

Educational Case: Urinary Stones

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*The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see <http://journals.sagepub.com/doi/10.1177/23742895211040209>.*¹

Keywords

pathology competencies, organ system pathology, bladder, urinary obstruction, nephrolithiasis, urolithiasis, urine crystals

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Primary Objective

Objective UTB3.2: Nephrolithiasis: List the different chemical types of nephrolithiasis, and explain the pathophysiologic mechanisms related to the development and therapy/prevention of urinary stones.

Competency 2: Organ System Pathology; Topic UTB: Bladder; Learning Goal 3: Urinary Obstruction

Patient Presentation

A 43-year-old man presents to the emergency department complaining of nausea and severe right flank pain that started one hour ago. The pain is intermittent, radiates to his groin, and has no associated aggravating or alleviating factors. He reports no previous similar episodes. The patient denies chest pain, shortness of breath, vomiting, diarrhea, constipation, changes in urination such as frequency and urgency, and visible blood in the stool or urine. He has no significant past medical history and takes no medications. His family history is noncontributory. He does not smoke, drink, or use illicit drugs.

Diagnostic Findings, Part I

The patient's vital signs are as follows: temperature 36.7 °C, heart rate 110 beats per minute, respirations 14 per minute, and blood pressure 150/76 mm Hg. The patient is diaphoretic and unable to sit still due to pain (rated 10 of 10 on the pain scale).

His abdominal examination reveals active bowel sounds without tenderness to percussion or palpation and no guarding or rebound tenderness. No organomegaly or masses are palpable. Tenderness is present at the right costovertebral angle. The remainder of the physical examination is normal.

Questions/Discussion Points, Part I

What Is the Differential Diagnosis for This Patient Based on the Provided History and Physical Examination?

The differential diagnosis for flank pain includes renal pathology such as renal cell carcinoma, pyelonephritis, and renal ischemia (due to emboli or frank bleeding). Similarly, urinary calculi lodged in the kidney, ureter, or bladder can cause pain like the type described in this patient. Cardiovascular problems that can present as flank pain include an aortic aneurysm and

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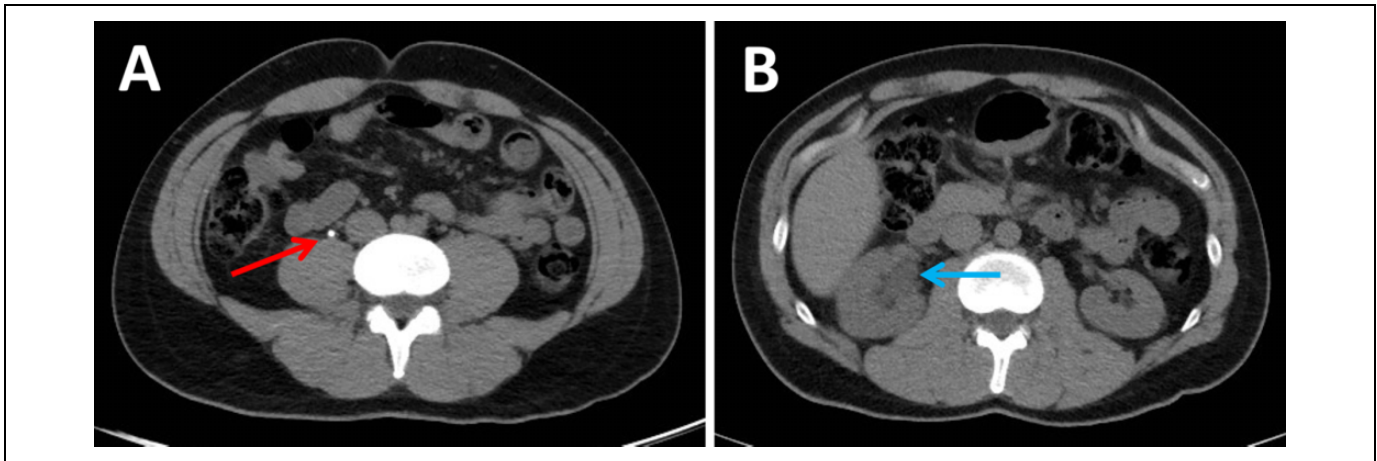


