AJKD

Core Curriculum in Nephrology

# Update on Nephrolithiasis: Core Curriculum 2016

Anja Pfau, MD,[1] and Felix Knauf, MD[1,2]

Nephrolithiasis has historically been considered as a common, painful, but isolated condition. In recent years, we have learned that nephrolithiasis is not simply an isolated urologic disease, but instead a disorder with systemic complications, including an increased risk for chronic kidney disease (CKD). Therefore, it is mandatory for every nephrologist to be able to evaluate and treat patients with nephrolithiasis. This Core Curriculum outlines the epidemiology, pathophysiology, diagnosis, and management of nephrolithiasis.

## EPIDEMIOLOGY OF KIDNEY STONES

### Overview

Kidney stones are a common and increasing problem worldwide. During the past few years, we have learned significantly about the prevalence and risk factors for nephrolithiasis from epidemiologic studies, high-quality collaborative reviews, and meta-analyses.

### Prevalence, Sex, and Geography

In the United States, up to 16% of men and 8% of women will have 1 or more symptomatic stones by the age of 70 years. Although men continue to have a higher risk for nephrolithiasis, in the last 2 decades, the male to female ratio has changed from 3:1 to about 2:1, presumably secondary to changes in lifestyle. More strikingly, the prevalence of kidney stones has been substantially increasing: in 1994, it was reported at 5.2% (1 in 20 persons), but in 2012, it was close to 10% (1 in 11 persons).

Nationwide cross-sectional surveys demonstrated that the lifetime prevalence of kidney stones varies by geographic region in the United States, increasing from North to South and from West to East, resulting in a "stone belt" across North and South Carolina, Georgia, Alabama, Mississippi, and Tennessee. Climatologic, dietary, and lifestyle factors appear to play a major role with regard to the risk for having kidney stones and may explain the geographic distribution, which is reviewed in more detail in subsequent sections.

### Stone Recurrence

After an episode of nephrolithiasis, risk for recurrence is high: having passed a first kidney stone, patients have a risk of ~15% to develop a second stone within a year and a risk of almost 50% within 10 years. To estimate the risk for recurrence, Rule et al introduced the ROKS nomogram shown in Fig 1. Using 11 clinical features and risk factors of the individual patient, the nomogram estimates the risk of a symptomatic recurrence after the first event and identifies patients who may benefit from a medical intervention.

### Systemic Diseases

Several epidemiologic studies have studied the relationship between nephrolithiasis and metabolic syndrome traits. The relative risk for developing a kidney stone was increased for participants weighing >220 lb compared with those weighing 140 lb and those with a body mass index >30 versus 21 kg/m$^2$, suggesting that weight gain and obesity are independent risk factors for developing kidney stones. The magnitudes of the associations were greater for women compared with men, which may be one explanation for the increasing incidence of nephrolithiasis among women and changes in the male to female ratio in developed countries. Similarly, it has been shown that diabetes mellitus is associated with an increased risk for kidney stone formation. Diabetic patients have lower urine pH, which may increase the risk for uric acid calculi. Likewise, higher amounts of urinary oxalate have been detected in patients with diabetes. One may speculate that the prevalence of stone disease may continue to increase as type 2 diabetes mellitus becomes more common. Although nephrolithiasis seems to be a risk factor for the development of incident hypertension, the risk for incident nephrolithiasis is not different in those with and without a history of hypertension. In summary, the observations described suggest that nephrolithiasis is a systemic metabolic disorder.

### Diet and Medication as Risk Factors

Because kidney stone formation is dependent on the physicochemical properties of urine, changes in urine composition can contribute to an increased

*From the [1]Department of Nephrology und Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany; and [2]Department of Internal Medicine, Yale University School of Medicine, New Haven, CT.*

*Received December 17, 2015. Accepted in revised form May 10, 2016. Originally published online August 3, 2016.*

*Address correspondence to Felix Knauf, MD, Department of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Schwabachanlage 12, 91054 Erlangen, Germany. E-mail: felix.knauf@uk-erlangen.de*



*0272-6386*

*http://dx.doi.org/10.1053/j.ajkd.2016.05.016*

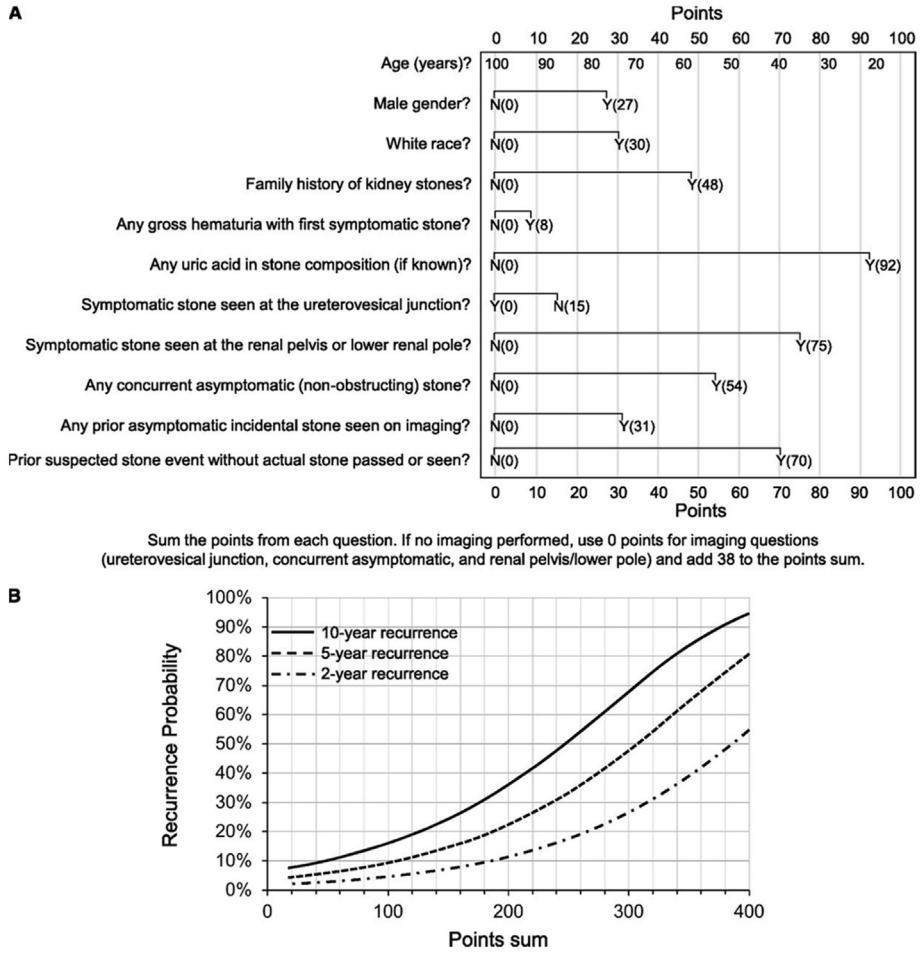



**Figure 1.** The Recurrence of Kidney Stone (ROKS) nomogram for first-time symptomatic stone formers. (A) Total points are determined based on the sum of 11 predictors. (B) Estimated recurrence risk at 2, 5, and 10 years based on total points. Reproduced from Rule et al (*J Am Soc Nephrol* 2014;25[12]:2878-2886) with permission of the American Society of Nephrology.

