addition, stones often recur, and each stone event can be associated with significant metabolic and intervention-related morbidity.

■ PRESENTATION: SEVERE COLIC

Most patients present with moderate to severe colic, caused by the stone entering the ureter. Stones in the proximal (upper) ureter cause pain in the flank or anterior upper abdomen. When the stone reaches the distal third of the ureter, pain is noted in the ipsilateral testicle or labia. A stone at the junction of the ureter and the bladder often causes dysuria, urgency, and frequency and may be mistaken for a lower urinary tract infection.

TABLE 1

Nephrolithiasis: Composition, frequency, causes

COMPOSITION	FREQUENCY	CAUSES AND MECHANISMS

Calcium oxalate or calcium phosphate	70%–80%	Hypercalciuria
		  High dietary sodium and protein intake
		  Hypercalcemia
		  Idiopathic
		  Chronic metabolic acidosis
		Low urine volume
		  Chronic dehydration, hot climate with increased
		    water loss
		Hyperuricosuria
		  High-purine, high-protein diet
		  Gout
		Hyperoxaluria
		  Low dietary calcium, high-oxalate diet,
		    genetic hyperoxaluria
		Low urine citrate
		  Chronic metabolic acidosis
		  Renal tubular acidosis
		  Inflammatory bowel disease
		  Idiopathic

Uric acid	10%–15%	Low urine pH, defect in renal ammonium secretion Chronic metabolic acidosis Hyperuricosuria Obesity, metabolic syndrome
Magnesium ammonium phosphate (struvite, infection-related)	10%–15%	Urine infection (urea-splitting bacteria)

Cystine	< 1%	Cystinuria
		  Autosomal recessive disorder of cystine, ornithine,
		    arginine, and lysine

Others
 Indinavir (Crixivan)
 Triamterene (Dyrenium)
 	
 Xanthine
	< 1%	
		Indinavir is an antiretroviral therapy for HIV
		Triamterene is a potassium-sparing diuretic used to
		  treat hypertension
		Xanthine oxidase inhibitor therapy, eg, allopurinol
		  (Zyloprim), for hyperuricemia or gout

Lifetime prevalence of stones: 10% in men, 5% in women, and increasing

Less often, patients present with silent ureteral obstruction, unexplained persistent urinary infection, or painless hematuria. However, even in patients with symptoms, the absence of hematuria does not exclude urolithiasis. In a study of 397 patients presenting with acute symptomatic urolithiasis, 9% did not have hematuria.[4]

The differential diagnosis in a patient with symptoms suggesting renal colic includes:

- Musculoskeletal pain
- Herpes zoster
- Diverticulitis
- Duodenal ulcer
- Cholecystitis
- Pyelonephritis
- Renal infarct
- Renal hemorrhage
- Gynecologic disorders
- Ureteral obstruction from renal papillary necrosis with sloughed papillae, a blood clot, or a ureteral stricture.

HELICAL CT WITHOUT CONTRAST IS THE PREFERRED IMAGING STUDY

The diagnosis can be confirmed by computed tomography (CT), renal ultrasonography, or intravenous pyelography.

Helical CT without contrast is the preferred imaging study in patients with suspected nephrolithiasis. It has several advantages over other imaging studies: it requires no radiocontrast material; it shows the distal ureters; it can detect radiolucent stones (ie, uric acid stones), radio-opaque stones, and stones as small as 1 to 2 mm; and it can detect hydronephrosis and intra-abdominal and renal disorders other than stones that could be causing the patient's symptoms.

In a study in 100 consecutive patients presenting to an emergency department with flank pain, helical CT had a sensitivity of 98%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 97% for the diagnosis of ureteral stones.[5] In a study of 1,000 consecutive patients with suspected stones, helical CT identified significant, additional, or alternative reasons for the patient's symptoms in 10% of cases.[6]

Ultrasonography has the advantage of not using radiation, but it is less sensitive for detecting stones and can image only the kidney and the proximal ureter. A retrospective study in 123 patients found that, compared with helical CT as the gold standard, ultrasonography had a sensitivity of 24% and a specificity of 90%.[7] Ultrasonography may also miss stones smaller than 3 mm in diameter.