Figure 1. A, Axial computed tomography (CT) reveals an opaque stone in the patient's right ureter (red arrow). B, The pelvis of the right kidney is dilated (blue arrow), indicating obstructive hydronephrosis.

atypical angina due to myocardial infarction. Multiple gastrointestinal disorders such as acute intestinal obstruction, diverticulitis, or appendicitis may present with colicky flank pain. Biliary colic and cholecystitis should also be considered in the differential diagnosis. If the patient had an overlying rash on his flank, herpes zoster might also be a consideration. If the patient was female, gynecologic conditions such as ovarian torsion could also be possible.

Given the severity of the pain, radiation to the groin, and costovertebral angle tenderness, a stone in the urinary tract is high on the differential diagnosis. Of note, the term “urolithiasis” refers to a stone located anywhere within the urinary tract, while “nephrolithiasis” is more specific to the kidneys. Since most urinary stones originate in the kidneys, some sources may use the terms interchangeably. Additional information in the history and physical examination points away from acute gastrointestinal and cardiovascular disorders. Other renal disorders are less likely but can be assessed with further studies.

What Tests Should Be Performed Next in This Patient's Evaluation?

A complete blood count (CBC) and comprehensive metabolic panel (CMP) should initially be performed on a peripheral blood sample. Urine should be collected for a urinalysis with microscopic examination and, in female patients of childbearing age, a pregnancy test. A urine culture should be considered, especially if the urinalysis results are indicative of a urinary tract infection (UTI; eg, positive nitrite and/or leukocyte esterase, microscopic examination showing leukocytes and bacteria). A radiologic study such as a computed tomography (CT) scan should be performed; and a noncontrast CT scan is the gold standard for the diagnosis of the favored entity in the differential diagnosis, urinary stones. In some cases, an ultrasound or abdominal (kidney–ureter–bladder, KUB) radiograph may be used. However, operator experience may affect

ultrasound results; and some stones are radiolucent on a KUB radiograph. Additional studies such as serum uric acid, parathyroid hormone, and 25-hydroxy vitamin D may be needed based on the results of these initial studies.

Diagnostic Findings, Part 2

Results of a CBC and CMP are within normal limits, including creatinine, calcium, phosphorus, bicarbonate, and potassium. A urinalysis is negative for protein, glucose, nitrite, and leukocyte esterase and has a pH of 6.5. Microscopic examination of the urine shows 8 red blood cells per high-power field and 1 to 5 calcium oxalate crystals per low-power field but no bacteria, white blood cells, or casts. A noncontrast CT scan of the patient's abdomen and pelvis reveals a kidney stone in the right ureter and associated hydronephrosis of the right kidney (Figures 1 and 2).

Questions/Discussion Points, Part 2

What Are the Common Presenting Clinical Features of Urinary Stones?

The classic presentation of nephrolithiasis is tachycardia, diaphoresis, flank pain, and hematuria. Nausea and vomiting are often also associated. However, a patient's presentation varies depending upon the anatomical location in which the stone is lodged. For instance, distinct symptoms may be described in patients with a renal stone (flank pain) versus those with a bladder stone (urinary symptoms such as frequency and urgency).² Also, as implied above, patients are not always symptomatic. In fact, there is a relatively high prevalence of asymptomatic stones, as per one study which used abdominal and retroperitoneal ultrasound to evaluate for asymptomatic nephrolithiasis.³ This study used ultrasound, which has a lower sensitivity than CT, implying that the rate of asymptomatic stones is potentially higher than that detected by the investigators.

