American Urological Association
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KIDNEY STONES

KEYWORDS: Nephrolithiasis, Urinary Stones, Urolithiasis, Hypercalciuria, Hyperoxaluria, Hypocitraturia, Hyperuricosuria, Cystinuria

At the end of medical school, the medical student will understand and be able to…

1. List the major risk factors for the most common types of kidney stones.
2. Contrast differences between the clinical presentations of acute renal colic versus an acute abdomen.
3. Name the five most common kidney stone chemical compositions and describe the recommended medical prophylaxis options for each of them.
4. Describe the best imaging study to diagnose kidney and ureteral stones.
5. Describe three types of medications that are effective for relief of renal colic pain.
6. List three clinical situations that warrant urgent surgical decompression of a ureteral stone.
7. List two types of medications that may help medical expulsion therapy of a distal ureteral stone.
8. List the three common surgical techniques to manage renal and ureteral stones that fail to pass with observation.
9. Identify the factors that help predict the likelihood of spontaneous stone passage.

INTRODUCTION

Urinary stones are estimated to affect up to 8.8% of the US population, including 10.6% of men and 7.1% of women. The overall incidence of nephrolithiasis is increasing. There is traditionally a high incidence of urinary stones in the Southeastern and South Central United States, termed the "Stone Belt", which probably reflects the hot weather climate and relative dehydration that occurs in these areas. Prior to the development of modern urologic techniques for treatment, mortality from untreated staghorn (infection) calculi was 27%. Currently, overall mortality from stone disease is rare, although there is still a significant rate (28%) of renal deterioration with certain stone types.

PATHOPHYSIOLOGY

Urinary calculi may have various compositions which include, in order of decreasing frequency: calcium oxalate, uric acid, struvite or infection (triple phosphate = magnesium ammonium calcium phosphate), calcium phosphate and cystine. There are other less common stones, such as xanthine and drug-related stones, as well. Calculi are typically composed of urinary chemicals that are usually soluble in urine but occur in amounts too high to stay dissolved and as a result of supersaturation, the solutes tend to precipitate and aggregate to form crystalline concretions or stones.

Calcium Oxalate Stones

Calcium oxalate is by far the most common renal stone material. These stones typically form from an initial calcium phosphate concretion that originates near the renal papilla's epithelium in the highly concentrated, alkaline environment of the distal terminal collecting duct. This calcium phosphate concretion (called a Randall's plaque) eventually erodes through the urothelium in the renal papilla and forms a nidus for eventual calcium oxalate deposition when it is directly exposed to urine. (Figure 1).
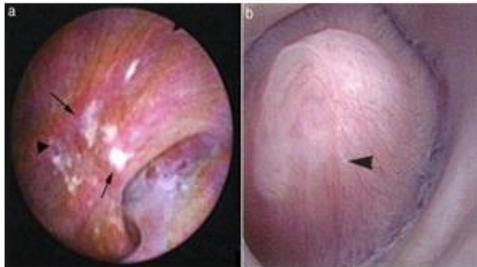
Figure 1. Intrarenal view of renal papillae. (A) stone former showing many Randall's plaques (arrows), and (B) non-stone former with far fewer lesions. (From: Matlaga et al. J Urol 2007; 177: 31-38)

The calcium oxalate deposition continues and grows until the stone becomes large enough to break free of its urothelial "anchor" and passes into the collecting system. Here it may continue to grow in size over time or move andcause obstruction and pain. Calcium oxalate monohydrate crystals appear as ovals or dumbbells under microscopy, while calcium oxalate dihydrate crystals look like little envelopes or octohedrons.

The most important factors that promote calcium oxalate supersaturation and precipitation are dehydration, hypercalciuria, hyperoxaluria, hypernatrituria, hypocitraturia and hyperuricosuria.

Uric Acid Stones

Uric acid is a product of purine metabolism and forms 7 - 10% of all urinary calculi. Uric acid is 100 times more soluble at a pH > 6 compared to a pH < 5.5. The most common risk factor for uric acid lithiasis is persistently acidic urine including the lack of a normal postprandial alkaline tide. Gout or hyperuricemia is only associated with about 20% of cases of pure uric acid lithiasis. Hyperuricosuria is also associated with diseases such as insulin resistance, diabetes mellitus and Lesch-Nyhan syndrome. Chemotherapy for treatment of lymphoma or leukemia causes the sudden lysis of millions of cells which releases a large quantity of purines into the circulation and urine that may then precipitate in the renal tubules causing uric acid stones. Uric acid crystals appear as rounded parallelograms under microscopy. As will be discussed later, urinary alkalinization is the cornerstone of uric acid stone management.