Conventional radiography (kidney-ureter-bladder view) is inadequate for diagnosis as it may miss stones in the kidney or ureter (even small radio-opaque stones) and provides no information about possible obstruction.

Intravenous pyelography has few advantages in renal lithiasis, exposes the patient to the risk of radiocontrast infusion and contrast-mediated acute renal injury, and gives less information than noncontrast CT.

MEDICAL MANAGEMENT OF ACUTE STONE EVENTS

Most stones are smaller than 5 mm and readily pass without interventions such as lithotripsy, ureteroscopy, or percutaneous nephrolithotomy. (For more information on these interventions, see the review by Samplaski and colleagues in this issue of the *Cleveland Clinic Journal of Medicine*.[8])

Even if the stone is as large as 1 cm, I would let the patient try to pass it spontaneously if it is in the distal ureter, and I would allow up to 4 weeks for this to happen.

For most patients, pain management is paramount. Randomized controlled trials suggest that parenteral nonsteroidal anti-inflammatory drugs (NSAIDs) are as effective as narcotics for controlling the pain of renal colic.[9] Diclofenac (Voltaren) has been used in several studies.

To hasten stone passage, some recommend inducing high urine flow with oral intake of at least 2 to 3 L of fluids per 24 hours to ensure a urine output of at least 2 L per day.

Drugs may also help the stone to pass. A recent study in 210 patients with ureteral stones averaging 6 mm in diameter showed that tamsulosin (Flomax) increased the likelihood of spontaneous stone passage.[10] A meta-analysis of 693 patients in nine randomized trials concluded that alpha-blockers and calcium channel blockers increased the likelihood of stone passage compared with no treatment.[11] Borghi et al,[12] in a randomized, double-blind study in 86 patients with unilateral ureteral stones, reported a higher rate of stone passage in patients treated with methylprednisolone (Medrol) 16 mg/day plus nifedipine (Procardia) 40 mg/day than in those given methylprednisolone alone.

Helical CT is the best imaging study for suspected nephrolithiasis

PREVENTING RECURRENT STONES: PRINCIPLES AND SPECIFICS

Urinary stone disease recurs in 30% to 50% of patients within 5 years.[1,13,14]

In preventing recurrent stones, some principles apply to all patients and some are specific to the type of stone the patient had.

Stones form when the urine is supersaturated

Nephrolithiasis occurs when the concentration of stone-forming salts such as calcium oxalate, calcium phosphate, or uric acid is high. When the concentration is high enough to

allow crystals to form or preformed crystals to grow, the urine is said to be supersaturated.

Several factors are the major determinants of whether the urine is supersaturated by different salts:

- Calcium oxalate—low urine volume and high concentrations of calcium and oxalate
- Calcium phosphate—a high urine calcium concentration and alkaline urine
- Uric acid—acidic urine
- Cystine—a high urinary cystine concentration and acidic urine.

Increasing daily fluid intake

Since the urinary concentration of stone-forming salts is strongly affected by the daily urine volume, it follows that increasing daily fluid intake is important in preventing recurrent stone disease.

In one study,[15] 199 patients with a first calcium stone were randomized to a program of high oral fluid intake or no intervention. Five years later, 12 (12%) of the 99 patients in the high-fluid intake group had had a second stone, compared with 27 (27%) in the untreated group (P = .008). Of interest, the baseline 24-hour urine volumes were significantly lower in patients with stones than in 101 normal controls (P = .001), suggesting that habitual low daily fluid intake is a risk factor for calcium stone disease.[13]

◼ PREVENTING CALCIUM STONES

Most stones are composed of calcium oxalate or calcium phosphate. Calcium stone disease occurs most often in the 3rd to 5th decades of life.