incidence of nephrolithiasis. Therefore, dietary habits and medications need to be evaluated when evaluating a patient with kidney stones. Low fluid intake leads to high concentrations of lithogenic substances in urine and may explain why inhabitants living in a hot climate have higher risk for developing kidney stones. Greater dietary calcium intake is independently associated with lower risk for symptomatic kidney stones. Calcium is presumed to bind oxalate in the intestinal lumen, reducing the amount of soluble oxalate available for absorption. Hence, it is generally accepted that a low-calcium diet is not recommended as a means of calcium stone prevention. Similar to calcium intake, consumption of potassium-rich foods is inversely associated with incident kidney stones in both men and older women. The effect of higher potassium intake is most likely related to the cation being accompanied by an organic anion (eg, citrate), representing an alkaline load. In addition, potassium deficiency stimulates proximal tubule citrate absorption, thereby reducing urinary citrate excretion. In contrast, high animal protein intake is the main source of acid in the human body and lowers urine pH, which then increases the risk for uric acid stones. However, epidemiologic studies examining the association of protein intake and risk for incident stone formation have not demonstrated an association with calcium oxalate stones. A diet high in salt increases urinary calcium because calcium parallels sodium reabsorption in the proximal tubule. Following high salt intake, sodium and calcium reabsorption is reduced, resulting in higher urinary calcium excretion and thereby increasing the risk for nephrolithiasis. Higher urinary oxalate excretion is another important risk factor for nephrolithiasis. Hyperoxaluria can be secondary to high oxalate intake and is commonly associated with short bowel syndrome, malabsorptive bariatric surgery, or pancreatic insufficiency.

Drugs that crystallize in urine (such as atazanavir, indinavir, acyclovir, sulfadiazine, methotrexate, triamterene, quinolones, or aminopenicillins) can similarly lead to nephrolithiasis. In addition, medications

that alter urine pH (topiramate and acetazolamide) may predispose to kidney stone formation.

### Additional Readings


» Asplin JR, Coe FL. Hyperoxaluria in kidney stone formers treated with modern bariatric surgery. *J Urol.* 2007;177(2):565-569.
» Heilberg IP, Goldfarb DS. Optimum nutrition for kidney stone disease. *Adv Chronic Kidney Dis.* 2013;20(2):165-174.
» Perazella MA. Drug-induced nephropathy: an update. *Expert Opin Drug Saf.* 2005;4(4):689-706.
» Rule AD, Lieske JC, Li X, Melton LJ 3rd, Krambeck AE, Bergstralh EJ. The ROKS nomogram for predicting a second symptomatic stone episode. *J Am Soc Nephrol.* 2014;25(12):2878-2886.
» Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. *Eur Urol.* 2012;62(1):160-165.
» Taylor EN, Curhan GC. Dietary calcium from dairy and nondairy sources, and risk of symptomatic kidney stones. *J Urol.* 2013;190(4):1255-1259.
» Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol.* 2004;15(12):3225-3232.
» Ticinesi A, Nouvenne A, Maalouf NM, Borghi L, Meschi T. Salt and nephrolithiasis. *Nephrol Dial Transplant.* 2016;31(1):39-45.
» Wong YV, Cook P, Somani BK. The association of metabolic syndrome and urolithiasis. *Int J Endocrinol.* 2015;2015:570674.


## CLINICAL FEATURES

### Clinical Presentation

Renal colic is the most common presenting symptom of nephrolithiasis and describes the sudden onset of waxing and waning pain. The localization of the pain tends to correlate with the position of the stone along the urinary tract and can radiate to the testicles or labia. The intensity can vary from a dull pressure or a slight dragging sensation to excruciating pain.

Hematuria occurs in the majority of patients. However, it is important to note that in >10% of proven kidney stone passage, no hematuria can be detected. One explanation is the time delay between first pain sensation and time of testing for a stone. In a retrospective study with more than 450 patients with proven acute nephrolithiasis, hematuria could be detected in 95% of all cases when testing was performed on the first day, but only 65% of all cases when testing was performed on days 3 to 4 following pain onset. However, only 5% of patients receiving a workup for hematuria of unknown cause are found to have urinary calculi.

Additional symptoms include nausea, vomiting, dysuria, and the persistent urge to urinate (especially when the stone is located in the distal ureter). Stone size is the major determinant for stone passage, with most stones <5 mm passing spontaneously.

### Imaging Studies

Imaging modalities most commonly used to visualize and confirm the diagnosis of nephrolithiasis have changed during recent years. While intravenous pyelogram (IVP) and plain films (kidneys, ureter, bladder [KUB]) are used less frequently, the focus has now shifted toward noncontrast computed tomography (CT) and ultrasonography to diagnose kidney stones. In the United States, noncontrast CT has been the gold standard for initial imaging in patients with suspected nephrolithiasis (sensitivity, 97%; specificity, 95%). Ultrasonography exhibits lower sensitivity and higher user dependence. As a consequence, the use of CT for a suspected kidney stone has increased by a factor of 10 during the past 15 years. However, CT is high in cost and associated with radiation exposure compared to ultrasonography. Given the high radiation dose associated with CT, ultrasonography is always recommended as a first choice in children and pregnant women. In addition, ultrasound can be useful in cases when the stones are not disclosed by showing indirect signs of passing stones. With ultrasonography, it should be considered that small stones (<5 mm) and more distal stones are more likely to be missed.

In 2014, Smith-Bindman et al presented results of a multicenter comparative effectiveness trial that may change our approach to the radiologic assessment of kidney stones. More than 2,500 patients who arrived at the emergency department with suspected nephrolithiasis were randomly assigned to ultrasonography done by an emergency department physician, ultrasonography done by a radiologist, or CT. Despite the lower sensitivity of ultrasonography, secondary outcomes such as pain scores, hospital admissions, readmissions, and severe complications due to missed diagnosis (eg, sepsis) did not differ when comparing ultrasonography with CT. One limitation of the study is the exclusion of obese patients. In addition, follow-up CT is frequently necessary when a surgical intervention is being considered. Of note, some centers have already moved to low-dose CT techniques to reduce radiation exposure (<3 vs 14 mSv with standard CT), which may offer an alternative imaging approach.

### Additional Readings


» Kobayashi T, Nishizawa K, Mitsumori K, Ogura K. Impact of date of onset on the absence of hematuria in patients with acute renal colic. *J Urol.* 2003;170:1093-1096.
» Moe OW. Kidney stones: pathophysiology and medical management. *Lancet.* 2006;367(9507):333-344.
» Sharp VJ, Barnes KT, Erickson BA. Assessment of asymptomatic microscopic hematuria in adults. *Am Fam Physician.* 2013;88(11):747-754.
» Smith-Bindman R, Aubin C, Bailitz J, et al. Ultrasonography versus computed tomography for suspected nephrolithiasis. *N Engl J Med.* 2014;371(12):1100-1110.

## MECHANISMS OF STONE FORMATION

### Saturation and Stone Growth

Understanding the underlying causes of nephrolithiasis is imperative to establish medical treatment and for the prevention of future kidney stones. A salt can dissolve in a given solution until reaching equilibrium between the solid and aqueous phase at a defined pH and temperature. Supersaturation sufficiently high to induce crystallization, which is referred to as upper limit of metastability, is needed for the formation of kidney stones. Inhibitors raise the limit, whereas promoters lower it.

As shown in Fig 2, crystal nucleation encompasses the process of free ions building loose clusters. Special cell types (eg, renal epithelial cells) and casts can act as nucleating centers. When a nucleus is established, additional crystal components can be added to the existing nucleus in a process defined as crystal growth. Larger crystal particles combine in a process called crystal aggregation.