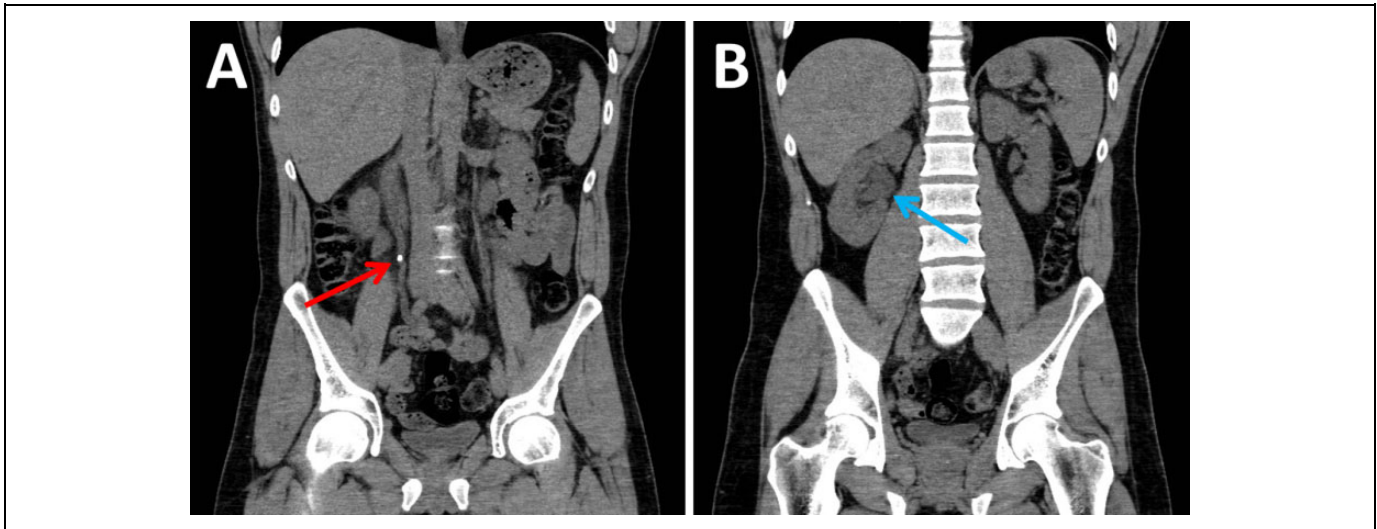


Figure 2. The coronal computed tomography (CT) views also show an opaque stone in the patient's right ureter (A, red arrow) and the dilated renal pelvis (B, blue arrow).

The etiology of flank pain is thought to be obstructive in nature. As urine passage is blocked, pressure builds up in the renal calyces, which distends the renal capsule and causes discrete, localized flank pain. Alternatively, renal colic derives from the contraction of smooth muscle on the obstructed stone. A thorough understanding of the pain's etiology can help one determine the probable location of the stone. Local pain in the ureter distributes along the ilioinguinal nerve and the genital branch of the genitofemoral nerve toward the scrotum or vulva. Contrast this with obstructive pain that coincides with the urinary collecting system and is manifested by costovertebral tenderness (a common physical examination finding) and flank pain.²

What Are Other Possible Causes of Urinary Tract Obstruction?

Urinary tract obstruction can be unilateral or bilateral and can originate within any part of the urinary tract, including the renal pelvis, ureter, bladder, or urethra. One potential cause common to all of these locations is tumors. Strictures may occur at the uteropelvic junction or the posterior urethral valve. Functional changes to the bladder may also lead to obstruction, for example, neurogenic bladder in patients with diabetes or spinal cord damage. Ureteral obstruction can be due to intrinsic or extrinsic disorders. Additional causes of intrinsic ureteral obstruction other than stones and tumors include inflammation, sloughed renal papillae, and blood clots. Extrinsic causes included intraabdominal and retroperitoneal masses (eg, tumors, gravid uterus) or fibrosis. In males, prostate diseases such as tumors, hyperplasia, or inflammation may cause obstruction at the bladder outlet.⁴

What Are the Potential Complications of Urolithiasis?

Depending on how long the patient has been obstructed, the composition of the stone, and the presence of a comorbid UTI,

patients can present in distributive shock. The patient in distributive shock secondary to pyelonephritis presents with fever, chills, tachycardia, hypotension, nausea, vomiting, and flank pain. The stone causes obstruction and stasis, and therefore, a nidus for infection. In such cases, emergent surgical intervention is required.⁵

A concern of prolonged obstruction is the risk of developing acute kidney injury or, if the patient is a chronic stone former, a decline in renal function. If prolonged, permanent renal impairment becomes a primary concern, with chronic kidney disease and renal failure being the feared result. For this reason, a patient's renal function is determined by following the trend in serum creatinine and blood urea nitrogen.⁶