Naturally occurring inhibitors of calcium crystal formation in the urine include citrate, nephrocalcin, uropontin, and magnesium. Of these, only citrate and magnesium levels are routinely measured; low levels of citrate are treated as a cause of calcium stone disease. It follows that the risk of calcium nephrolithiasis is the result of the interplay between the supersaturated state and the level of urinary inhibitors.[16]

Hypercalciuria and calcium oxalate stones

Calcium oxalate stones begin as crystals that form on the surface of the renal papillae over collections of suburothelial calcium phosphate particles called Randall plaque.[17] The driving force for calcium oxalate overgrowth on plaque is calcium oxalate supersaturation, which is strongly linked to high urinary calcium excretion. The fraction of papillary surface covered by plaque in patients with idiopathic calcium oxalate stones correlates directly with the urine calcium level and inversely with urine volume and pH.[18]

Most patients with calcium oxalate stones have hypercalciuria (defined as 24-hour urinary calcium excretion > 300 mg in men, > 250 mg in women, or > 4 mg/kg in men or women).

Hypercalciuria can be idiopathic

Hypercalciuria can occur in primary hyperparathyroidism, sarcoidosis, vitamin D excess, corticosteroid treatment, renal tubular acidosis, hyperthyroidism, and malignant neoplasms. If none of these conditions is present, elevated urinary calcium excretion is considered idiopathic.

Some patients with idiopathic hypercalciuria have a strong family history of hypercalciuria and, likely, a genetic basis for the disease. This condition has been categorized by the presumed site of the primary abnormality:

Absorptive hypercalciuria. Most patients with idiopathic hypercalciuria absorb too much calcium from the intestine. In many of them, 1,25 dihydroxyvitamin D levels are slightly high and serum phosphorous levels are slightly low; the hypothesis is that they produce more 1,25 dihydroxyvitamin D or are more sensitive to it.[19] However, Breslau et al[20] showed that not all patients with idiopathic hypercalciuria have absorptive hypercalciuria mediated by 1,25 dihydroxyvitamin D, which suggests that the intestinal hyperabsorption of calcium has other mechanisms.

Resorptive hypercalciuria occurs if increased bone turnover leads to urinary loss of bone calcium.

Renal leak is due to a primary defect in renal tubular transport that causes loss of calcium into the urine and a secondary increase in intestinal calcium absorption or mobilization from bone.

This categorization is based on measuring fasting and 24-hour urine calcium, urinary calcium responses to a low-calcium diet, and

NSAIDs may be as effective as narcotics for controlling the pain of renal colic

responses to an oral calcium load.[21] However, these studies are difficult to do and have been shown to have minimal clinical value.

To reduce calcium in the urine, limit sodium, give thiazides

Idiopathic hypercalciuria is worsened by a diet high in sodium[22,23] and animal protein.[24] Thiazide diuretics lower urinary calcium excretion and promote mineral retention.[25] Therefore, treatment of idiopathic hypercalciuria consists of high fluid intake, dietary sodium restriction, and thiazide diuretics.

Calcium restriction is not advised

For several reasons, a calcium-restricted diet is not advised for patients with idiopathic hypercalciuria.[26] Dietary calcium restriction can put the patient into negative calcium balance. Further, it is thought that with less calcium to bind to dietary oxalate, more unbound oxalate can be absorbed in the colon and eventually excreted in the urine. This increase in urinary oxalate can be to the point of supersaturation, even though urinary calcium levels remain unchanged.[25,27,28] This, in turn, increases the likelihood of stone formation.