### Sites of Stone Growth

In 1937, Randall suggested that calcium phosphate deposits located on the tip of renal papillae build an ideal foundation for the formation of calcium oxalate stones (thereafter called Randall's plaque). Research from investigators at the University of Chicago and the Indiana University has further advanced the field over the past decades by demonstrating that Randall's plaque forms at the basement membranes of the thin loops of Henle, moving through the interstitium, occasionally encasing the renal tubules and vasa recta, and ultimately protrudes into the uroepithelium in the renal papillae. Using techniques such as digital endoscopy, transmission electron microscopy, and histopathologic evaluation, they were able to show different phenotypes with respect to patterns of tissue mineralization and injury among stone formers, and that stone type is the key evidence to the mechanism in a particular patient. Recently, a vascular theory concerning the development of Randall's plaques has been hypothesized that may mirror the coincidence of kidney stones with diabetes, hypertension, or arteriosclerosis. It has been suggested that stone formation may resemble plaque aggregation after vascular injury or represent papillary necrosis in the setting of advanced arteriosclerosis. Future research defining the mechanisms of plaque formation has the potential to increase our ability to choose appropriate treatments for our patients.

### Inhibitors and Promoters

As described, inhibitors decrease the likelihood of stone formation even if the criteria of supersaturation are met. An example of a potent inhibitor of stone formation is citrate. Besides its ability to form soluble complexes with calcium (thereby reducing urinary calcium supersaturation), citrate has been demonstrated to exert inhibitory effects on crystal growth and aggregation. Similarly, magnesium can inhibit stone formation by a mechanism that is not yet fully understood. In vitro experiments have suggested that magnesium is able to destabilize calcium oxalate ion pairs. However, a randomized controlled trial (RCT) examining the effect of magnesium on reducing stone risk did not demonstrate benefit.

Although an alkaline pH is not considered a promoter in itself, pH $\geq$ 6.7 alters supersaturation, which enhances calcium phosphate crystallization as observed in patients with distal renal tubular acidosis (RTA), primary hyperparathyroidism, or milk-alkali

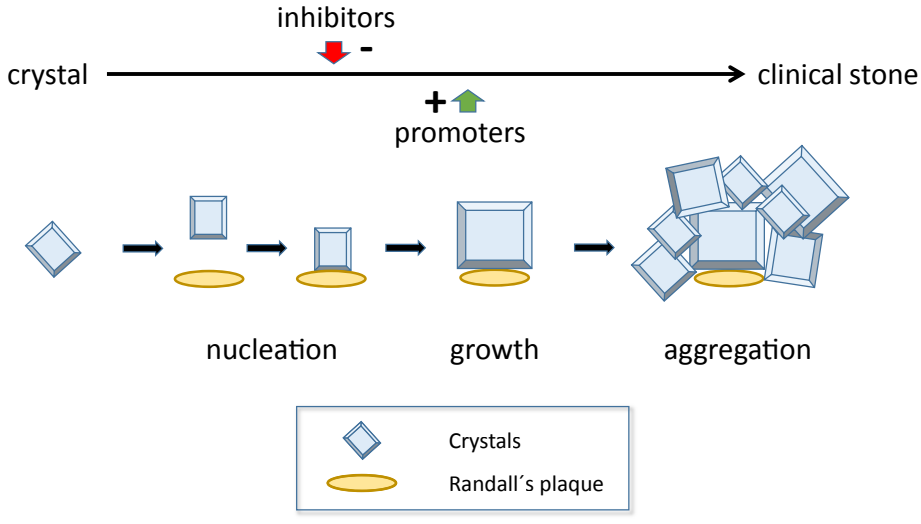



**Figure 2.** Mechanisms of stone formation.

syndrome or patients undergoing treatment with carbonic anhydrase inhibitors (acetazolamide used for glaucoma or topiramate used for migraine/seizures).

In contrast, an acid urine pH (ie, ≤5.5) encourages uric acid precipitation. When uric acid stones or cystine stones are present, urine alkalinization can prevent further crystallization.

To summarize, when evaluating a patient with nephrolithiasis and interpreting the urine risk profile, the following 3 questions driving stone formation must be examined: (1) Is there an increased concentration present of lithogenic substances due to either high rates of excretion, low urine flow, or both? (2) Is there a stone promoter present, such as hyperuricosuria? (3) Is there reduced inhibitor present, particularly a low citrate concentration?

### Additional Readings


» Aggarwal KP, Narula S, Kakkar M, Tandon C. Nephrolithiasis: molecular mechanism of renal stone formation and the critical role played by modulators. *Biomed Res Int.* 2013;2013:292953.

» Bagga HS, Chi T, Miller J, Stoller ML. New insights into the pathogenesis of renal calculi. *Urol Clin North Am.* 2013;40(1):1-12.

» Evan AP, Lingeman JE, Worcester EM, et al. Contrasting histopathology and crystal deposits in kidneys of idiopathic stone formers who produce hydroxy apatite, brushite, or calcium oxalate stones. *Anat Rec (Hoboken).* 2014;297(4):731-748.

» Matlaga BR, Coe FL, Evan AP, Lingeman JE. The role of Randall's plaques in the pathogenesis of calcium stones. *J Urol.* 2007;177(1):31-38.

» Randall A. The origin and growth of renal calculi. *Ann Surg.* 1937;105(6):1009-1027.


## CALCIUM NEPHROLITHIASIS

### Clinical Features

More than 80% of all kidney stones contain calcium, predominantly in the form of calcium oxalate. Calcium oxalate stones can occur as monohydrate or dihydrate stones. While calcium oxalate monohydrate stones appear as smooth hard black calculi and crystals have dumbbell appearance on urine microscopy, calcium oxalate dihydrate forms a yellowish irregular calculus and microscopically, crystals present with an envelope shape. Stones mainly containing calcium phosphate are defined as calcium phosphate stones. They are less common than calcium oxalate stones, their shape can vary depending on the main chemical component, and they usually demonstrate wedge-shaped prisms on urine microscopy. Figure 3 summarizes urine sediments with the appearance of crystals described in this article. It is important to note that calcium oxalate, calcium phosphate, and uric acid crystals are not uncommon among healthy non−stone-forming individuals. Hence, their diagnostic specificity is limited as compared with cystine, struvite, or drugs that crystallize.

### Urinary Risk Factors for Calcium Nephrolithiasis

#### *Low Urine Volume*

Reduced urine volume will intensify the saturation of solutes and increase supersaturation and risk for calcium stones. Clinical clues to low urine volume are urine output $<$ 1 L/d or urine osmolarity $>$ 600 mOsm/kg, and it is observed secondary to habitual reduced fluid intake or fluid loss induced by hot climate (sweating) or gastrointestinal loss (diarrhea). Increasing fluid intake and urine output in patients with recurrent nephrolithiasis has the potential to induce an undersaturated state and thereby reduce the risk for calcium nephrolithiasis.

#### *Hypercalciuria*

Calcium excretion $>$ 250 mg/d in women and $>$300 mg/d in men is defined as hypercalciuria, as shown in Table 1. It is important to note that the reference values listed in Table 1 are continuous rather than fixed variables, and stone risk can be increased even with values in the "normal" range. Urinary calcium amplifies the ionic activity of crystallizing calcium salts and binds stone inhibitors such as urinary citrate. Hypercalciuria can occur secondary to an underlying systemic disorder such as primary hyperparathyroidism, sarcoidosis, malignant neoplasm, Cushing syndrome, distal RTA, or vitamin D excess. Hence, when approaching a patient with calcium stones, a treatable underlying disease must be excluded. When plasma calcium level is elevated, it is imperative to measure parathyroid hormone and 25-hydroxyvitamin D as part of the stone evaluation. Rare monogenetic disorders such as Dent disease or mutations of the calcium-sensing receptor similarly present with hypercalciuria.

