Kidney Stone Pathophysiology, Evaluation and Management: Core Curriculum 2023

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Kidney stone disease, also known as nephrolithiasis or urolithiasis, is a disorder in which urinary solutes precipitate to form aggregates of crystalline material in the urinary space. The incidence of nephrolithiasis has been increasing, and the demographics have been evolving. Once viewed as a limited disease with intermittent exacerbations that are simply managed by urologists, nephrolithiasis is now recognized as a complex condition requiring thorough evaluation and multifaceted care. Kidney stones are frequently manifestations of underlying systemic medical conditions such as the metabolic syndrome, genetic disorders, or endocrinopathies. Analysis of urine chemistries and stone composition provide a window into pathogenesis and direct ancillary studies to uncover underlying diseases. These studies allow providers to devise individualized strategies to limit future stone events. Given its complexity, kidney stone disease is best addressed by a team led by nephrologists and urologists with input from multiple other health professionals including dietitians, endocrinologists, interventional radiologists, and endocrine surgeons. In this installment of *AJKD*'s Core Curriculum in Nephrology, we provide a case-based overview of nephrolithiasis, divided by the individual stone types. The reader will gain a pragmatic understanding of the pathophysiology, evaluation, and management of this condition.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Nephrolithiasis describes a syndrome characterized by the development of solid crystalline masses within the urinary space of the kidney. There is significant diversity in its pathogenesis, risk factors, clinical course, and treatments. The factors that predispose individuals to kidney stone formation can be genetic, metabolic, and environmental. Nephrolithiasis is now recognized as a marker for systemic disease and a predictor of metabolic and cardiovascular complications.

The medical community's perspective on nephrolithiasis has gradually shifted from viewing it as a primarily urologic illness to a chronic medical condition requiring long-term surveillance and management. The management of nephrolithiasis is grounded in identifying the urine chemistries that predispose the individual to stone formation. This is done by quantifying the excretion rate of several urinary solutes as well as by determining stone composition when possible. In a few instances, a single cause of the kidney stone can be determined and treated. More commonly, the clinician identifies multiple presumptive risk factors and must devise a plan that favorably modifies these risk factors through pharmacologic or dietary interventions.

Epidemiology

Nephrolithiasis is common, affecting approximately 1 in 11 people in the United States. By age 70, 19.1% of men and 9.4% of women report ever having a kidney stone. The burden of this disease appears to be growing, with the National Health and Nutrition Examination Survey noting an increase in the self-reported prevalence of kidney stones, from 3.2% in 1976-1980 to 8.8% in 2014. The male-to-female ratio has decreased from 3:1 to about 2:1 in the past 2 decades, attributed to an increasing prevalence of obesity. Obesity and diabetes are strongly associated with a history of kidney stones in multivariate models, particularly for women.

Racial and ethnic differences are also evident, with the prevalence of nephrolithiasis being higher in White male patients, intermediate in Hispanic and Asian patients, and less common in Black patients. The highest risk of stone formation is reported in men in the United Arab Emirates and Saudi Arabia. In the United States, there is an increasing prevalence of nephrolithiasis from North to South and from West to East. Heat-related increases in urinary concentration from nonrenal water losses, geographic differences in diabetes and obesity rates, and other environmental and genetic factors likely explain these variances. The link between increased environmental temperatures and increased rates of stone disease is well documented, thus predicting a further increase in its incidence with climate change.

Case 1: *A 28-year-old woman with no past medical history presented to the emergency department (ED) for flank pain. A computed tomography (CT) scan showed a 2-mm stone in her lower ureter. She was treated with pain medication and subsequently spontaneously passed a calcium oxalate stone.*

Question 1: Which of the following is a potential risk factor for recurrent stone formation in this patient?
(a) Female gender
(b) Older age of initial episode
(c) Family members with nephrolithiasis
(d) Calcium oxalate stone

For the answer to this question, see the following text.

The risk of stone recurrence is high, with a relapse rate of 50% in 5-10 years and 75% in 20 years. Risk factors for recurrent stones include multiple prior stone episodes, younger age of onset, male gender, family history of kidney stones, and higher body mass index (BMI). Stone characteristics which predict recurrence include the presence of 2 or more stones across both kidneys, the presence of stones in the renal pelvis or lower kidney pole, and a stone composition consisting of uric acid, struvite, or brushite (a particularly hard form of calcium phosphate). Therefore, the answer to Question 1 is (c). The online Recurrence of Kidney Stone (ROKS) nomogram (https://www.qxmd.com/calculate/calculator_438/roks-recurrence-of-kidney-stone-2018) estimates the risk of recurrence at varying time points in symptomatic stone-formers using baseline characteristics.

Nephrolithiasis has been associated with significant morbidity beyond the urologic system. Among a cohort in Olmsted County, Minnesota, stone-formers were at increased risk of developing chronic kidney disease (CKD) compared to non-stone-formers. In a population cohort study from Canada with a median follow-up period of 11 years, the risks of end-stage kidney disease, late-stage CKD, and doubling of serum creatinine were significantly higher among participants with 1 or more episodes of nephrolithiasis, especially in women and those younger than 50 years. Struvite stone-formers with staghorn calculi and patients with cystinuria are at especially high risk for CKD.

Nephrolithiasis is also associated with an increased risk of cardiovascular disease. Studies reveal a greater prevalence of hypertension and possibly increased carotid wall thickness in stone patients, even when controlling for major atherosclerotic risk factors. One analysis revealed a 31% increase in risk for myocardial infarction in those with a history of nephrolithiasis despite adjusting for known risk factors for cardiovascular disease.

Finally, the link between kidney stones and reduced bone mineral density and fractures is particularly robust. The skeleton commonly serves as a source for the excessive urinary calcium excretion rates that frequently predispose individuals to stones.

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Overview of Pathogenesis

Case 2: *A 57-year-old woman with history of osteoporosis is referred for evaluation of recurrent kidney stones. She has had recurrent bladder infections with Escherichia coli. Prior urinalyses consistently have shown a pH > 6.7.*

Question 2: Which stone type is most likely to occur with this urine pH?
(a) Calcium oxalate
(b) Calcium phosphate
(c) Cystine
(d) Uric acid

For the answer to this question, see the following text.

The formation of kidney stones is a complex biologic process (Fig 1). Identification of modifiable pathogenic factors is essential for the treatment and prevention of future kidney stones.

Urinary solute supersaturation provides the necessary milieu for stone formation. Supersaturation refers to a state in which solutes in a solution are present at concentrations