Several studies showed that a higher intake of dietary calcium is actually associated with fewer calcium stone events in both men and women.[25,27,28]

Further, a study in 120 Italian patients with hypercalciuric calcium oxalate stones concluded that a diet that is normal in calcium, low in sodium, and low in animal protein was associated with a lower frequency of calcium stones than a low-calcium diet.[29] Although both diets were associated with a reduction in urinary calcium concentrations, urinary oxalate excretion rose in those on a low-calcium diet and fell in those on a normal-calcium diet. The reduction in urinary oxalate excretion in patients on a normal-calcium diet was attributed to intestinal binding of dietary oxalate by dietary calcium, thus lessening the amount of free oxalate available for absorption. Although calcium oxalate excretion fell in both groups, it fell more in those on a normal calcium intake. Compared with those on a low-calcium diet, the patients on the normal-calcium, low-sodium, low-protein diet had a 50% lower risk of stones at 5 years.

Hyperparathyroidism

Primary hyperparathyroidism can cause hypercalciuria and nephrolithiasis. In one series,[30] 56 (4.9%) of 1,132 consecutive patients with nephrolithiasis had a confirmed diagnosis of hyperparathyroidism. Parathyroidectomy prevented subsequent stone disease in 48 patients.

However, only 17% to 24% of patients with primary hyperparathyroidism have urinary stones composed of calcium oxalate or calcium phosphate.[31,32] In many studies, it was difficult to determine why a minority of these patients develop stones, but two studies shed some light on this.

Parks et al[30] found that, compared with nephrolithiasis patients with idiopathic hypercalciuria, those with primary hyperparathyroidism have elevated serum calcium levels (but usually < 11.5 mg/dL), greater degrees of hypercalciuria (352 mg/day vs 252 mg/day, $P <$ .001), and lower serum phosphate levels (2.45 vs 3.10 mg/dL, $P <$ .001).

Odvina et al[33] found, in a study of 131 patients with proven primary hyperparathyroidism, that 78 had nephrolithiasis and 53 did not. Those with stones excreted more calcium (343 mg/day) than those without stones (273 mg/day), had a higher urinary saturation of calcium oxalate and brushite, and excreted twice as much calcium following a 1-g oral calcium load.

These studies suggest that in patients with primary hyperparathyroidism, the risk of forming stones is related to the degree of hypercalciuria, and in particular to the increased intestinal absorption of dietary calcium.

Renal tubular acidosis

Features of distal renal tubular acidosis are systemic metabolic acidosis, alkaline urine, hypokalemia, hypercalciuria, hypocitraturia, and nephrolithiasis. The chronic metabolic acidosis results in loss of bone calcium, contributes to hypercalciuria, and is responsible for the hypocitraturia.[34] Stone formation is the result of excessive urinary calcium excretion, the deficiency of the urinary crystal inhibitor citrate, and persistently alkaline urine.

Treatment with sodium bicarbonate or potassium citrate corrects the metabolic acidosis, reduces the loss of calcium from bone, corrects hypokalemia, and increases urinary citrate.

Up to half of stones recur within 5 years

Too much uric acid in the urine

Elevated urinary uric acid excretion (> 800 mg/day in men, > 750 mg/day in women) is associated with formation of calcium oxalate stones[35] and, in conjunction with low urine pH, with uric acid stones. An increase in dissolved uric acid salts induces heterogeneous calcium oxalate nucleation.[36] In one randomized clinical trial,[37] giving allopurinol (Zyloprim) lowered urinary uric acid excretion and was associated with a lower rate of calcium stone disease.

Too much oxalate in the urine

The 95th percentile for urinary oxalate excretion is 45 mg/day in women and 55 mg/day in men.[38] Hyperoxaluria increases calcium oxalate supersaturation and contributes to calcium stone formation.

Normally, 90% of dietary oxalate binds to dietary calcium in the small intestine and passes into the stool as calcium oxalate; 10% of dietary oxalate remains free and is absorbed in the colon and subsequently excreted in the urine.

Hyperoxaluria may simply be a result of high dietary oxalate intake. However, increased enteric absorption of dietary oxalate can occur in those on a low-calcium diet (in which less calcium is available to bind to dietary oxalate, as described above) and may partially explain why a low-calcium diet has been associated with increased frequency of calcium stone disease.