Struvite (Triple Phosphate, Infection) Stones

Struvite stones are considered an infectious stone because they are formed specifically by urease producing organisms, the most common being *Proteus mirabilis*. Less common pathogens include *Klebsiella, Enterobacter*, or *Pseudomonas.* (*E. coli* is **not** a urease

producing organism!) Urease cleaves each mole of (soluble) urea into two moles of (relatively insoluble) ammonium. As this cleavage occurs, free H+ is bound to NH3 to produce NH4+, yielding free OH ions from water, ultimately making the urine more alkaline. Phosphate is less soluble at alkaline than acidic pH, so phosphate precipitates onto the insoluble ammonium products, yielding calcium ammonium magnesium phosphate (hence the name "triple phosphate"). As the bacteria that produce urease remain within the stone and in the urine, the urease they produce continues to cleave urea resulting in persistently alkaline urine. Under these conditions, very large staghorn shaped stones may develop quite rapidly, filling the entire renal pelvis and all the calyceal spaces of the kidney (Figure 2). A urease inhibitor is available (Lithostat or acetohydroxamic acid) and can be useful as an adjunct to definitive treatment which requires culture-specific antibiotic therapy and complete surgical removal of the stone and all its fragments. This stone type should not be confused with other types of stones (i.e. calcium oxalate) that may harbor a variety of bacteria including E coli within the stones.

Figure 2. Example of a staghorn calculus (struvite stone) that has molded to shape of the calyceal space in the kidney.

Calcium Phosphate Stones

Most calcium stones will have a nidus or core of calcium phosphate which originally came from Randall's plaques. Stones that are substantially or primarily calcium phosphate suggest an underlying metabolic disorder such as renal tubular acidosis, primary hyperparathyroidism or medullary sponge kidney, so patients should be screened for these disorders. (For example, renal tubular acidosis will demonstrate severe hypocitraturia; hyperparathyroidism can be identified by elevated parathyroid hormone levels together with hypercalcemia.) Calcium phosphate stones typically form in an alkaline pH of 7.2 or higher which is a good reason to avoid prolonged overtreatment with urinary alkalinizing agents.

Cystine Stones

Cystine stones are produced in patients with a homozygous recessive gene for cystine transport resulting in excessive urinary cystine levels. Cystine is a dibasic non-essential amino acid composed of cysteine-S-S-cysteine. (The four dibasic amino acids are cystine, ornithine, lysine and arginine, hence the mnemonic: COLA.) Under microscopy, cystine urinary crystals appear as perfect hexagons. Normal individuals generally have urinary excretion of < 100 mg cystine/day whereas the majority of homozygous cystinurics excrete > 600 mg/day. Cystine solubility and precipitation depends greatly on urinary cystine concentration and pH as there are no known inhibitors of cystine production. Cystine is much more soluble at a pH of 9.6 and higher compared to lower pH's, but it is practically impossible to achieve such a high

urinary pH by oral alkalinizing agents alone (and certainly not without the risk of calcium phosphate stone formation).

Renal Physiology with Obstruction

All stones may produce obstruction and pain. Pain is thought to occur from ureteral dilation from the obstruction and/or renal capsular distension. With acute unilateral obstruction, in the setting of a normal contralateral kidney, the affected kidney responds in two phases to the blockage:

- Initial 2 hours: There is increased renal pelvic pressures and renal blood flow. As renal pelvic pressure increases, glomerular filtration rate (GFR) decreases, as GFR represents the sum of net hydrostatic and oncotic pressures across the glomerulus.

- At 6 - 24 hours: Renal pelvic pressures remain elevated, but renal blood flow diminishes.

- After 24 hours: Renal pelvic pressures trend down towards baseline (but remain elevated) and renal blood flow continues to diminish. If persistent, the obstruction eventually leads to renal ischemia.

Thus, obstruction from urinary stones threatens GFR, reduces renal blood flow and, if the obstruction is not relieved, renal ischemia which leads eventually to irreversible renal impairment. In general, with high-grade obstruction, renal impairment will occur within two weeks.

CLINICAL PRESENTATION

The classic presentation of a renal stone is acute, colicky flank pain radiating to the groin or scrotum, often associated with nausea and vomiting. As the stone descends in the ureter, pain may localize to the abdomen overlying the stone. Renal and ureteral colic are often considered the most severe pain ever experienced by patients, and many female stone patients describe the pain as even more intense than that of childbirth. As the stone approaches the ureterovesical junction, lower quadrant pain, urinary urgency, frequency and dysuria are common, mimicking bacterial cystitis. A family history of renal calculi is present in 55% of patients with recurrent stones. Stones occur three times more frequently in men with a family history of stones.