Describe the General Mechanism of Urinary Calculi Formation

Urine is a solution of various solutes excreted from the body. Renal calculi form as a result of changes to the solution or the environment. The factors at play include the concentration of each solute, the total volume of solvent, and the pH of the solution. The excreted contents of urine are the sum of the filtered, nonreabsorbed solutes from the blood, and solutes that are secreted into urine throughout the renal tubule. Increases in the quantity of solute excreted from the body can occur due to increases in that solute's concentration in the blood. This can be seen in the setting of hyperparathyroidism, which results in excess filtered calcium, or indinavir urolithiasis, which is the product of oversaturated tubular reabsorption mechanisms.⁷

One of the well-accepted precipitating factors for renal calculi formation is decreased solvent volume due to decreased fluid intake. In the United States, the incidence of symptomatic nephrolithiasis is significantly greater in the Southeast where there are, on average, greater ambient temperatures and sunlight exposure.⁸ Decreased volume of solvent leads to

Table 1. Features of the 4 Main Types of Urinary Calculi.

Type of calculus	Composition	Urine pH	Radiologic appearance	Microscopic appearance of crystals	Associated clinical conditions
Calcium	Calcium oxalate	Acidic	Radiopaque	Envelopes, dumbbells, or ovals	Hyperparathyroidism, sarcoidosis, metastatic bone disease, primary oxaluria, conditions leading to gastrointestinal malabsorption (eg, inflammatory bowel disease)
	Calcium phosphate	Alkaline		Amorphous, plates, or splinter-like	
Struvite (staghorn)	Magnesium ammonium phosphate (triple phosphate)	Alkaline	Radiopaque	“Coffin-lid” shaped	Infection with urea-splitting organisms, such as <i>Klebsiella</i> , <i>Proteus</i> , <i>Providencia</i> , <i>Pseudomonas</i> , and some species of staphylococci
Uric acid	Uric acid	Acidic	Radiolucent	Four-sided plates, rounded parallelogram	Gout, Lesch-Nyhan syndrome, tumor lysis syndrome, diabetes mellitus
Cystine	Cystine	Acidic	Radiolucent	Hexagons	Cystinuria

increased concentration of solute, consequently leading to stone formation.

The environment of the solution plays a role in calculi formation as well, most prominently, the pH of the solution. Normal urine pH is typically 6.0 to 7.5, although the normal range may extend from 4.5 to 8.0 and depends on a specific lab’s reference range.⁹ Because each solute is soluble at certain pH ranges, when urine pH falls outside of that range, the solute is more likely to precipitate out of solution, creating a nidus for calculi formation. For instance, cystine solubility at a pH of 7.0 is 200 to 400 mg/L. At a pH of 5.0, cystine solubility is 150 to 300 mg/L. For this reason, one of the mechanisms for the treatment of cystinuria is alkalization of the patient’s urine.²

What Are the 4 Main Types of Urinary Calculi?

The 4 most common urinary stones are calcium, struvite, uric acid, and cystine.

What Factors Impact Formation of the 4 Main Types of Urinary Calculi?

General features affecting stone formation include diet, medications, family history, occupation, and, as previously mentioned, climate. Each type of calculus also has specific factors that contribute to the formation of that type of stone. The features below are summarized in Table 1.

Calcium stones comprise approximately 70% of stones in the general population and are primarily composed of calcium oxalate but can be made of calcium phosphate or a combination of the 2. These stones form in patients with hypercalciuria (with or without hypercalcemia), hyperuricosuria, hyperoxaluria, hypocitraturia, or in those with no identifiable cause. Examples of conditions associated with hypercalcemia and hypercalciuria include hyperparathyroidism and sarcoidosis. Hypercalciuria without hypercalcemia may be identified in patients with impaired reabsorption of calcium in renal tubules or to excessive calcium absorption in the intestine. Increased secretion of uric acid as in patients with excess intake of purines or secretion of uric acid.⁴ Patients with chronic enteric

diseases such as Crohn disease may absorb excess oxalate in the intestine. Normally, calcium in the gut would bind to oxalate and prevent its absorption. In patients with malabsorption, fat and bile salts in the intestinal lumen increase; and these bind calcium so that it does not attach to oxalate. Thus, more oxalate is absorbed. Excess oxalate intake, as occurs in ethylene glycol poisoning, is another source of hyperoxaluria.² It is less frequently due to primary oxaluria, a rare hereditary condition. Hypocitraturia may be seen in patients with chronic diarrhea and acidosis or may be idiopathic.⁴ Calcium oxalate stones develop in acidic urine, and calcium phosphate stones develop in alkaline urine.²