Patients with enteric malabsorption of fat (eg, due to inflammatory bowel disease or intestinal bypass surgery for obesity) may also develop hyperoxaluria. This occurs because the excess enteric fat binds dietary calcium and allows free oxalate to be more readily absorbed in the colon.[39]

Rarely, hyperoxaluria is caused by one of several recessively inherited disorders of oxalate metabolism.[40]

The growing number of people with obesity has resulted in an upsurge in gastric bypass surgery. Although the current procedures do not pose the same metabolic risks as were noted in the 1970s when a different type of bypass was performed, the incidence of kidney stones does appear to be higher after these procedures. A recent analysis of 1,436 patients undergoing Roux-en-Y gastric bypass surgery found that 60 of them developed calcium stones afterward. Of these, 31 who underwent metabolic studies were found to have higher oxalate and lower citrate levels at 12 months of follow-up.[41]

Not enough citrate, a stone inhibitor

Hypocitraturia is defined as a daily urine citrate excretion less than 500 mg in women and 434 mg in men.[42] As already mentioned, citrate plays an important role in inhibiting calcium crystal formation and preventing stone formation.

Urinary citrate excretion is mainly determined by tubular reabsorption, which is increased by acid loads and decreased by alkali loads.[43] Low urine citrate levels are often seen in conditions that cause chronic metabolic acidosis, such as inflammatory bowel disease, intestinal malabsorption, and renal tubular acidosis—all of which are associated with increased occurrence of nephrolithiasis. However, in most nephrolithiasis patients with hypocitraturia, the cause is not apparent, and the mechanism of the hypocitraturia cannot be determined.[44]

In recent years, high-protein, low-carbohydrate diets have become popular for weight reduction, but they also have metabolic effects that increase the risk of stones.[45] The metabolism of a diet high in animal protein produces more hydrogen ions that are buffered by bone, releasing calcium from bone and increasing urinary calcium excretion. These diets also cause intracellular acidosis, resulting in decreased urinary excretion of citrate. As a result of these effects, the stone-forming propensity of the urine is increased.

■ STRUVITE STONES MUST BE REMOVED

Struvite stones are the result of chronic upper urinary infection with urease-producing bacteria (*Proteus* sp, *Haemophilus* sp, *Klebsiella* sp, and *Ureaplasma urealyticum*).[46,47] The hydrolysis of urea yields ammonium and hydroxyl ions and a persistently alkaline urine, and this scenario promotes the formation of stones composed of magnesium ammonium phosphate, ie, struvite.

High-protein, low-carb weight-loss diets increase the risk of calcium stones

Struvite stones, which are often branched ("staghorn" stones), occur more often in women and in patients who have chronic urinary obstruction or a neurologic disorder that impairs normal emptying of the bladder.

Treatment requires eradicating the infection with antibiotics and removing the bacteria-laden stones by one of several interventional techniques. Acetohydroxamic acid inhibits urease and has been used to treat struvite stone disease, but it has frequent and serious adverse effects.[48]

■ URIC ACID STONES FORM IN VERY ACIDIC URINE

Uric acid stones occur especially in patients with unusually low urine pH and hyperuricosuria. In some patients, this very low urine pH is the result of a defect in renal ammonia secretion, which results in less buffering of secreted hydrogen ions.[49]

The tendency to form uric acid stones is reported to be increasing in obese people with the metabolic syndrome. Some studies have shown that the defect in ammonia production by the kidney may be the result of insulin resistance.[50]

Urate stones are radiolucent but can be seen on ultrasonography and helical CT. On helical CT, they can be distinguished from calcium stones by their lower density.[51]

Since uric acid is much more soluble in an alkaline solution, both prevention and treatment should consist of alkalinization of urine to a pH of more than 6.0 with oral sodium bicarbonate or citrate solution and hydration. This treatment may actually dissolve uric acid stones. If hyperuricemia or hyperuricosuria is present, allopurinol can be prescribed.