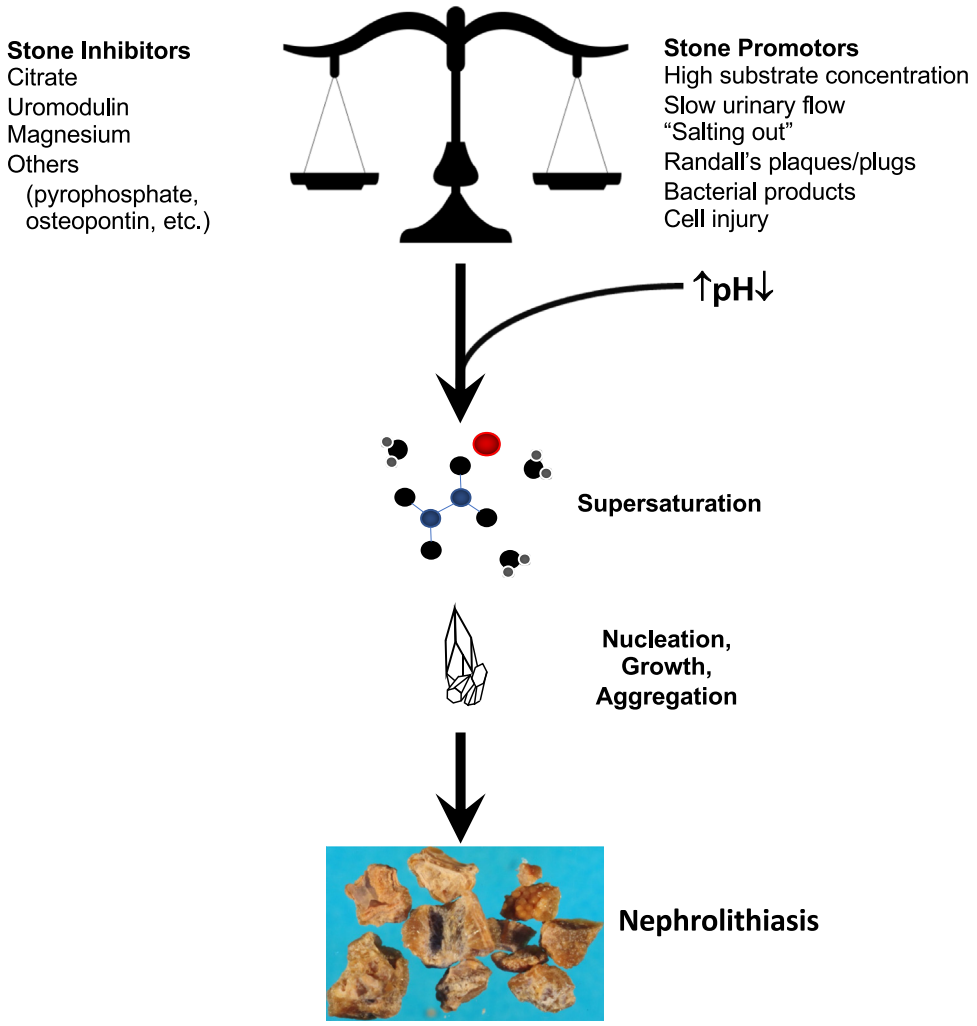

Figure 1. Overview of the pathogenesis of nephrolithiasis.

that exceed their solubility. Supersaturation can be quantified as a ratio of the product of their concentration in the urine to their solubility product. A ratio > 1 indicates that the urine is supersaturated and those solutes would spontaneously precipitate if the urine were stagnant.

Supersaturation is modulated by the balance of crystallization inhibitors and promoters, urine volume, and urine pH. Known inhibitors include citrate, pyrophosphate, and magnesium, as well as proteins such as uromodulin, glycosaminoglycans, osteopontin, and calgranulin. Urinary citrate inhibits the formation of calcium-containing (calcareous) stones by sequestering calcium, thus limiting calcium oxalate or calcium phosphate crystallization. Low urine volume increases the concentration of lithogenic solutes, thus predisposing them to crystallization.

Urine pH modifies the solubility of these solutes. Calcium phosphate and struvite are less soluble at a higher pH; thus, in alkaline urine these components are predisposed to form stones. By contrast, uric acid and cystine are less soluble at a lower pH, making their stones more likely to form in acidic urine. So the answer to Question 2 is (b), calcium phosphate.

Although supersaturation is necessary, it is not sufficient for stone disease. Indeed, urine is normally supersaturated with several solutes, but most individuals do not develop nephrolithiasis. Stone formation typically begins with a nucleus that provides a substrate for crystal growth in supersaturated urine. Injured epithelial cells may serve as nuclei. Nucleation can also occur on structures called Randall's plaques, calcium phosphate deposits originating in the basement membrane of the thin limbs of the loop of Henle. These concretions progressively enlarge, eventually rupturing through the uroepithelium over the renal papilla and extending into the calices. Calcium phosphate or calcium oxalate crystals can grow on these nucleating surfaces and aggregate with other crystals before becoming nephroliths.

A genetic component to recurrent stone formation has been recognized for decades. Studies have confirmed the

heritability of patterns of urinary excretion of calcium, citrate, oxalate, and uric acid. Many genetic loci have been implicated in modifying disease risk but have not yet been translated into actionable therapeutics. Monogenic causes of nephrolithiasis do exist and include cystinuria, primary hyperoxaluria, adenine phosphoribosyltransferase deficiency, and Dent's disease. Commercially available testing is available for many of these. Although no specific guidelines for genetic testing have been developed, it is reasonable to consider this option for individuals with early onset stones, severe recurrent disease, or a strong family history.

Anatomic abnormalities such as medullary sponge kidney, polycystic kidney disease, or urothelial diverticula are associated with an increased risk of kidney stones. Urinary stasis is likely to be a major mechanism for these associations, although local alterations in the previously described modifiers of lithogenesis may be playing a role. Multiple studies have suggested a role for inflammation in the development of stone disease. How this might advance clinical care is still an unanswered question.

Additional Readings

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Clinical Presentation and Evaluation

Pain of variable intensity with hematuria is the most common presentation of nephrolithiasis. It is classically abrupt in onset, paroxysmal, and waxing and waning in character. The site of obstruction correlates with the site of pain, and the location of the pain may change as the stone migrates. Gross or microscopic hematuria occurs in most patients. In a retrospective study among patients with proven, acutely symptomatic nephrolithiasis, microhematuria had a sensitivity of 95% when testing was performed on the first day but declined to 65% when testing occurred on days 3-4 after pain onset. Other associated symptoms include dysuria, urgency, nausea, and vomiting. Stone passage provides almost instantaneous relief in most cases. Some patients pass "gravel" often seen with uric acid stones. The complications of nephrolithiasis include infection and acute kidney injury from obstructive nephropathy. The acute management of the symptomatic stone is illustrated in Figure 2.

Stones can frequently be asymptomatic and be discovered incidentally on imaging. There are no definitive guidelines for the management of these patients. With multiple or large stones, additional workup and urology referral for consideration of stone removal would be appropriate. However, if a conservative approach is chosen for individuals with minimal stone burden, serial imaging is necessary to detect silent increases in size and number. Studies suggest that about a quarter of asymptomatic, conservatively managed stones will eventually become symptomatic and that 10% to 15% will require urologic interventions.

Case 3: *A 40-year-old man with a history of recurrent nephrolithiasis and hypertension presents to the ED with acute pain, nausea, and vomiting, similar to his previous 4 episodes of kidney stones over the past 2 years. He has never undergone evaluation of the cause of his kidney stones and has said he has no family history of stones. He takes hydrochlorothiazide for hypertension, topiramate for migraines, and uses ibuprofen and diphenhydramine for breakthrough headaches. His physical examination is remarkable for right flank tenderness and a BMI of 28.*

Question 3: Which of his medications may increase his risk for recurrent stone formation?
(a) Hydrochlorothiazide
(b) Topiramate
(c) Ibuprofen
(d) Diphenhydramine

Question 4: The patient is admitted for pain control. The workup for recurrent nephrolithiasis during this current admission includes all the following *except:*
(a) Complete metabolic profile
(b) Urine microscopy
(c) CT abdomen and pelvis without intravenous contrast
(d) 24-hour urine stone risk profile

For the answers to these questions, see the following text.

A detailed history targeting the risk factors for kidney stones is crucial to identify potential etiologies and directed therapies. The history should include the age at first stone occurrence, number and frequency of stone events, laterality of stones, type of stone, type and number of surgical interventions, associated infections, and family history of stones. The history should also focus on dietary habits, including the amount of fluid consumed and the intake of sodium, protein, oxalate, calcium, and simple sugars. Questions about frequency and amount of urination, the color of urine, and nocturia are frequently more informative than asking for fluid intake volume. Specific foods to ask about include fast food, canned soups, cured meats and animal protein more generally, soft drinks, nuts, dairy, chocolate, and spinach. When required, a more thorough review of sources of dietary oxalate can be