Struvite (also called magnesium ammonium phosphate or triple phosphate) stones are also often referred to as staghorn calculi, which is often how they appear in radiologic studies. These stones are often large and obstructive—to the point of filling the collecting calyces of the kidney—and form in alkaline urine.⁵ Patients affected by struvite stones are also affected by comorbid UTIs, though sometimes not contemporaneously.¹⁰ The organisms implicated in the UTIs of patients with struvite stones are overwhelmingly urea splitting. This means that they possess an enzyme, urease, to breakdown urea, which is abundant in urine.⁴ Examples of these organisms include *Klebsiella*, *Proteus*, *Providencia*, *Pseudomonas*, and some species of staphylococci.²

Uric acid stones form in acidic urine and in the setting of hyperuricemia and hyperuricosuria. Consequently, individuals with medical conditions leading to increased uric acid production or altered metabolism (eg, gout, Lesch-Nyhan syndrome, tumor lysis syndrome) or decreased urine pH (eg, chronic diarrhea, metabolic syndrome) have a higher incidence of uric acid calculi.^{4,11,12} Of interest, more than half of uric acid stones do not occur in the setting of hyperuricemia.⁴

Cystine stones occur in the setting of cystinuria, which is an autosomal recessive genetic disorder. Patients with cystinuria have an impaired ability to transport the amino acids cystine, ornithine, lysine, and arginine in the proximal nephron due to a dysfunctional transporter subunit in renal tubular epithelia.¹³ Cystinuria should be suspected in individuals who present with

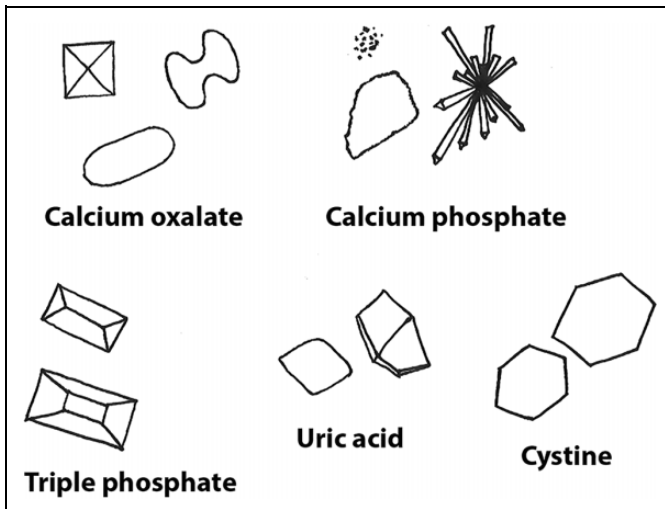


Figure 3. If crystals are visualized on microscopic examination of the urine, the findings may help determine which type of stone is present.

urolithiasis at an age younger than 30 years. As previously mentioned, cystine stones develop in acidic urine.²

Urine crystals may sometimes be identified in the urine of patients with nephrolithiasis and may provide a clue as to the type of stone (Figure 3). Calcium oxalate dihydrate crystals are bipyramidal or envelope-shaped, and calcium oxalate monohydrate crystals are shaped like dumbbells. Calcium phosphate crystals may be amorphous, form plates, or appear splinter-like. The shape of struvite stones is often likened to coffin lids. Uric acid crystals are rounded parallelograms or flat, 4-sided plates. Cystine crystals are shaped like hexagons. It is worth noting that calcium and triple phosphate crystals may be found in persons without stones, especially in urine that has been allowed to sit at room temperature for several hours or has been refrigerated, but struvite and cystine stones are never normal.² Many other normal or abnormal types of urine crystals may be seen as well that are not associated with stone formation but are beyond the scope of this article.