In the vast majority of patients, no specific cause for hypercalciuria can be identified, and it is referred to as idiopathic hypercalciuria. Idiopathic hypercalciuria comprises a variety of physiologic defects that lead to the same "symptom," namely hypercalciuria. It is frequently observed among young and middle-aged men and is associated with higher risk for hypertension, obesity, and osteopenia. Whereas no single cause for this phenomenon has been identified, several features mimicking tissue vitamin D activation have been described, such as increased intestinal calcium absorption and bone mineral mobilization.

#### *Hyperoxaluria*

There are 2 main sources of urinary oxalate in humans: endogenous oxalate production and exogenous oxalate absorption. The kidney is responsible for oxalate excretion. Oxalate enters the proximal tubule

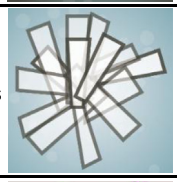
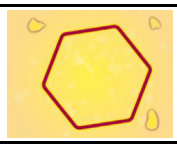
| Stone type | Morphology of Associated Crystals (Urine Microscopy) | Urinary Risk Factor | Clinical Settings |
|---|---|---|---|
| **Calcium oxalate monohydrate** | Dumbbell  | Hypercalciuria | Hyperparathyroidism, immobilization, vitamin D excess, sarcoidosis, Cushing syndrome, high sodium intake, genetic disorders (eg, Dent disease), idiopathic, etc |
| | | Hyperoxaluria | • Increased oxalate absorption (eg, bowel pathologies)<br>• Primary hyperoxaluria<br>• Excess vitamin C intake |
| **Calcium oxalate dihydrate** | Envelope (X)  | As outlined for calcium oxalate monohydrate | As outlined for calcium oxalate monohydrate |
| **Calcium phosphate** | Flat shaped or wedge-shaped prisms; prisms often in rosettes  | • Hypercalciuria<br>• Hypocitraturia<br>• Urine pH > 7 | • As outlined for calcium oxalate monohydrate<br>• Distal renal tubular acidosis<br>• Drugs with carbonic anhydrase inhibitory function (eg, topiramate, acetazolamide) |
| **Struvite** | Coffin-lid  | High levels of ammonium and bicarbonate | Urinary tract infections with urease-splitting microorganisms |
| **Uric acid** | Rhomboid/ football-shaped; multiple forms possible; often yellow/brown  | • Urine pH < 5.5<br>• Hyperuricosuria | Patients with metabolic syndrome, insulin resistance, type-2 diabetes |
| **Cystine** | Hexagonal  | Cystinuria | Genetic disorder |

**Figure 3.** Kidney stone type, corresponding urine sediment, urinary risk factors, and associated clinical settings.

through filtration and secretion. Hyperoxaluria is present in 10% to 50% of calcium stone formers and defined as urinary oxalate excretion $>$ 40 mg/d. Elevated urinary oxalate excretion increases supersaturation, risk for crystal formation, and tubular damage.

Primary hyperoxalurias are autosomal recessive disorders that lead to oxalate overproduction in the liver secondary to defects in glyoxylate metabolism. Currently, primary hyperoxaluria types I, II, and III have been described, with type I being the most common. Primary hyperoxaluria is associated with recurrent kidney stones, progressive nephrocalcinosis, and end-stage renal disease. As kidney disease ensues and oxalate is not sufficiently excreted by the kidney (glomerular filtration rate $<$ 30-40 mL/min/1.73 $m^2$), plasma oxalate levels increase and patients are at risk for systemic oxalosis, characterized by oxalate deposition in heart, bone, retina, and skin.

In addition to endogenous oxalate production, dietary oxalate is absorbed by passive and paracellular transport across the tight junctions of the intestine, mainly in the colon. Foods high in oxalate include spinach, rhubarb, beetroot, cocoa, and iced tea. Similarly, vitamin C is metabolized to oxalate, and increased supplementation has been shown to increase hyperoxaluria and stone risk.

Fat malabsorption observed in patients with chronic inflammatory bowel disease, cystic fibrosis, chronic pancreatic insufficiency, and biliary cirrhosis and with certain medications (eg, the lipase inhibitor orlistat) increases free fatty acids that bind calcium in the intestinal lumen and impair calcium from binding

**Table 1.** Reference Values for Lithogenic and Protective Substances in a 24-Hour Urine Sample

| Analyte | Reference Ranges[a] |
|---|---|
| Calcium, mg | Women, <250; men, <300 |
| Oxalate, mg | <40 |
| Uric acid, g | Women, <0.75; men, <0.8 |
| Citrate, mg | >325 |
| pH | 5.8-6.2 |
| Urine volume, L | 2.5-4 |
| Sodium, mmol | <100 |

[a]Non−stone formers.

oxalate. This in turn increases the amount of soluble oxalate available for intestinal absorption. Fatty acids and unabsorbed bile salts have also been shown to increase the colonic mucosal permeability of oxalate. Furthermore, colonization of the intestinal tract with *Oxalobacter formigenes*, a bacterial species using oxalate as an energy source, reduces intestinal oxalate absorption and hyperoxaluria. Following bariatric surgery or frequent antibiotic treatment, colonization with *O. formigenes* is reduced, increasing the amount of oxalate available for absorption. Therefore, the conditions described foster calcium oxalate stone formation.

#### *Hypocitraturia*

Citric acid is a tricarboxylic acid that mostly stems from endogenous oxidative metabolism. It is freely filtered through the glomerulus and, in contrast to oxalic acid, actively reabsorbed in the proximal tubule. Hypocitraturia is associated with calcium nephrolithiasis in 20% to 60% of all cases. It is defined by citrate concentration < 325 mg/d. Citrate inhibits stone formation by complexing with calcium in urine, reducing spontaneous nucleation, and preventing agglomeration of crystals. Acid-base balance is the key determinant of tubular citrate reabsorption; acidosis and hypokalemia increase the demand of citrate as a bicarbonate source and as a consequence, reduce urinary citrate concentration. Hence, systemic acid-base status, serum potassium level, and urine pH have profound effects on risk for stone formation. Several clinical settings that are associated with metabolic acidosis can therefore cause hypocitraturia: chronic diarrhea, high protein intake, and RTA. Hypocitraturia can be treated with alkali (bicarbonate or citrate); because sodium load is a risk factor for kidney stones itself, potassium-containing alkali products are preferred.

#### *Hyperuricosuria*

Hyperuricosuria is detected in 10% of all calcium stone formers and defined as uric acid excretion > 750 mg/d in women or >800 mg/d in men. Hyperuricosuria decreases the solubility of calcium oxalate and may promote calcium oxalate crystallization. However, Curhan et al could not demonstrate a correlation between higher urine uric acid excretion and risk for calcium oxalate stone formation in a cross-sectional study of more than 3,000 participants.

### Metabolic Evaluation of Calcium Nephrolithiasis

In a patient presenting with a first kidney stone, there is no uniformity in the literature with regard to the extent of workup indicated. There is general consent that the evaluation of all stone patients—independently of stone composition or even if stone composition is unknown—should include a careful medical, dietary, and family history, including assessment of the severity of stone disease, the presence of systemic diseases, and assessment of the patient's preference for further evaluation. Urinalysis and microscopy should be performed routinely on all patients with stones because both tests are efficient and economic and can identify pathognomonic crystals that reveal the origin of the stone (Fig 3). All calculi that have been retrieved should be submitted for stone analysis. Several studies have demonstrated that first-time kidney stone formers carry the same metabolic risk factors as patients with recurrent nephrolithiasis. The newly established ROKS nomogram described earlier may help identify patients at increased risk for recurrence who may benefit from a more extensive metabolic evaluation with a 24-hour urine sample to guide a pathophysiology-based treatment approach (Table 2). Obtaining 24-hour urine samples is necessary to determine urine volume, pH, calcium, citrate, uric acid, sodium, and oxalate (reference values summarized in Table 1). Specialized laboratories can provide a detailed analysis and summary of stone risk factors, including saturation values for stone-forming salts and interpretive paragraphs offering therapeutic suggestions. However, although these services are established in the United States, they are not yet available in many other countries.