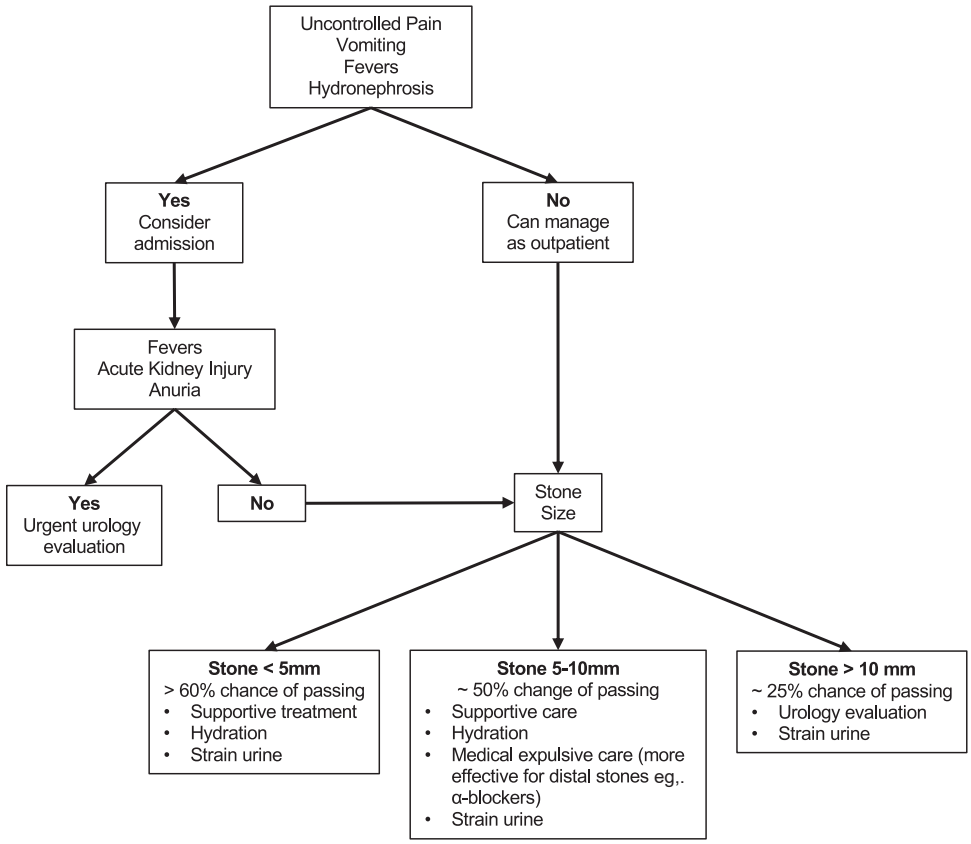


Figure 2. Acute management of nephrolithiasis.

performed with the assistance of online resources (https://kidneystones.uchicago.edu/how-to-eat-a-low-oxalate-diet/).

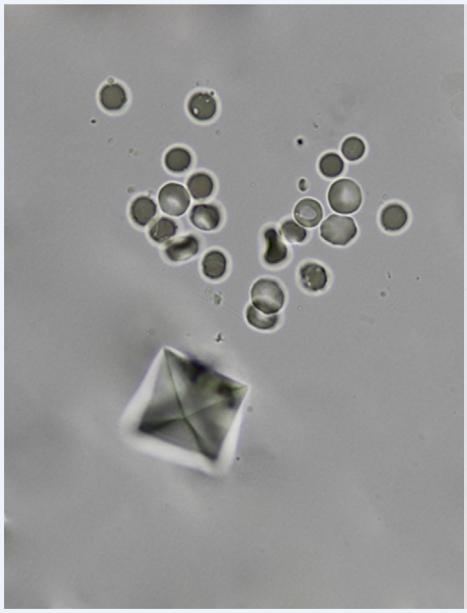
Kidney stones can present as a complication of a known clinical condition or be the initial manifestation of disease. One of the most frequently encountered predisposing conditions is the metabolic syndrome. Patients with malabsorption due to cystic fibrosis, gastric bypass, Crohn's disease, or celiac disease are predisposed to calcium oxalate stones. A history of radiation to the neck, lithium use, or a family history of multiple endocrine neoplasia raises the possibility of primary hyperparathyroidism. People with autoimmune disorders such as Sjögren's syndrome may be predisposed to stone disease due to distal renal tubular acidosis (RTA). Systemic diseases and their associated stone types are summarized in Boxes 1-4.

The history also should include medication use, including over-the-counter medications and supplements. Drug-induced nephrolithiasis is rare and represents 1% to 2% of all renal calculi. Two major mechanisms whereby drugs may promote stone formation are (1) direct crystallization of the drug or its metabolites (see Box 4), and (2) altering the supersaturation of normally occurring solutes, seen with topiramate and other inhibitors of carbonic anhydrase (see Box 2). The resulting alkaline urine and hypocitraturia from metabolic acidosis predisposes individuals to calcium phosphate nephrolithiasis. The answer to Question 3 is thus (b), topiramate.

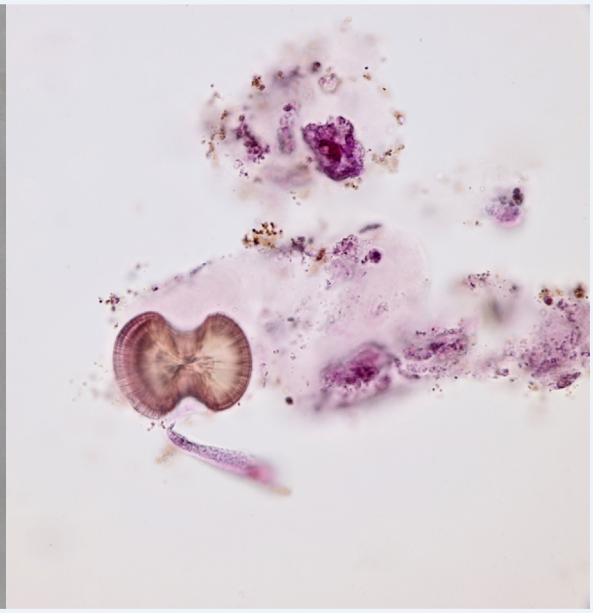
Laboratory tests for the evaluation of nephrolithiasis should routinely include a complete metabolic profile, serum uric acid, serum phosphate, intact parathyroid hormone, and a urinalysis with microscopy. In a patient with signs of a urinary tract infection, a urine culture should also be obtained. Hypokalemia and metabolic acidosis are suggestive of RTA, especially with a urine pH that is ≥ 6.5. High urine specific gravity suggests inadequate fluid intake. Urine microscopy may reveal crystalluria, providing clues to stone subtype. Boxes 1-4 reveal the appearance of the crystals that one may find.

Noncontrast helical CT is the imaging modality of choice for diagnosing kidney stones due to its high sensitivity and specificity, the ability to detect nearly all types of stones (except those caused by protease inhibitors), and the accurate delineation of size and location. The major disadvantages are cost and radiation exposure. Ultrasound has good specificity but poor sensitivity. This modality is used in pediatric and pregnant patients to limit their radiation exposure, and it is also an excellent screening test for obstruction in the acute setting. In patients with documented radiopaque stones, plain abdominal X-ray imaging can be used for assessing stone clearance, recurrence, or growth in order to minimize radiation exposure.

Box 1. Characteristic Crystalluria, Predisposing Factors, and Chronic Management Principles for Calcium Oxalate Nephrolithiasis



Calcium oxalate dihydrate



Calcium oxalate monohydrate

Predisposing Factors

- Low urine volume
  - ◇ Inadequate intake
  - ◇ Extrarenal fluid losses (diarrhea, sweating)
- Hypocitraturia
  - ◇ Metabolic acidosis
  - ◇ Potassium depletion
  - ◇ Excess animal protein intake
- Hypercalciuria
  - ◇ Idiopathic hypercalciuria
  - ◇ High sodium intake
  - ◇ Primary hyperparathyroidism
  - ◇ Vitamin D excess states
  - ◇ Osteolytic conditions
  - ◇ Metabolic acidosis
  - ◇ Excess simple sugar consumption
  - ◇ High animal protein intake
  - ◇ Dent's disease
  - ◇ Thick ascending limb defects (Bartter syndrome, familial hypomagnesemia with hypercalciuria)
  - ◇ Cadmium toxicity
- Hyperoxaluria
  - ◇ Fat malabsorption
  - ◇ Dietary excess
  - ◇ Primary hyperoxaluria
  - ◇ Reduced colonic *Oxalobacter*
  - ◇ Vitamin C excess
  - ◇ Excess glycine intake
- Medullary sponge kidney
- Polycystic kidney disease

(Continued)