Describe the Management of Urinary Stones, Including the Therapies Available to Assist Stone Passage

A symptomatic patient with a confirmed urinary stone should be managed based on the size and location of the stone, in the context of the patient's clinical history of stone formation and other concomitant conditions, and with respect to their clinical status, specifically pain control, infection, and hemodynamic stability. Many ureteral stones are passed without intervention.

The American Urological Association (AUA) and European Association of Urology have constructed a guideline for treating the "index patient" with urolithiasis.¹⁴ The index patient is defined as:

... A nonpregnant adult with a unilateral noncystine/nonuric acid radiopaque ureteral stone without renal calculi requiring therapy whose contralateral kidney functions normally and

whose medical condition, body habitus, and anatomy allow any one of the treatment options to be undertaken.¹⁴

This guideline provides standard treatment recommendations regarding the size and location of the stone. Calculi smaller than 10 mm are managed with aggressive hydration, medical expulsion therapy, and pain medication.¹⁵ Medical expulsion therapy consists of administration of α -blockers such as tamsulosin or calcium channel blockers like nifedipine. The idea is to facilitate stone passage by targeting smooth muscle receptors to promote relaxation.¹⁵ Patients whose pain cannot be controlled are often managed by one of the surgical methods discussed below.

Calculi larger than 10 mm ought to be managed surgically by either ureteroscopy or percutaneous nephrolithotomy. In ureteroscopy, a device is passed through the urethra into the bladder and the obstructed ureter. Various methods can be used to break up and remove the stone. This is the treatment of choice for middle and distal ureteral calculi. Another means of treating ureterolithiasis is extracorporeal shockwave lithotripsy. This procedure involves pulsing shock waves generated by electromagnetic induction, microexplosions, or even lasers through the patient in an attempt to break up the stone. This process can be done with minimal damage to surrounding structures.⁵ Percutaneous nephrolithotomy is a more invasive procedure in which an incision is made, and the ureter is entered from the proximal end. This procedure is preferred for proximal and complex stones.¹⁴ Struvite stones must be completely removed.

As briefly mentioned above, patients who are unstable and showing signs of urosepsis ought to be managed surgically by a urologist. Similar populations are considered outside the normal guidelines of the index patient. These include patients who are pregnant or obese, have duplicated collecting systems or decreased renal function, and patients with anatomical variants such as a single kidney.^{5,6,14}

How Is the Composition Analysis of Urinary Stones Performed? For Which Patients Should This Be Done?

Learning the composition of a patient's stone provides valuable information that guides pharmacotherapy for prevention and, in the case of recurrence, treatment of a recurrent episode of nephrolithiasis. A stone must be saved for an accurate analysis to be performed. Although a 24-hour urine study provides valuable information regarding the contents of a patient's urine and their metabolic status, it does not substitute for stone analysis. Per the most recent AUA guideline for the medical management of kidney stones, when a stone is available, it should be sent for analysis.¹⁶

Stone analysis can be performed by various methods; however, the "gold standard" is infrared spectroscopy.¹⁷ The key to stone analysis is analyzing all components of the stone, as many contain multiple components. Other methods include wet chemical analysis and radiograph diffraction.¹⁷ Recent discussion has suggested a potential role for specialized CT scanning with imaging enhancement to determine stone composition.¹⁸

This method would prove helpful in a patient's first episode of urolithiasis, as it could guide the means of intervention.

Diagnostic Findings, Part 3

The patient is admitted and treated with hydration, nifedipine, and pain control. He passes the stone 4 hours later, and it is collected and sent for composition analysis. The results show that the stone is primarily composed of calcium oxalate. A 24-hour urine specimen is collected as an outpatient, with significant findings including a volume of 1300 mL and elevated oxalate. Additional history indicates that the patient eats a large spinach salad for lunch every day and has been eating multiple rhubarb-containing foods for the past month due to a bumper crop in his garden.

Questions/Discussion Points, Part 3

What Interventions May Prevent Future Stone Formation?