During the collection, patients are advised to maintain their usual diet and fluid intake. Samples should not be obtained during an acute urinary tract infection (UTI), obstruction, or following a recent urologic intervention. To avoid misinterpretation, measurement should be obtained in a steady state 1 to 3 months after a last stone. Two measurements are recommended in order to obtain representative results because a single 24-hour sample may not be adequate for evaluating patients and misdiagnosis is common, leading to inappropriate treatment. If 2 different measurements are not consistent, it is important to investigate dietary or lifestyle changes that may account for the changes as an important clue to identify factors that may prevent stone formation.

**Table 2.** Suggested Approach to Metabolic Evaluation of a Patient With Nephrolithiasis

| Clinical Situation | Extent of Workup |
|---|---|
| First kidney stone (low risk for recurrence) | • Complete medical history (risk factors, family history, underlying/concomitant diseases, medications)<br>• Stone analysis<br>• Urine analysis (dipstick including pH, urine sediment) |
| Recurrent kidney stones, and first kidney stone, but moderate or high risk for recurrence | Workup as described for first kidney stone (low risk), and:<br>• Serum panel: creatinine, sodium, potassium, chloride, calcium, phosphate, magnesium, uric acid, venous blood gas analysis; if calcium is elevated or high normal, parathyroid hormone and 25-hydroxyvitamin D[a] should be measured<br>• 24-h urine (at least 2 samples): volume, pH, sodium, calcium, oxalate, uric acid, citrate (cystine) |

*Note:* The extent of metabolic evaluation depends on risk for recurrence (see Fig 1), concomitant diseases, and patient's preference.

[a]In some patients (eg, when sarcoidosis is suspected), 1,25-dihydroxyvitamin D may be more helpful.

When the decision has been made to initiate medical kidney stone prevention by reversing a defined metabolic abnormality (eg, hypercalciuria), 24-hour urine samples should be repeated to monitor the response of therapy. Treatment goals are directed to reduce both the absolute amount of a lithogenic factor and its supersaturation. We recommend repeating 24-hour urine testing at 6 to 12 weeks after a medical or dietary intervention has been initiated and monitoring treatment goals at month 6 and then annually.

## Prevention of Calcium Nephrolithiasis

Institution of preventative dietary and medical measures has been shown to result in substantial reduction in calcium stone recurrence rates in several RCTs.

### *Fluid Intake*

Increased fluid intake with the goal of maintaining urine output greater than 2 or 2.5 L/d has been shown to reduce the risk for stone recurrence in 2 trials. Low sodium content water seems to be an adequate choice. Beer consumption remains controversial: it has been demonstrated to be protective in calcium stone formers but may exert negative effects on urate kidney stones.

### *Diet*

A variety of dietary risk factors have been identified that represent targets for intervention. Several RCTs have examined the impact of multicomponent diets on risk for stone recurrence. In one RCT, participants with hypercalciuria were advised to avoid excess oxalate, maintain a normal- to high-calcium diet (1,200 mg/d), and aim for low animal protein and low sodium intake. Compared with patients assigned to a control diet including low calcium content (400 mg/d), risk for stone recurrence was reduced in patients with higher dietary calcium intake. Although it is unclear which dietary component was attributable to reduced stone risk, it is well accepted that reduced dietary calcium intake increases intestinal absorption of soluble oxalate, and the formation of oxalate-containing stones is favored. Besides, low calcium intake has been shown to cause lower bone mass in kidney stone formers.

Treatment approaches of patients with calcium oxalate stones secondary to enteric hyperoxaluria include general recommendations such as maintaining high urine volume and adhering to a low-oxalate and calcium-rich diet. Furthermore, a fat-restricted diet should be maintained. If this is not feasible because the patient has to maintain a minimum caloric intake, medium-chain fatty acids should be added as a substitute for long-chain fatty acids.

### *Drugs of Choice*

In addition to the mentioned fluid intake and diet modifications, pharmacologic therapy for preventing stone recurrence has been examined in several clinical trials (Table 3).

*Thiazide diuretics.* These drugs remain the pharmacologic cornerstone in patients with idiopathic hypercalciuria but also among normocalciuric stone formers. Thiazide diuretics inhibit the $Na^+/Cl^-$ cotransporter in the distal convoluted tubule, leading to volume depletion and increased calcium reabsorption in the proximal tubule. Maximum effect is achieved in combination with low salt intake. Results from one study indicated that stone recurrence did not seem to differ depending on the type of thiazide used (hydrochlorothiazide, indapamide, and chlorthalidone), although no RCTs studied a hydrochlorothiazide or chlorthalidone dose less than 50 mg/d and 25 mg/d, respectively. Hence, thiazides are recommended in known hypercalciuric patients and recurrent stone formers, even if normocalciuric. Adverse effects of thiazide treatment include potassium depletion that may aggravate hypocitraturia and require potassium supplementation (ideally in the form of potassium citrate).

*Potassium citrate.* Six RCTs have examined the effect of citrate predominantly on calcium stones with

**Table 3.** Drugs Used for Treatment of Nephrolithiasis

| Drug | Dosage | Common Indications |
|---|---|---|
| Thiazides (hydrochlorothiazide and chlorthalidone) | 25 mg, 2×/d, for hydrochlorothiazide; 25 mg, 1×/d, for chlorthalidone | Hypercalciuria in calcium oxalate and calcium phosphate stone formers; recurrent calcium stone formers without metabolic abnormality |
| Potassium citrate | 20-80 mEq/d divided into 3-4 doses; dosage has to be adjusted to urinary pH; one must be careful in calcium phosphate stone formers as pH > 6.5-7 favors calcium phosphate precipitation | Hypocitraturia in calcium oxalate and calcium phosphate stone formers; recurrent calcium stones without metabolic abnormality; uric acid stones (goal: urinary pH > 6); cystine stones (goal: urinary pH > 7) |
| Allopurinol | 100-300 mg/d | Calcium stone formers with hyperuricosuria; primary gout; attention: no first-line therapy in uric acid stone formers |
| Cholestyramine | 4×4 g (limited data available on dosing) | Enteric hyperoxaluria |
| Penicillamine | 500-2,000 mg/d (3-4 doses) | Cystine stones |
| Tiopronin | 400-1,200 mg/d (3 doses) | |
| Acetohydroxamic acid | 15 mg/kg/d | Struvite stones; when other possibilities/ interventions have failed |

moderate-strength evidence that citrate reduces the risk for stone recurrence. Of note, in 4 trials, patients were also assigned increased fluid intake, which makes it difficult to determine which intervention was attributable to the reduced stone risk. The American Urological Association (AUA) recommends potassium citrate in patients with recurrent calcium stones with low or low-normal urinary citrate excretion, in recurrent calcium stone formers with normal urinary citrate excretion but low urinary pH, and even in patients with recurrent calcium stones without a detectable metabolic disorder. Furthermore, in calcium phosphate stone formers, citrate is understood to be a competent inhibitor of calcium phosphate crystallization. We recommend 20 to 80 mEq of potassium citrate divided into 3 to 4 doses per day. Urinary pH must be monitored and dosage must be adjusted because urine pH should not increase above 6.5 to 7.