Box 1 (Cont'd). Characteristic Crystalluria, Predisposing Factors, and Chronic Management Principles for Calcium Oxalate Nephrolithiasis

Treatment

- Address reversible factors
- Increase urine volume at 2.5 L/d
- Restrict sodium (<2,300 mg/d)
- Optimize calcium intake (1,000-1,200 mg/d)
- Administer thiazide if hypercalciuric
- Restrict animal protein
- Administer potassium citrate and/or treat potassium deficiency if hypocitraturic
- RNA interference for primary hyperoxaluria
- Possibly helpful:
  - ◇ Oxalate restriction for significant hyperoxaluria
  - ◇ Sucrose/fructose restriction
  - ◇ Xanthine oxidase inhibitor if hyperuricosuric
  - ◇ Cholestyramine for fat malabsorption

Stone collection for formal compositional analysis should be attempted in all patients, either at the time of stone extraction procedures or by the diligent use of a urine strainer. A patient is classified as a uric acid, struvite, or cystine stone-former if the stones contain any proportion of these minerals. For calcium stones, the patient is typically classified as a calcium oxalate or calcium phosphate stone-former by which mineral exceeds 50%. A 24-hour urine collection—2 collections, if feasible—is the cornerstone of evaluation in patients with recurrent nephrolithiasis. This may be the only tool to guide therapy when stone composition is unknown, as is the case in as many as half of incident stone-formers. The collection should be done in an outpatient setting under stable conditions, when the patient is consuming his or her usual diet, because individuals tend to change their habits during an acute episode. Thus, the answer to Question 4 is (d), 24-hour urine stone risk profile.

Box 5 lists the 24-hour urine parameters that are useful for assessing stone risk and describes their interpretation. These parameters must be interpreted as continuous risk variables rather than risk factors with absolute thresholds. Some laboratories report supersaturation ratios for calcium oxalate, calcium phosphate, and uric acid from these 24-hour urine results. The supersaturation ratios capture the interrelatedness of the individual urine components in defining risk. Reducing supersaturation by addressing specific contributory factors is a reasonable strategy to reduce stone risk. The therapeutic supersaturation goal for calcium oxalate is 4, for calcium phosphate is 1, and for uric acid is 1.

Because calcium stones are the most common, it is reasonable to institute therapy directed toward this stone type when formal stone composition is not available, unless the 24-hour urine studies suggest otherwise. Long-term management of kidney stone disease, especially for individuals with frequent recurrences, requires periodic reevaluation of the impact of dietary changes and medications on these urine indices as well as reassessments of stone burden by imaging (Fig 3).

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Calcium Stones

Calcium Oxalate Stones

Case 4: *A 45-year-old woman with a history of recurrent calcium oxalate stones is referred for evaluation. She has previously undergone partial colectomy with primary anastomosis for localized colon cancer. She has frequent loose stools. She is otherwise healthy and denies any family history of stones. Her physical examination is normal. She only takes cholecalciferol, 1,000 IU, and calcium, 500 mg, daily. Laboratory studies were obtained.*

Laboratory Studies	Value
Serum	
Sodium, mEq/L	142
Potassium, mEq/L	4.1
Chloride, mEq/L	109
Bicarbonate, mEq/L	21
SUN, mg/dL	22
Creatinine, mg/dL	0.8
Glucose, mg/dL	110
Calcium, mg/dL	10.8
Serum phosphorus, mg/dL	3
Intact PTH, pg/mL	70
25-Hydroxyvitamin D, ng/mL	30
24-hour urine stone profile	
Volume, L	2.5
pH	5.1
Calcium, mg	300
Oxalate, mg	30
Phosphorus, mg	840
Uric acid, mg	450
Sodium, mEq	180
Potassium, mEq	27
Magnesium, mg	42
Sulfate, mmol	21
Ammonium, mmol	82
Citrate, mg	280

Abbreviations: PTH, parathyroid hormone; SUN, serum urea nitrogen.

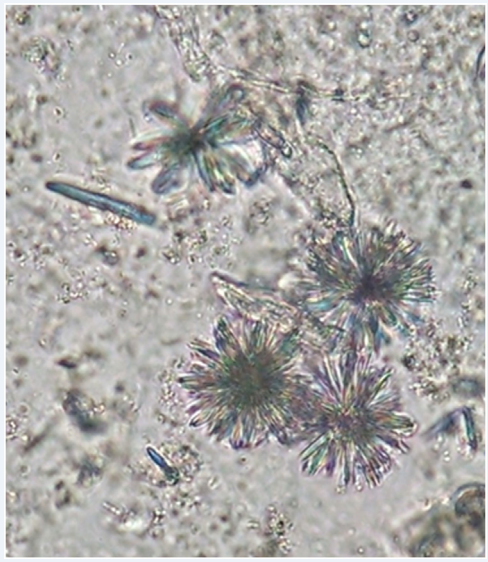
Question 5: Which of the following would be the most helpful therapy to prevent recurrent calcium oxalate stone formation in this case?

(a) Low oxalate diet
(b) Thiazide diuretic
(c) Parathyroidectomy
(d) Potassium citrate
(e) Cessation of vitamin D

For the answer to the above question, see the following text.

Approximately 80% of kidney stones are calcareous stones, the majority composed of calcium oxalate, with a small percentage made of calcium phosphate. The pathophysiological mechanisms for calcium oxalate stone formation are complex and include low urine volume, hypercalciuria, hypocitraturia, hyperoxaluria, and hyperuricosuria. These factors and their associated conditions and management are summarized in Box 1 and are discussed further here.

Box 2. Characteristic Crystalluria, Predisposing Factors, and Chronic Management Principles for Calcium Phosphate Nephrolithiasis



Predisposing Factors

- Higher urine pH
  - ◇ Secretory defect distal RTA (genetic or acquired, as occurs in Sjögren's syndrome)
  - ◇ "Incomplete" RTA
  - ◇ Carbonic anhydrase inhibitors (eg, acetazolamide, topiramate, or zonisamide)
  - ◇ Excess alkali administration, including potassium citrate
- Low urine volume[a]
- Hypocitraturia[a]
- Hypercalciuria[a]
- Medullary sponge kidney

Treatment

- Address reversible factors
- Increase urine volume
- Restrict sodium
- Administer thiazide if hypercalciuric
- Treat hypokalemia if hypocitraturic
- Treat metabolic acidosis with potassium citrate while avoiding excessive urinary alkalinization

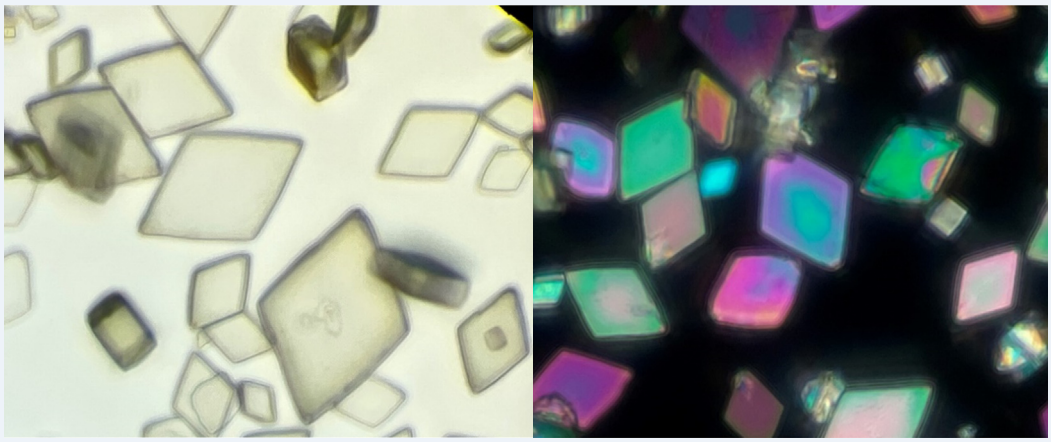
Abbreviation: RTA, renal tubular acidosis.
[a]Additional detail provided in Box 5.