Without prophylaxis, approximately half of patients with urolithiasis will experience a recurrence within 5 years.² The goal of therapy is to decrease the solute or to maximize its solubility in urine. Thus, intervention is geared toward dietary and other lifestyle modification and pharmacologic therapy.¹⁹ Test results from a 24-hour urine collection performed as an outpatient during a typical weekday can guide prophylaxis and also assist in determining stone composition if a stone was not available for analysis. Testing should include volume, pH, and sodium, calcium, oxalate, citrate, phosphate, uric acid, and sulfate concentrations. Treatable conditions such as hyperparathyroidism or a UTI should also be excluded with testing as needed.² An accurate medication history is also important, as some agents can cause stones. The protease inhibitors indinavir and atazanavir have been shown to precipitate in the urine of patients in many studies.^{20,21}

The main prophylactic intervention recommended for individuals at risk for urinary stones is increased water intake. Patients are advised that their urine volume should be approximately 2 liters per day.⁶ The increase in the amount of liquid they are requested to drink is often determined from the volume (urine output) from the 24-hour urine collection (2 liters minus volume collected = amount of suggested increase in fluid intake). Fluid intake is especially of importance for those with cystinuria, who are even encouraged to awake in the middle of the night in order to continue hydration.¹³

Diet is particularly important in individuals who form calcium oxalate stones. Interestingly, contrary to prior held beliefs that diets high in calcium predisposed patients to calcium stones, diets high in calcium are encouraged. Investigators revealed that higher concentrations of intraluminal calcium resulted in decreased enteric absorption of oxalate. This made a significant impact on the management of nephrolithiasis in patients with primary hypercalciuria.²² Eliminating oxalate-containing foods from a patient's diet is also a measure

by which physicians attempt to prevent recurrent calcium oxalate stones. Some of these foods include spinach, rhubarb, potatoes, and almonds. Patients are also typically prescribed a low-salt diet. Dietary changes may also be aimed at altering urine pH, as for patients with uric acid stones. Since low urine pH is a primary risk for uric acid stones, patients may be advised to increase their intake of foods such as fruits and vegetables which are alkali-rich and reduce intake of acid-producing foods such as meat.⁶

Pharmacologic interventions depend on which solute is too high (or too low) in the patient's urine. In patients with hypercalciuria, thiazide diuretics, like chlorthalidone, increase the amount of calcium reabsorbed in the distal convoluted tubule of the nephron, thereby decreasing the concentration in the urine. In patients with hyperuricosuria, allopurinol is utilized to decrease the concentration of uric acid in their urine. Stones can also form due to a relative decrease in urine citrate, which, when supplemented, significantly reduces stone formation.²³

Teaching Points

- Urolithiasis is a common cause of abdominal and flank pain seen in both men and women. A thorough history and physical examination are helpful in the diagnosis of urolithiasis; however, the gold standard diagnostic test is a noncontrast computed tomography (CT) scan.
- The 4 most common types of urinary stones are calcium, struvite, uric acid, and cystine.
- Aberrations in calcium metabolism, genetic predisposition, and patient hydration status are 3 important factors that lead to the formation of calcium stones. Struvite stones are mostly seen in patients with a comorbid urinary tract infection caused by urea-splitting organisms such as *Klebsiella*, *Proteus*, some staphylococci, and *Pseudomonas*. The primary risk factors for uric acid stones are high uric acid excretion and low urine pH. Hereditary cystinuria causes cystine stones.
- Depending on their size and location, stones can be removed surgically or endoscopically, or they can pass with the assistance of pharmacotherapeutics and hydration or shockwave therapy.
- Urinary stones can be analyzed by infrared spectroscopy. An analysis of the patient's urine collected for 24 hours can also facilitate the prevention of future stones.
- Patients with a history of urinary stones are encouraged to increase hydration, cut sodium from their diet, and can be placed on diuretic therapy to decrease the risk of stone formation.
- Obstruction can occur within any portion of the urinary tract and can be due to many causes. In addition to calculi, some of the other etiologies include tumors originating within the urinary tract or in adjacent organs, pregnancy, congenital anomalies such as ureteropelvic junction obstruction and posterior urethral valves, and inflammatory disorders.

Author's Note

The opinions expressed herein are those of the author and not necessarily representative of those of the Uniformed Services University of the Health Sciences (USUHS), the Department of Defense (DOD), the US government, or the United States Army, Navy, or Air Force.


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