*Allopurinol.* Four RCTs have examined the effect of allopurinol on calcium stones, which has suggested a reduced stone recurrence. Similar to studies with potassium citrate, studies were small and included increased fluid intake in addition to allopurinol in some trials. It is administered in a dosage of 100 to 300 mg/d.

*Cholestyramine.* This treatment approach uses a bile acid sequestrant to reduce oxalate hyperabsorption in the presence of enteric hyperoxaluria. Cholestyramine binds free bile acids and reduces the irritating effect of free bile acids on the colonic mucosa. In addition, it has been shown to bind oxalate in vitro. Unfortunately, there are no RCTs on treatment of enteric hyperoxaluria available.

### Additional Readings


» Bhasin B, Urekli HM, Atta MG. Primary and secondary hyperoxaluria: understanding the enigma. *World J Nephrol.* 2015;4(2):235-244.

» Curhan GC, Taylor EN. 24-h uric acid excretion and the risk of kidney stones. *Kidney Int.* 2008;73(4):489-496.

» Dogliotti E, Vezzoli G, Nouvenne A, et al. Nutrition in calcium nephrolithiasis. *J Transl Med.* 2013;11:109; http://dx.doi.org/10.1186/1479-5876-11-109.

» Ferraro PM, Curhan GC, Granodambaro G, Taylor EN. Total, dietary, and supplemental vitamin C intake and risk of incident kidney stones. *Am J Kidney Dis.* 2016;67(3): 400-407.

» Ferreira LG, Pereira AC, Heilberg IP. Vitamin D receptor and calcium-sensing receptor gene polymorphisms in hypercalciuric stone-forming patients. *Nephron Clin Pract.* 2010;114(2):c135-c144.

» Fink HA, Wilt TJ, Eidman KE, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians clinical guideline. *Ann Intern Med.* 2013;158(7):535-543.

» Hess B, Hasler-Strub U, Ackermann D, Jaeger P. Metabolic evaluation of patients with recurrent idiopathic calcium nephrolithiasis. *Nephrol Dial Transplant.* 1997;12(7): 1362-1368.

» Knauf F, Ko N, Jiang Z, et al. Net intestinal transport of oxalate reflects passive absorption and SLC26A6-mediated secretion. *J Am Soc Nephrol.* 2011;22(12):2247-2255.

» Parks JH, Goldfisher E, Asplin JR, Coe FL. A single 24-hour urine collection is inadequate for the medical evaluation of nephrolithiasis. *J Urol.* 2002;167(4):1607-1612.

» Vezzoli G, Terranegra A, Arcidiacono T, Soldati L. Genetics and calcium nephrolithiasis. *Kidney Int.* 2011;80(6): 587-593.


## CALCIUM PHOSPHATE STONES AND DISTAL RTA

### Clinical Features and Pathogenesis

In general, patients with calcium phosphate stones have the same underlying risk factors as those with calcium oxalate stones. In addition, high urine pH fosters calcium phosphate stones (usually urine pH > 6 on a 24-hour basis). Distal RTA is a rare condition characterized by impaired hydrogen ion secretion in the distal nephron. Distal RTA can occur as an inherited defect of proteins that are involved in ion excretion (eg, apical proton pump), secondary to

an autoimmune disease (eg, Sjögren syndrome), or idiopathically. Hypokalemia is usual, as is hypocitraturia. In addition, laboratory findings demonstrate normal anion gap metabolic acidosis and usually high urine pH. Incomplete distal RTA shows the same findings in urine (high urine pH, hypocitraturia, and hypercalciuria), yet serum bicarbonate levels are frequently within the normal range. Incomplete distal RTA can be further examined by demonstrating an inability to lower urine pH to <5.3 despite proton loading (by administering oral ammonium chloride or, with fewer side effects, simultaneous furosemide and fludrocortisone treatment). If untreated, distal RTA and concomitant calcium phosphate nephrolithiasis can lead to nephrocalcinosis and bone disorders.

### Treatment

Unfortunately, no RCTs exist regarding the treatment of calcium phosphate stones and distal RTA. Furthermore, individual response to therapy can differ from patient to patient. General measures include high fluid and low sodium intake. In addition, treatment with potassium citrate is recommended with the goal of increasing serum bicarbonate level and urinary citrate excretion. Following therapy with citrate, urinary pH should be monitored closely and not increase above 6.5 to 7 (because risk for precipitating calcium phosphate crystals increases). A thiazide diuretic can be added, especially when hypercalciuria or low bone density is present (see the Prevention of Calcium Nephrolithiasis section and Table 3).

### Additional Readings


» Buckalew VM Jr. Nephrolithiasis in renal tubular acidosis. *J Urol.* 1989;141(3, pt 2):731-737.

» Goldfarb DS. A woman with recurrent calcium phosphate kidney stones. *Clin J Am Soc Nephrol.* 2012;7(7):1172-1178.

» Walsh SB, Shirley DG, Wrong OM, Unwin RJ. Urinary acidification assessed by simultaneous furosemide and fludrocortisone treatment: an alternative to ammonium chloride. *Kidney Int.* 2007;71(12):1310-1316.


## URIC ACID STONES

### Clinical Features and Pathogenesis

Uric acid stones are responsible for 5% to 10% of all kidney stones. Uric acid gravel or stones are often orange or red in appearance and form rhomboid/football-shaped crystals on urine microscopy. Uric acid (insoluble form) is in equilibrium with urate (soluble form) at pH of 5.5, while at pH < 5.5, the insoluble uric acid concentration is higher than that of urate followed by crystal precipitation. Low urinary pH is therefore the principal driving force (80%) for uric acid crystal formation, followed by hyperuricosuria (20%), defined as uric acid excretion > 800 mg/d in men and >750 mg/d in women.

Uric acid stones are common in patients with gout, metabolic syndrome, and diabetes. Less common causes of uric acid stones are myeloproliferative disorders, purine overingestion, or rare hereditary enzyme deficiency states such as Lesch-Nyhan syndrome. Recently, an association between uric acid stones and insulin resistance, diabetes mellitus, and obesity has been demonstrated. Diabetic patients more often experience uric acid stones (30%-40%) as compared to the general stone-forming population (5%-10%).

### Treatment

Because low urine pH is the most important pathogenic factor of uric acid stone formation, urine alkalinization is an effective intervention to reduce uric acid crystallization and dissolve uric acid stones. Potassium citrate is recommended (20-30 mEq 2-3 times daily) with a goal urine pH of 6 to 6.5 (Table 3). Although potassium citrate salts are effective, urinary overalkalinization should be avoided to prevent calcium phosphate supersaturation and stone formation. In patients with hyperuricosuria, dietary purine restriction is recommended and if insufficient, pharmacologic intervention with allopurinol may be considered (especially in patients with primary gout). Febuxostat, 80 mg, an xanthine oxidase inhibitor, has been shown to decrease urinary uric acid excretion in calcium stone formers with hyperuricosuria. However, its role in preventing calcium or even uric acid stones remains to be defined and warrants future investigations.

### Additional Readings


» Abate N, Chandalia M, Cabo-Chan AV Jr, Moe OW, Sakhaee K. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. *Kidney Int.* 2004;65(2):386-392.

» Arowojolu O, Goldfarb DS. Treatment of calcium nephrolithiasis in the patient with hyperuricosuria. *J Nephrol.* 2014;27:601-605.