Hypercalciuria

Mechanisms. High urine calcium is the most common metabolic abnormality found in recurrent calcium stone-formers, being present in 30% to 60% of such individuals. The definition of hypercalciuria in the context of kidney stones is controversial. Some define it as a 24-hour urinary calcium excretion that exceeds 200-300 mg/day or 4 mg/kg/day (0.1 mmol/kg/day). In reality, urinary calcium has a graded influence on stone risk, even at levels below these thresholds. In a cross-sectional study of 3,350 patients, the risk of stone formation progressively increased with increasing urinary calcium excretion rates above 150 mg/day (3.75 mmol/day).

Increased gut absorption as the sole mechanism for hypercalciuria is uncommon but can be seen with excessive exogenous vitamin D supplementation, CYP24A1 mutations, or diseases of calcitriol excess such as sarcoidosis. Standard doses of vitamin D supplementation do not

Box 3. Characteristic Crystalluria, Predisposing Factors, and Chronic Management Principles for Uric Acid Nephrolithiasis



Standard lighting Light

Predisposing Factors

- Markedly acidic urine
  - ◇ Metabolic syndrome
  - ◇ High animal protein intake
  - ◇ Metabolic acidosis
  - ◇ Potassium excess
- Low urine volume[a]
- Polycystic kidney disease
- Hyperuricosuria
- Lesch-Nyhan disease/partial HGPRT deficiency
- Excess purine intake or high cell turnover
- Glycogen storage disease

Treatment

- Address reversible factors
- Increase urine volume
- Apply alkali therapy to achieve urine pH 6.5-7.0
- Consider allopurinol if hyperuricosuric

Abbreviation: HGPRT, hypoxanthine-guanine phosphoribosyltransferase.
[a]Additional detail in Box 5.

increase kidney stone risk. Bone resorption as a sole cause of hypercalciuria can occur with hyperparathyroidism, immobilization, and bony involvement by cancer. Dietary factors can also contribute to hypercalciuria. High sodium intake results in decreased proximal tubular calcium reabsorption. High animal protein intake can enhance urinary calcium excretion as well, perhaps through the acid loading that it provokes. Excess simple sugar intake has also been associated with hypercalciuria via unclear mechanisms.

In most cases, the precise cause of hypercalciuria is unclear. In this so-called idiopathic hypercalciuria there are varying degrees of excessive dietary calcium absorption and bone resorption at play as well as variable defects in renal tubular calcium conservation. This syndrome is associated with loss of bone mineral, explaining its association with osteoporosis.

Evaluation. Specific tests to determine the cause of hypercalciuria may include PTH, 1,25 vitamin D, PTH-related peptide, and protein electrophoresis, depending on the clinical presentation, although cancer-associated hypercalcemia/hypercalciuria rarely produces stones. Depending on other elements of the clinical context, it may be reasonable to obtain bone densitometry in cases of primary hyperparathyroidism and idiopathic hypercalciuria.

Treatment. Clinical studies have shown that increasing water intake to ensure a urine volume of ~2.5 L/day is associated with reduced urinary supersaturation of calcium oxalate and a significant reduction in stone recurrence. A low-sodium diet and thiazides decrease hypercalciuria and reduce stone recurrence by stimulating proximal tubular calcium reabsorption through volume contraction. Thiazide-induced hypokalemia should be adequately treated because low potassium can decrease urine citrate. Restriction of dietary calcium intake is recommended only when hypercalciuria is due to excessive intestinal calcium absorption, such as with

Box 4. Characteristic Crystalluria, Predisposing Factors, and Chronic Management Principles for Noncalcareous, Nonuric Acid Nephrolithiasis

Magnesium-Ammonium-Phosphate (Struvite) Nephrolithiasis

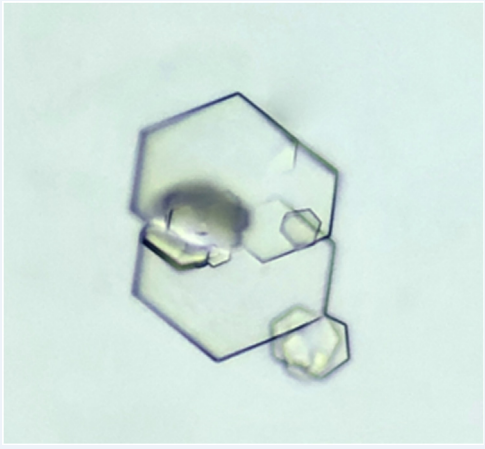
Predisposing Factors

- Urinary tract infection with urease expressing bacteria resulting in urinary alkalinization and excess ammonium production
- Low urine volume[a]

Treatment

- Eliminate infected stones and treat urinary tract infection
- Increase urine volume
- Possibly helpful: Urease inhibitor (acetohydroxamic acid or hydroxyurea)

Cystine Nephrolithiasis



Predisposing Factors

- Cystinuria
- Low urine volume[a]

Treatment

- Increase urine volume to achieve urine cystine < 250 mg/L
- Restrict sodium
- Recommend low-protein diet

(Continued)

Box 4 (Cont'd). Characteristic Crystalluria, Predisposing Factors, and Chronic Management Principles for Noncalcareous, Nonuric Acid Nephrolithiasis

- Treat with alkali therapy to achieve urine pH 7.0-8.0
- Treat with thiol drug (tiopronin or, less desirably, penicillamine or captopril)

Drug Nephrolithiasis

Sulfadiazine crystalluria

Predisposing Factors

- High-dose therapy with offending medications
  - o Allopurinol
  - o Ceftriaxone
  - o Ephedrine
  - o Fluoroquinolones
  - o Guaifenesin
  - o Magnesium trisilicate
  - o Phenazopyridine
  - o Protease inhibitors (eg, indinavir, atazanavir) and efavirenz
  - o Sulfonamides
  - o Triamterene
- Low urine volume[a]

Treatment

- Withdraw offending medication
- Increase urine volume

[a]Additional detail in Box 5.

uncontrolled sarcoidosis. Rather, dietary calcium intake should be maintained at 1,000-1,200 mg/day because restriction can exacerbate bone mineral loss and cause hyperoxaluria due to enhanced intestinal oxalate absorption. Moderate restriction of animal-derived protein can be considered. Bisphosphonates have been suggested because they reduce urine calcium in some cases and treat associated osteoporosis.

The patient in Case 4 has hypercalciuria, hypercalcemia, and nonsuppressed PTH, consistent with primary hyperparathyroidism. Although a thiazide diuretic may reduce urinary calcium excretion, parathyroidectomy would be the most appropriate therapy, so (c) is the correct response for Question 5.

Box 5. Interpreting 24-Hour Urine Studies to Address Risk for Recurrent Stones

Creatinine
- Allows an assessment of the completeness of 24-hour collection.
- Expect 15-20 mg/kg/d for females and 20-25 mg/kg/d for males.

Total Volume
- A goal of 2.5 L/d, sometimes more, is typical for reducing recurrence risk.

Calcium
- Though > 4 mg/kg is clearly excessive, a graded increase in stone risk is noted with levels > 150 mg/d.
- Correlate with urine sodium to determine of hypercalciuria is driven by excessive sodium intake.

Sodium
- A goal of <100 mg/d is sought if hypercalciuria is present.

Oxalate
- Values > 40 mg/d are excessive, though lower excretion rates may also increase risk.
- For values > 80 mg/d, consider primary hyperoxaluria.

Citrate
- Values > 400 mg/d may limit risk for calcareous stones, with even higher levels sometimes needed.

pH
- Values < 6.0 may increase the risk of uric acid stones.
- Values > 6.0 with metabolic acidosis suggests renal tubular acidosis and a risk for calcium phosphate stones.
- Values > 7.0 may indicate urine infection by bacteria with urease and a risk for struvite stones.

Uric Acid
- Consider xanthine oxidase inhibitor or reduced purine intake if >750-800 mg/d and other measures for calcium oxalate stones or uric acid stones fail.

Ammonium
- Values of >45 mmol/d suggest excess acid production from diet, chronic diarrhea, or other cause.

Sulfate
- Values of >30 mmol/d suggest excessive dietary animal protein.