■ CYSTINE STONES ALSO FORM IN ACIDIC URINE

Cystine stone disease occurs in people who have inherited an autosomally recessive gastrointestinal and renal tubular transport disorder of four amino acids, ie, cystine, ornithine, arginine, and lysine.[52] Of these, cystine is the most insoluble in normally acidic urine and thus precipitates into stones. The onset is at a younger age than in calcium stone disease;

TABLE 2

The diagnostic workup of nephrolithiasis

Stone analysis

Serum and blood testing
Calcium, parathyroid hormone, vitamin D, electrolytes

Urine dipstick and microscopic examination
Urine pH
Urine sediment examination for crystals, leukocytes, erythrocytes
  bacteria

Urine culture

24-Hour urine collection
Volume, creatinine, calcium oxalate, sodium, citrate, uric acid,
  cystine (when indicated)

Helical computed tomography (no contrast)

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the stones are radio-opaque.

Cystine solubility is about 243 mg/L in normal urine and rises with pH. Some patients can excrete as much as 1,000 mg per day.

Treatment[53,54] consists of:
- Hydration, to achieve daily urine volumes of 3 to 3.5 L
- Alkalinization of the urine to a pH higher than 6.5 with potassium alkali (potassium citrate) or sodium bicarbonate
- Reduction of protein and sodium intake to reduce cystine excretion.

If these measures fail, D-penicillamine (Depen), tiopronin (Thiola), or captopril (Capoten)[55–57] can be given to convert the cystine to a more soluble disulfide cysteine-drug complex. Captopril has only a modest effect at best and is usually given with another disulfide-complexing drug; it also has the disadvantage of producing hypotension. Adverse effects of D-penicillamine and tiopronin include abdominal pain, loss of taste, fever, proteinuria, and, in rare cases, nephrotic syndrome.

■ WORKUP AND MANAGEMENT OF NEPHROLITHIASIS

The diagnostic evaluation of a first stone (**TABLE 2**) includes a routine chemistry panel (electrolytes, creatinine, calcium), urinaly-

Anyone under age 20 with an initial stone should undergo a more extensive evaluation

sis, parathyroid hormone measurement, and helical CT without contrast. Stone analysis should always be done whenever stone material is available.

Anyone under age 20 with an initial stone deserves a more extensive evaluation, including screening for renal tubular acidosis, cystinuria, and hyperoxaluria. A more extensive workup is also warranted in patients with a history of chronic diarrhea, sarcoidosis, or a condition associated with renal tubular acidosis (eg, Sjögren syndrome), in patients with a family history of kidney stones, in patients with high-protein weight-loss diets, and in those undergoing gastric bypass surgery for obesity. In these high-risk patients, the evaluation should include 24-hour urine studies to measure calcium, oxalate, citrate, uric acid, creatinine, sodium, and volume.

Other diagnostic clues are often helpful in the decision to do a more comprehensive evaluation.

- Nephrocalcinosis on roentgenography suggests hyperparathyroidism, medullary sponge kidney, or renal tubular acidosis.
- Hypercalcemia that develops after treatment of hypercalciuria with a thiazide diuretic suggests latent hyperparathyroidism.
- A history of recurrent urinary tract infections or of anatomic abnormalities in the urinary tract should lead to an evaluation for struvite stone disease.
- Uric acid stones should be suspected in a patient with metabolic syndrome or a history of gout and are usually accompanied by a urine pH lower than 5.5.
- A urinalysis showing cystine crystals always indicates cystinuria, which should be confirmed by 24-hour urine cystine determination.
- A family history of renal stones is more common in idiopathic hypercalciuria, cystinuria, primary hyperoxaluria, and renal tubular acidosis.

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ADDRESS: *Phillip M. Hall, MD, Department of Nephrology, Q7, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail hallp@ccf.org.*