» Bres-Niewada E, Dybowski B, Radziszewski P. Predicting stone composition before treatment–can it really drive clinical decisions? *Central Eur J Urol.* 2014;67(4):392-396.

» Daudon M, Lacour B, Jungers P. High prevalence of uric acid calculi in diabetic stone formers. *Nephrol Dial Transplant.* 2005;20(2):468-469.

» Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY. Association of urinary pH with body weight in nephrolithiasis. *Kidney Int.* 2004;65(4):1422-1425.

» Moe OW, Abate N, Sakhaee K. Pathophysiology of uric acid nephrolithiasis. *Endocrinol Metab Clin North Am.* 2002;31(4):895-914.


## INFECTION STONES

### Clinical Features and Pathogenesis

Infection stones are calculi that occur in association with UTIs as a consequence of microbial proliferation.

They are usually composed of magnesium-ammonium-phosphate (struvite) and/or carbonate apatite. Risk factors include recurrent UTIs, urinary tract obstruction, neurogenic bladder, voiding dysfunction, and urinary catheters. Women are more likely to be affected than men (10% vs 4%), whereas the overall incidence has declined in developed countries. It is important to note that a minority of women and majority of men can present with mixed stones of struvite and calcium oxalate, most likely from secondary infection in hypercalciuric patients who initially have calcium-oxalate stones. Symptoms are related to UTIs and may include flank pain or hematuria. Urease-producing Gram-negative organisms (eg, *Proteus* spp, *Klebsiella* spp, *Pseudomonas* spp, or *Providencia* spp) metabolize urinary urea into ammonium and bicarbonate. Ammonium combines with magnesium, phosphate, and water to form magnesium-ammonium-phosphate stones. Infection stones can branch and result in staghorn calculi, presenting as kidney abscess, urosepsis, and decreased kidney function. Urinalysis demonstrates pH $>$ 7, leukocytes, and bacteria. Urine sediment reveals coffin-lid–shaped crystals.

### Treatment

As compared with other stone types, removal of the infected stone is the main goal of treatment because bacteria can survive within the calculus and cannot be easily eradicated by antibiotics. Nevertheless, urine cultures should be obtained and antibiotics should be selected according to the resistance pattern of the identified pathogen. The AUA guidelines recommend percutaneous nephrolithotomy monotherapy as the treatment of choice for staghorn calculi; under certain circumstances, combination with shockwave lithotripsy, shockwave lithotripsy monotherapy, ureteroscopy, or open approaches might be necessary. In addition, because struvite stones may be secondary calcium-oxalate stones in the setting of hypercalciuria, it is important to define and treat any metabolic abnormality. Additional options of medical treatment are limited: acetohydroxamic acid is a urease inhibitor and can significantly reduce stone growth of struvite stones, but use is limited by its severe side effects, including phlebitis and hypercoagulable disorders. The AUA guidelines recommend that acetohydroxamic acid (15 mg/kg/d) may be a feasible approach for patients with residual and/or recurrent struvite stones after surgical interventions have failed.

### Additional Readings


» Kristensen C, Parks JH, Lindheimer M, Coe FL. Reduced glomerular filtration rate and hypercalciuria in primary struvite nephrolithiasis. *Kidney Int.* 1987;32(5):749-753.

» Marien T, Miller NL. Treatment of the infected stone. *Urol Clin North Am.* 2015;42(4):459-472.

» Miano R, Germani S, Vespasiani G. Stones and urinary tract infections. *Urol Int.* 2007;79(suppl 1):32-36.

» Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. *J Urol.* 2014;192(2):316-324.

» Preminger GM, Assimos DG, Lingeman JE, et al. Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. *J Urol.* 2005;173(6):1991-2000.

» Rodman JS, Williams JJ, Jones RL. Hypercoagulability produced by treatment with acetohydroxamic acid. *Clin Pharmacol Ther.* 1987;42(3):346-350.


## CYSTINURIA

### Clinical Features and Pathogenesis

Cystinuria is an autosomal inherited form of nephrolithiasis caused by a defective multisubstrate basic amino acid transporter expressed in the renal proximal tubule and small intestine. Although the inactivating mutations cause urinary wasting of cystine, ornithine, lysine, and arginine (COLA amino acids), the phenotype is primarily driven by the insolubility of cystine in urine. Cystine stones are found in 1% to 2% of kidney stone patients, with a higher percentage among children (5%). The first symptomatic cystine stone usually occurs between ages 2 to 40 years (median age of onset: girls, 12 years; boys, 15 years). The clinical presentation includes flank pain and hematuria, as seen with other renal calculi. Urinalysis demonstrates pathognomonic hexagonal cystine crystals in one-quarter of patients. The cyanide-nitroprusside screen of urine represents a qualitative screening test that detects urinary cystine concentrations $>$ 75 mg/L. However, specificity is limited because false-positive results can be obtained in patients with Fanconi syndrome or ingesting ampicillin or sulfa-containing medications. Patients with confirmed cystine stones, urinary cystine crystals, or a positive cyanide-nitroprusside test result should undergo 24-hour urine collection to quantify cystine excretion.

### Treatment

Treatment of patients with cystinuria is challenging and can be divided into conservative measures and administration of thiol-containing drugs. Conservative interventions are directed at reducing cystine supersaturation by increasing fluid intake and urine pH and restricting salt intake. Before initiating drug therapy, all conservative measures should be pursued unless the urinary cystine concentration is extremely high ($>$1,000 mg) and conservative measures are unlikely to be sufficient. Fluid intake is recommended to be 3 to 4 L/d with the goal of decreasing urine cystine concentration to $<$250 mg/L at pH 7. Solubility increases substantially, with alkaline pH warranting administration of potassium citrate. An

increase in both urine output and pH should be evenly divided throughout the day, including high fluid intake prior to sleep and potassium citrate being administered in higher dosages up to 3 to 4 mEq/kg per day (divided into 3-4 doses) with a goal urine pH > 7.0. Salt restriction reduces urinary cystine excretion by a mechanism not yet fully understood. Persistence of urine cystine excretion > 250 mg/L, cystine crystals on urine sediment (despite conservative measures), and failure to elevate pH to >7.0 may require initiation of thiol-based drugs, namely D-penicillamine (500-2,000 mg/d in 3-4 divided doses) and tiopronin (400-1,200 mg/d in 3 divided doses). Both drugs reduce the disulfide bonds of cystine-generating mixed disulfides with increased solubility. Use of thiol-based drugs is generally limited because of the concern for severe adverse effects, including rash, pemphigus, agranulocytosis, thrombocytopenia, and membranous nephropathy, which are generally less frequently observed with tiopronin. The angiotensin-converting enzyme inhibitor captopril may represent an alternative for patients who cannot tolerate D-penicillamine/tiopronin. Captopril contains sulfhydryl groups that form captopril-cysteine disulfides that are more soluble than cystine alone. Unfortunately, high doses are required (>150 mg/d), which may cause a decrease in blood pressure, which limits its use. In addition, experiences using captopril in cystinuria have been contradictory and no RCTs are available.

### Additional Readings


» Claes DJ, Jackson E. Cystinuria: mechanisms and management. *Pediatr Nephrol.* 2012;27(11):2031-2038.
» Fattah H, Hambaroush Y, Goldfarb DS. Cystine nephrolithiasis. *Transl Androl Urol.* 2014;3(3):228-233.
» Rogers A, Kalakish S, Desai RA, Assimos DG. Management of cystinuria. *Urol Clin North Am.* 2007;34(3):347-362.
» Sumorok N, Goldfarb DS. Update on cystinuria. *Curr Opin Nephrol Hypertens.* 2013;22(4):427-431.