Cystine
- Normal individuals typically excrete < 30 mg/d.
- Patients with cystinuria generally excrete > 400 mg/d.
- For cystinuria patients, target a concentration < 250 mg/L to limit stone risk.

Supersaturation
- Though the relationship between stone risk and supersaturation is continuous and imperfect, general supersaturation targets for reducing risk are < 4 for calcium oxalate stones and < 1 for calcium phosphate and uric acid stones.

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Hypocitraturia

Mechanisms. Citrate is an endogenous inhibitor of calcium stone formation. Citrate complexes with calcium to create a soluble salt—limiting the binding of calcium with oxalate or phosphate—and directly inhibits crystal aggregation. Hypocitraturia, defined as citrate excretion of <320 mg/day, is encountered in 20%-60% of cases of calcium nephrolithiasis.

The major determinant of urinary citrate excretion is acid-base balance. Metabolic acidosis increases proximal tubule citrate reabsorption and metabolism, leading to decreased urinary excretion. Clinical conditions associated with hypocitraturia include CKD, chronic diarrhea, RTA (genetic or drug-induced), high dietary animal protein intake, and potassium depletion. Low bone mass is also associated with hypocitraturia.

Evaluation. Urine pH can provide important information. A low urine pH suggests nonrenal alkali losses, such

as chronic diarrhea. A high urine pH may suggest the presence of an RTA, though calcium phosphate stones would be more likely in this scenario.

Treatment. Treatment of the underlying cause of hypocitraturia, if possible, is the first step. Both sodium and potassium alkali salts effectively raise urinary citrate, but potassium citrate is preferred because sodium would tend to augment calciuria. The required dose of potassium citrate is typically 15 to 30 mEq, 2 or 3 times a day. Serum potassium needs to be monitored closely for hyperkalemia among patients with reduced kidney function.

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Hyperoxaluria

Case 5: *A 55-year-old man is referred for evaluation of recurrent stones. He has a history of hypertension, diabetes, and severe obesity. He underwent malabsorptive bariatric surgery 2 years ago and lost 100 pounds, achieving improved glycemic and blood pressure control. Subsequently, he developed recurrent stones. The physical examination is unremarkable, and laboratory studies are obtained.*

Laboratory Studies	Value
Serum	
Sodium, mEq/L	142
Potassium, mEq/L	3.9
Chloride, mEq/L	108
Bicarbonate, mEq/L	24
SUN, mg/dL	22
Creatinine, mg/dL	1.1
Glucose, mg/dL	115
Calcium, mg/dL	9.3
Phosphorus, mg/dL	2.8
24-hour urine stone profile	
Volume, L	1.6
pH	6.0
Calcium, mg	210
Oxalate, mg	80
Phosphorus, mg	1,250
Uric acid, mg	610
Sodium, mEq	107
Potassium, mEq	67
Magnesium, mg	55
Sulfate, mmol	25
Ammonium, mmol	42
Citrate, mg	420

Abbreviation: SUN, serum urea nitrogen.

Question 6: What is the most likely cause of the high oxalate in his urine?
(a) Hepatic overproduction of oxalate
(b) Defect in renal oxalate reabsorption
(c) Excessive intestinal absorption of oxalate
(d) High dietary oxalate intake

Question 7: In addition to increasing his fluid intake to >2.5 L/day, what treatment should be recommended?
(a) Allopurinol
(b) Thiazide diuretic
(c) Potassium citrate
(d) Sodium/potassium phosphate supplement
(e) Calcium citrate

For the answers to these questions, see the following text.

Mechanisms. Hyperoxaluria, seen in 10%-50% of calcium stone-formers, increases calcium oxalate supersaturation to promote stone formation. Normal urinary oxalate excretion is < 40 mg/day (0.45 mmol/day). The mechanisms of hyperoxaluria include overproduction or excessive intestinal oxalate absorption.

The primary hyperoxalurias are autosomal recessive disorders of overproduction arising from the shunting of glyoxylate to oxalate. Type 1 primary hyperoxaluria, caused by a defect in alanine glyoxylate aminotransferase, often presents in childhood with nephrolithiasis, nephrocalcinosis, and kidney failure. Cardiac and vascular oxalate deposition occur as the development of kidney failure impairs oxalate elimination. Type 2 and type 3 primary hyperoxalurias, due to defects in glyoxylate reductase/hydroxypyruvate reductase and 4-hydroxy-2-oxoglutarate aldolase, respectively, are less prevalent and follow a milder course.

Ingestion of oxalate precursors such as high-dose vitamin C and foods containing high proline (tendons, gristle) can also lead to overproduction. The consumption of oxalate-rich foods (https://kidneystones.uchicago.edu/how-to-eat-a-low-oxalate-diet/) can cause hyperoxaluria through excessive intestinal absorption. A unique form of "enteric hyperoxaluria" can occur in patients with fat malabsorption: fatty acids bind to calcium in the intestinal lumen, displacing oxalate and enhancing its bioavailability. Common clinical scenarios include pancreatic exocrine insufficiency, inflammatory bowel diseases, and malabsorptive (not restrictive) bariatric surgeries. These conditions are often associated with other stone risk factors, including low urine volume, hypocitraturia, and hypomagnesuria. The answer to Question 6 is (c), excessive intestinal absorption of oxalate.

Evaluation. Gastrointestinal and dietary history are of paramount importance to determine the cause and direct the therapy. The diagnosis of primary hyperoxaluria requires a high index of suspicion because it can sometimes present initially in an adult patient. The family history is usually unremarkable, given the recessive pattern of

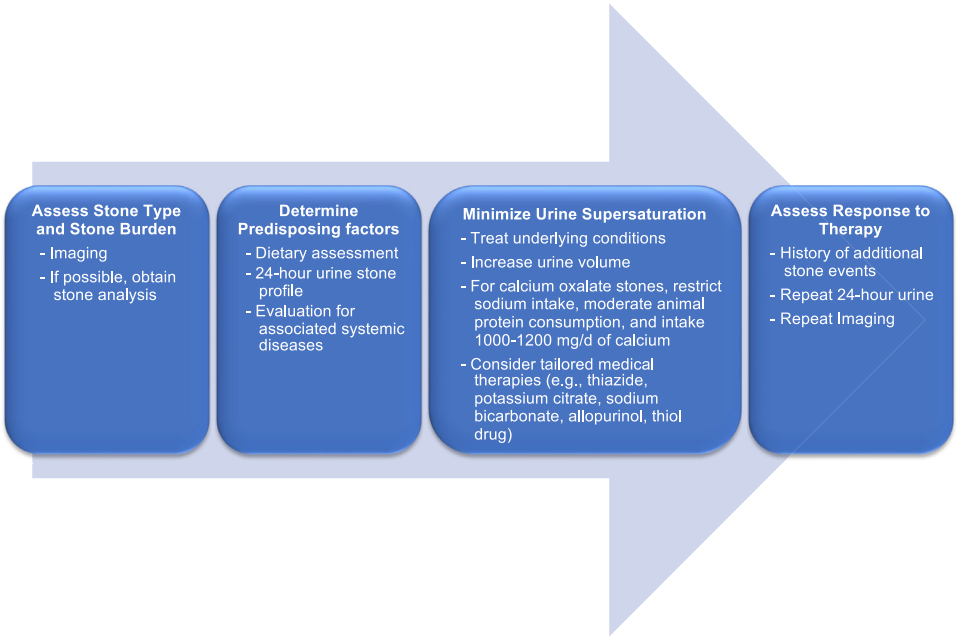

Figure 3. Overview of the chronic management of nephrolithiasis.

inheritance. A 24-hour urine oxalate of >80 mg/day without an alternate explanation should prompt further evaluation by genetic testing.

Treatment. The approach to reducing calcium oxalate supersaturation due to hyperoxaluria includes increasing urine volume and decreasing urine oxalate and calcium excretion rates. Increasing urine volume in individuals with chronic diarrhea can be very challenging. Restriction of dietary oxalate to <100 mg/day is reasonable. Excessive intake of vitamin C should be avoided. Disease-specific therapy (eg, pancreatic enzyme therapy for pancreatic insufficiency), a low-fat diet, and/or cholestyramine should be instituted for fat malabsorption states.