## ASSOCIATED CONDITIONS AND COMPLICATIONS OF NEPHROLITHIASIS

### Medullary Nephrocalcinosis

Nephrocalcinosis is defined as calcification of the renal parenchyma and typically affects the renal medulla. Hypercalciuria is the most common risk factor and presents with or without concomitant hypercalcemia. Nephrocalcinosis is often asymptomatic, chronic, and slowly progressive, which frequently leads to its incidental discovery during imaging (ultrasonography or CT). Primary hyperthyroidism, milk-alkali syndrome, distal RTA, and medullary sponge kidney (MSK) are the most common diagnoses when nephrocalcinosis is observed. During the past few years, several genetic disorders have been identified that are associated with nephrocalcinosis, such as Dent disease, Lowe syndrome, primary hyperoxaluria types 1 to 3, and familial hypomagnesemia with hypercalciuria and nephrocalcinosis. Renal prognosis of nephrocalcinosis depends on the underlying disease: patients with distal RTA or MSK rarely develop CKD. In contrast, primary hyperoxaluria or Dent disease is associated with a progressive decline in kidney function.

### Medullary Sponge Kidney

A malformative disorder of the kidney, MSK leads to collecting duct dilatation and the formation of medullary "cysts." It is widely thought to be a sporadic disorder, but autosomal dominant inheritance has been described. It manifests with nephrocalcinosis, UTIs, and recurrent kidney stones. Due to the anatomic feature of the disease, the dilatation of the collecting ducts can cause urinary stasis and enhance the precipitation of poorly soluble substances. Furthermore, affected patients may present with any of several established stone risk factors such as hypercalciuria and hypocitraturia. Hypercalciuria is presumed to be secondary to impaired calcium reabsorption in damaged collecting tubules. In addition, MSK is associated with impaired urinary acidification in the collecting duct and features of incomplete distal RTA.

Macro- and microhematuria, kidney injury, and hyperparathyroidism can occur as part of the disease. The pathogenesis of hyperparathyroidism remains poorly understood. It has been suggested as a consequence of negative calcium balance due to increased urinary calcium loss. Likewise, MSK is associated with higher risk for osteopenia/osteoporosis.

The diagnosis of MSK can be made by IVP demonstrating a characteristic brush appearance of the papillae, as shown in Fig 4. In some centers, CT urography is replacing this test. The movement away from IVP in general to noncontrast CT and ultrasonography results in fewer patients being diagnosed with MSK. Although CT and ultrasonography can point toward MSK by demonstrating gross calcification or medullary hyperechogenicity, these findings are not specific because they can similarly be observed in patients with other conditions, such as Dent disease. Hence, the confirmation of the diagnosis by using IVP or CT urography provides important prognostic information.

When symptoms such as nephrolithiasis are present, urinary risk factors must be evaluated by performing a 24-hour urine collection and treated according to the basic principles described in the Calcium Nephrolithiasis section. Treatment with alkali citrate appears to be of benefit, lowering hypercalciuria and improving bone mineralization.

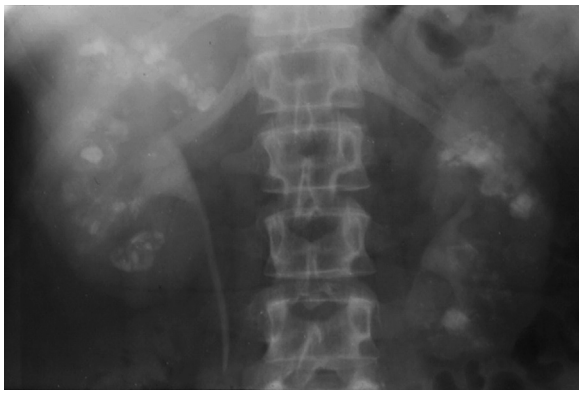


**Figure 4.** Medullary sponge kidney. Conventional intravenous pyelogram demonstrates accumulation of contrast agent in the ectatic renal collecting tubules, creating a paint brush-like appearance. Reproduced from Maw et al (*Am J Kidney Dis* 2007;50[1]:146-150) with permission of the National Kidney Foundation.

### Osteopenia and Osteoporosis

It is well established that nephrolithiasis is associated with loss in bone mineral density, osteopenia, and osteoporosis. One may argue that osteopenia is the most severe feature of nephrolithiasis given the increased mortality observed in association with bone fractures. There are various possible mechanisms for the pathogenesis of osteopenia in kidney stone formers, including hypercalciuria and high dietary animal protein intake leading to metabolic acidosis. In addition, release of cytokines that are known to increase bone resorption (eg, interleukin 1, interleukin 6, and tumor necrosis factor $\alpha$) is also associated with idiopathic hypercalciuria. Mutations of the renal sodium phosphate cotransporter leading to urinary phosphate wasting, stone formation, and osteopenia are examples of a genetic defect leading to kidney stones and osteopenia.

### Kidney Failure

Nephrolithiasis is an infrequent cause of kidney failure. However, struvite stones, which can be secondary to anatomic and functional urinary tract anomalies, and certain hereditary stone diseases (cystinuria, primary hyperoxaluria, and Dent disease) are associated with higher risk for acute kidney disease or CKD. A relationship between nephrolithiasis and CKD in the general population has been noted in several studies. Although it is well established that nephrolithiasis is associated with hypertension, obesity, coronary artery disease, or diabetes (which are generally regarded as risk factors for CKD), even following adjustment for these known risk factors, risk for clinical CKD was 50% to 65% greater in stone formers versus controls. What are the possible explanations for the association of kidney stones and CKD? Recurrent obstruction can lead to tubular damage by increased intratubular pressure promoting renal vasoconstriction, a decrease in renal blood flow, and tissue damage. Animal models have demonstrated that activation of the innate immune system by oxalate crystals plays a pivotal role in the progression of oxalate-induced CKD. Future research will need to examine whether targeted interventions to inhibit crystal-induced inflammation can slow the progression of CKD in humans.

### Additional Readings


» Arrabal-Polo MA, Cano-Garcia Mdel C, Canales BK, Arrabal-Martin M. Calcium nephrolithiasis and bone demineralization: pathophysiology, diagnosis, and medical management. *Curr Opin Urol.* 2014;24(6):633-638.

» Fabris A, Anglani F, Lupo A, Gambaro G. Medullary sponge kidney: state of the art. *Nephrol Dial Transplant.* 2013;28(5):1111-1119.

» Knauf F, Asplin JR, Granja I, et al. NALP3-mediated inflammation is a principal cause of progressive renal failure in oxalate nephropathy. *Kidney Int.* 2013;84(5):895-901.

» Shavit L, Jaeger P, Unwin RJ. What is nephrocalcinosis? *Kidney Int.* 2015;88(1):35-43.

» Zisman AL, Evan AP, Coe FL, Worcester EM. Do kidney stone formers have a kidney disease? *Kidney Int.* 2015;88(6):1240-1249.


## ACKNOWLEDGEMENTS


*Support:* Dr Knauf is supported by grants from the Deutsche Forschungsgemeinschaft (KN 1148/2-1), Gessler Foundation, The Oxalosis and Hyperoxaluria Foundation, and a network grant "TRENAL" from the German Academic Exchange Service (DAAD).

*Financial Disclosure:* Dr Knauf has received research grant support from Dicerna Pharmaceuticals, Cambridge, MA.

*Peer Review:* Evaluated by 4 external peer reviewers, the Education Editor, and the Editor-in-Chief.