Calcium carbonate or citrate given with meals reduces oxalate absorption. The answer to Question 7 is (e), calcium citrate, which would provide the calcium to bind intestinal oxalate and alkali to increase urinary citrate. Although some studies have revealed a negative correlation between urinary oxalate and the fecal abundance of *Oxalobacter formigenes*, an oxalate-consuming bacteria, the therapeutic value of augmenting intestinal *O formigenes* with probiotics remains unproven.

Pyridoxine supplementation may promote the conversion of glyoxylate to glycine and has demonstrated variable success in patients with type 1 primary hyperoxaluria. Liver transplant has been the definitive therapy for patients with primary hyperoxaluria. Recent trials have demonstrated the efficacy and safety of an interfering RNA (RNAi) that inhibits glycolate oxidase in primary hyperoxaluria type 1, offering an alternative to liver transplantation.

Hyperuricosuria. Although the mechanism is not completely understood, hyperuricosuria can facilitate the formation of calcium oxalate stones. In patients who continue to form calcareous stones despite the standard preventive measures previously discussed, a low-purine diet and xanthine oxidase inhibitors may be considered if urine uric acid excretion rates are relatively high.

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Calcium Phosphate Stones

Case 6: *A 24-year-old woman is referred for recurrent calcium phosphate stones. She has a history of Sjögren's syndrome and associated distal RTA. She has not had recurrent urinary tract infections. She is taking potassium citrate, 15 mEq, 3 times daily and drinks several liters of water daily. Her physical examination is normal, with a blood pressure of 110/70 and BMI of 20. Laboratory studies were obtained.*

Laboratory Studies	Value
Serum	
Sodium, mEq/L	138
Potassium, mEq/L	3.1
Chloride, mEq/L	112
Bicarbonate, mEq/L	20
SUN, mg/dL	22
Creatinine, mg/dL	0.8
Glucose, mg/dL	90
Calcium, mg/dL	9.6
Phosphorus, mg/dL	3.8
24-Hour urine stone profile	
Volume, L	2.7
pH	7.5
Calcium, mg	240
Oxalate, mg	33
Phosphorus, mg	1,050
Uric acid, mg	430
Sodium, mEq	143
Potassium, mEq	87
Magnesium, mg	65
Sulfate, mmol	21
Ammonium, mmol	22
Citrate, mg	80

Abbreviation: SUN, serum urea nitrogen.

Question 8: What is the most appropriate next step to reduce her frequency of recurrent stone formation?
(a) Add potassium chloride
(b) Increase potassium citrate
(c) Add a thiazide diuretic
(d) Restrict protein intake

For the answer to this question, see the following text.

Mechanisms

Calcium phosphate stones and uric acid stones are the next most common types of stones after calcium oxalate. In patients younger than 55 years of age, calcium phosphate nephrolithiasis is more common than uric acid stone disease. For patients older than 55 years of age, the reverse is true. A major pathophysiologic factor leading to calcium phosphate stone formation is higher urine pH (typically ≥6.2), often with hypocitraturia. The high urine pH diminishes the solubility of calcium phosphate while low citrate increases the availability of calcium for less soluble complexes. Female gender, younger age (between 20 and 30 years of age), and prior extracorporeal shockwave lithotripsy associate with higher urine pH and greater risk of calcium phosphate stones.

Some individuals will have overt RTA with hyperchloremic metabolic acidosis, hypokalemia, and a urine pH ≥ 6. This can be idiopathic, drug-induced (acetazolamide, topiramate, or zonisamide), or associated with systemic disease such as lupus or Sjögren's syndrome. Nephrocalcinosis (calcification of the renal parenchyma) from sustained hypercalciuria can itself lead to renal acidification defects, though more often results from RTA. At times the RTA is "incomplete," with high urine pH but normal serum bicarbonate.

Finally, excess alkali administration, including potassium citrate for calcium oxalate stones, can cause calcium phosphate stones.

Evaluation

Identifying reversible causes of excess urine pH is of paramount importance in the treatment of calcium phosphate stones. Genetic testing may be considered in young patients with overt features of an RTA. Sensorineural hearing loss can be present in some forms of hereditary distal RTA. Nephrocalcinosis is sometimes evident on renal imaging. Commonly hypercalciuria is also present in the typical calcium phosphate stone-former.

Treatment

Discontinuation of offending medications that increase urine pH is critical. Lowering the urine pH is not typically possible for calcium phosphate stones from other causes. Increasing urine volume and lowering the urine calcium excretion rate by sodium restriction and thiazides are reasonable initial interventions to decrease supersaturation to the goal of <1. If those interventions do not reduce stone formation, increasing the urine citrate with potassium citrate can be considered. This approach carries the risk of increasing supersaturation by further raising the urine pH, so monitoring the net effect on supersaturation after adding potassium citrate is mandatory.

For severe RTAs it is often very difficult to meaningfully raise the urine citrate without worsening supersaturation. When there is a concomitant potassium deficiency, potassium chloride supplementation may modestly help lower urine pH and increase urine citrate excretion rates. The correct answer to Question 8 is therefore (a), adding potassium chloride. A summary of the predisposing factors and management principles for calcium phosphate stones is provided in Box 2.

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Uric Acid Stones

Case 7: *A 52-year-old female with a history of hypertension, diabetes, and obesity presented to the ED with back pain. She had no urinary symptoms, and the kidneys, ureter, bladder (KUB) plain abdominal radiograph was unremarkable. She was discharged but returned 3 days later with back pain radiating to the groin. A CT of the abdomen and pelvis showed numerous stones. The 24-hour urine stone profile was as follows.*

24-Hour Urine Stone Profile	Value
Volume, L	0.8
pH	5.2
Calcium, mg	250
Oxalate, mg	33
Phosphorus, mg	1,050
Uric acid, mg	430
Sodium, mEq	143
Potassium, mEq	87
Magnesium, mg	65
Sulfate, mmol	35
Ammonium, mmol	22
Citrate, mg	300

Question 9: All the following may be true regarding why stones were seen on CT but not on KUB *except:*
(a) The stones were obscured by bowel gas.
(b) She had passed the major stone before having the KUB then re-formed stones.
(c) She has noncalcareous stones.
(d) KUB is less sensitive than CT for detecting nephrolithiasis.

Question 10: What is the major risk factor for this stone type that is evident in the 24-hour urine?
(a) Low urine pH
(b) Plant based diet
(c) High urine calcium
(d) High urine phosphate

Question 11: In addition to increasing urine volume, which of the following would be the most effective intervention to reduce stone recurrence?
(a) Initiate allopurinol
(b) Initiate thiazide diuretic
(c) Initiate sodium bicarbonate therapy
(d) None of the above

For the answer to these questions, see the following text.

Mechanisms

Uric acid stones are the most common radiolucent stone, which makes the answer to Question 9 (c). Low urine pH (<5.5), low urine volume, and hyperuricosuria (defined as uric acid excretion > 800 mg/d in men and > 750 mg/day in women) are factors in the pathogenesis of uric acid stones. Low pH is critical because uric acid exists more in its protonated, less soluble form in acidic urine, thus increasing its supersaturation. The answer to Question 10 is (a), low urine pH.

A diet high in animal protein and impaired renal ammoniagenesis are 2 common causes of acidic urine in uric acid stone-formers. Impaired ammoniagenesis has been described in patients with type 2 diabetes mellitus, obesity, and the metabolic syndrome. Gout almost doubles the risk of nephrolithiasis but not necessarily uric acid stones. The enhanced risk of nephrolithiasis appears to be driven by the association of gout with the metabolic syndrome, which is a risk factor for the more common calcium oxalate stone as well. Hyperuricosuria is a less common risk factor than low pH and low urine volume but may be seen in conditions with high cell turnover, such as myeloproliferative disorders, and genetic disorders of uric acid synthesis or renal tubular handling or excessive purine intake.

Evaluation

A history of chronic diarrhea should be excluded because this can predispose individuals to low urine volume and low urine pH through volume depletion and loss of alkali. A dietary history to assess animal protein intake is warranted. In addition to 24-hour urine studies, serum uric acid and tests for the metabolic syndrome (fasting glucose and glycosylated hemoglobin) are reasonable. Under unusual circumstances, testing for genetic disorders of uric acid metabolism may be required.

Treatment

Raising the urine pH and increasing urine volume are the most effective treatments for uric acid stones. Treat chronic diarrhea if it is present and advise a lower animal protein intake. Potassium citrate or sodium bicarbonate may be used to achieve a pH of 6.5-7.0, so the answer to Question 11 is (c), sodium bicarbonate therapy. Exceeding a urinary pH of 7.0 may predispose individuals to calcium phosphate stones. In patients who are hyperuricosuric and still forming stones despite raising their urine pH, one can consider initiating xanthine oxidase inhibitors. See Box 3 for a summary of the predisposing factors and management of uric acid stones.

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Struvite Stones (Magnesium Ammonium Phosphate or Triple Phosphate)

Case 8: *A 57-year-old woman with diabetes and hypertension presents to the ED with back pain and fever. She has recurrent urinary tract infections and takes chronic suppressive trimethoprim/sulfamethoxazole. She thinks that she has another urinary tract infection. She has never passed a stone and has no family history of stone disease. Her laboratory work reveals a serum creatinine of 1.6 mg/dL but otherwise normal chemistries, and a urinalysis is obtained, as well as a KUB (Figure 4).*

Urinalysis	Value
Color	Dark yellow
Specific gravity	1.031
pH	7.5
Glucose	1+
Protein	1+
Ketones	Negative
Blood	2+
WBCs	>100/hpf
Nitrites	Positive
Bacteria	Present

Abbreviations: hpf, high-power field; WBCs, white blood cells.

Question 12: What kidney syndrome is demonstrated in Figure 4?
(a) Medullary sponge kidney
(b) Xanthogranulomatous pyelonephritis
(c) Staghorn calculi
(d) Duplicated ureters

Question 13: What is the most likely composition of the stones in this case?
(a) Calcium oxalate
(b) Sulfamethoxazole
(c) Cystine
(d) Magnesium ammonium phosphate

For the answers to these questions, see the following text.

Mechanisms

Struvite stones or triple phosphate stones comprise about 1% of all stones. Composed of magnesium ammonium phosphate and calcium carbonate-apatite, these rapidly growing stones can fill the entire renal pelvis. These result from chronic urinary tract infection by urease-producing organisms such as *Proteus*. Urea is converted into ammonium and bicarbonate, increasing the urine pH and thus lowering the solubility of triple phosphate.

Treatment

The cornerstone of treatment for struvite stones is eradication of the infection with antibiotics and the early surgical removal of the bacteria-laden stones. Medical management alone with chronic antibiotic therapy is rarely successful and not recommended unless patients are too ill for surgery or refuse stone removal. Acetohydroxamic acid, a urease inhibitor, is the only drug approved for treating struvite nephrolithiasis; however, its use is limited by side effects, including nausea, thrombophlebitis, rash, and hemolytic anemia. Based on this individual's history and urinary findings, the best answer to Question 12 is (c), staghorn calculi; and the best answer to Question 13 is (d), magnesium ammonium phosphate. Note that although staghorn calculi are most often struvite, they can be composed of any of the previously mentioned stone types. Box 4 provides a summary of these concepts regarding the pathogenesis and management of struvite stones.

Figure 4. Imaging obtained in case 8.

Additional Reading

➢ Flannigan R, Choy WH, Chew B, Lange D. Renal struvite stones-pathogenesis, microbiology, and management strategies. *Nat Rev Urol.* 2014;11(6):333-341. https://doi.org/10.1038/nrurol.2014.99

Cystine Stones

Case 9: *A 19-year-old man with no past medical history presented to the ED with right flank pain. He reported a family history of kidney stones. The CT evaluation revealed a 2-mm stone in the midureter and bilateral calyceal stones varying from 5 to 13 mm in size. Urine microscopy showed hexagonal crystals. His blood chemistries were normal. He was sent home with tamsulosin and passed the stone 5 days later. Urine studies were performed and a 24-hour urine stone profile was obtained. He has been drinking fluids liberally and asks what else he can do to limit future stone formation.*

24-Hour Urine Stone Profile	Value
Volume, L	3.2
pH	6.1
Calcium, mg	180
Oxalate, mg	35
Phosphorus, mg	1,300
Uric acid, mg	750
Sodium, mEq	210
Potassium, mEq	65
Magnesium, mg	74
Sulfate, mmol	29
Ammonium, mmol	44
Citrate, mg	310
Cystine, mg	610

Question 14: All of the following initial interventions should be recommended *except:*
(a) Lower dietary protein intake
(b) Tiopronin
(c) Potassium citrate
(d) Lower sodium intake

For the answer to this question, see the following text.

Mechanisms

Cystinuria is a rare disorder but the most common of the Mendelian diseases that cause nephrolithiasis, accounting for about 1% to 2% of kidney stones in adults and 6% to 8% in children. The inheritance pattern is complex: while autosomal recessive inheritance is most common, autosomal dominant inheritance with variable penetrance is also possible. Mutations in the genes *SLC3A1* or *SLC7A9* result in defects in the subunits (tBAT and b^0AT) of the amino acid transporter governing renal tubular reabsorption of dibasic amino acids resulting in urinary wasting of cystine. The complexity of the genetics underpinning this condition explains the variability in disease severity that is observed.

Cystine, the homodimer of the amino acid cysteine, is poorly soluble in urine at typical pH, forming cystine stones when in excess. Patients with cystinuria excrete > 250 mg/day of cystine (normal < 30 mg/day). Cystinuria should be suspected in any patient presenting with early onset, recurring kidney stones.

Evaluation

A history of familial consanguinity should be explored. The diagnosis of cystinuria can be established by the presence of pathognomonic hexagonal cystine crystals on urine microscopy, stone analysis revealing pure or mixed cystine content, or measurement of urinary cystine excretion rate. Genetic testing is available.

Treatment

Treatment of cystinuria is aimed at decreasing the urinary cystine concentration to < 250 mg/L by increasing urine volume, restricting dietary sodium, and reducing methionine and cystine intake through dietary restriction of animal protein. The solubility of cystine is enhanced when the urine pH is maintained between 7.0 and 7.5. Although protein restriction may assist in achieving this, potassium citrate or sodium bicarbonate therapy is typically necessary.

Persistent stone production despite these initial measures may prompt treatment with thiols such as α-mercapto propionylglycine (tiopronin) or less desirable alternatives (eg, penicillamine or captopril). These drugs create a soluble mixed disulfide with cysteine, limiting its homodimerization. Their use, however, is limited by cost and side effects, which include rash, gastrointestinal intolerance, and the development of membranous nephropathy. Thus, the correct answer to Question 14 is (b), tiopronin. Box 4 summarizes the approach to cystine stones.

Additional Readings

- D'Ambrosio V, Capolongo G, Goldfarb D, Gambaro G, Ferraro PM. Cystinuria: an update on pathophysiology, genetics, and clinical management. *Pediatr Nephrol.* 2022;37:1705-1711. https://doi.org/10.1007/s00467-021-05342-y ★ESSENTIAL READING
- Servais A, Thomas K, Dello Strologo L, et al; Metabolic Nephropathy Workgroup of the European Reference Network for Rare Kidney Diseases (ERKNet) and eUROGEN. Cystinuria: clinical practice recommendation. *Kidney Int.* 2021;99:48-58. https://doi.org/10.1016/j.kint.2020.06.035

Conclusion

Nephrolithiasis is a common problem that is increasing in prevalence and is associated with significant morbidity. Although urinary supersaturation is a necessary substrate for stone formation, it is not sufficient. Local and systemic factors interact with supersaturated solutes to cause stones. These systemic factors can have important consequences beyond the urologic system, including adverse effects on bone and cardiovascular health. Lowering supersaturation is a fundamental principal in management. Achieving adequate urine volume is always helpful in achieving this. Additional interventions are tailored to the type of stone formed as well as the clinical context. Often a multidisciplinary approach led by nephrologists and urologists is needed for optimal management.

Article Information

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