The physical exam typically shows a distressed patient, often writhing and constantly moving while trying to find a comfortable position. In contrast, patients with an acute abdomen typically have board-like abdominal rigidity and do not wish to move at all. Costovertebral angle or lower quadrant tenderness may be present. Gross or microscopic hematuria is present in approximately 85% of patients. Importantly, the absence of hematuria with acute flank pain does not preclude renal or ureteral calculi as there may be complete obstruction. Hydronephrosis and renal capsular distension may also produce nausea and vomiting. Thus, the typical symptoms of urinary stones producing acute renal colic may mimic other acute abdominal conditions (Table 1), making rapid and accurate diagnosis important.

TABLE 1: DIFFERENTIAL DIAGNOSIS OF ACUTE RENAL COLIC IN ADULTS
Renal or ureteral stone
Hydronephrosis (ureteropelvic junction obstruction, sloughed papilla)
Bacterial cystitis or pyelonephritis
Lobar pneumonia
Rib fractures
Acute abdomen (bowel, biliary, pancreas or aortic abdominal aneurysm sources)
Gynecologic (ectopic pregnancy, ovarian cyst, torsion or rupture)
Radicular pain (L1 herpes zoster, sciatica)
Referred pain (orchitis)

DIAGNOSTIC EVALUATION

The current gold standard for confirming urinary stones in the setting of acute flank pain is an unenhanced, non-contrast helical computed tomography (CT) scan of the abdomen and pelvis. This study surpasses the intravenous pyelogram (IVP) which had been the standard imaging test for decades. In ambulatory settings where CT is not available, a plain abdominal radiograph (KUB) is useful as approximately 75 - 90% of urinary stones are radiopaque. A KUB is also recommended as an adjunct to any initial CT scan positive for urinary stones. The KUB provides an easy way to track progress of the stone over time, quickly establishes its radio-opacity when its location is known and is usually better than CT for determining stone shape. A contrast CT is recommended only when medication metabolite stones are suspected, such stones are associated with some HIV medications like Crixivan (Indinivir), as these stones would not otherwise be visible.

Historically ultrasound appeared to be vastly inferior to unenhanced CT for stones and insensitive for ureteral calculi. There is some new emerging data supporting the use of US but is currently beyond the scope of this review. The US is used to estimate the degree of urinary obstruction/hydronephrosis and to measure the Renal Resistive Index which is elevated when the kidney is obstructed. (Renal Resistive Index = (Peak Systolic Velocity – End Diastolic Velocity)/Peak Systolic Velocity. Normal = $\leq$0.65 while readings >0.70 suggest medical renal disease or obstruction.) However during pregnancy, ultrasound is the recommended first imaging test when a urinary calculus is suspected. MRI or low-dose CT can be used as 2nd or 3rd line imaging alternative, however decision should be collaborative between radiology, urology, and gynecology (Masselli references and ACOG statement listed below). Radiological imaging continues to evolve quickly and there will be variations on availability and reliability between institutions.

## INITIAL ASSESSMENT AND MANAGEMENT

The most pressing issue in managing patients with urinary stones is determining whether or not urgent intervention is needed. Necessary workup includes a midstream clean catch or catheterized urine specimen for urinalysis and microscopy with urine culture as indicated,

CBC to assess for leukocytosis, and creatinine to assess for any rise above the patient's baseline. Table 2 outlines the indications for immediate intervention.

TABLE 2: INDICATIONS FOR URGENT INTERVENTION WITH URINARY STONES
Obstructed upper tract with infection
Impending renal deterioration
Pain refractory to analgesics
Intractable nausea/vomiting
Patient preference

In addition, Figure 3 presents a clinical algorithm for patients with urinary stones. In general, fully obstructed or infected collecting systems should be surgically decompressed either by percutaneous nephrostomy or ureteral stent placement. If the patient is unstable or septic, drainage of the blocked collecting system is urgent and should be done emergently. Definitive treatment of the obstructing stone should be delayed until any infection is cleared. Infection is suggested by fever, elevated WBC count, and urine microscopy demonstrating pyuria and bacteriuria. Acute pyelonephritis cannot be reliably differentiated clinically from an infected kidney with an obstructing urinary calculus, so some type of urological imaging (KUB, ultrasound or CT scan) is recommended in these cases to avoid misdiagnosis and a potentially dangerous delay in surgical intervention. Infection proximal to an obstructing stone differs from an infection (struvite) renal stone. In the absence of obstruction, most struvite calculi may be temporized with antibiotics without decompression, pending definitive treatment.

Figure 3
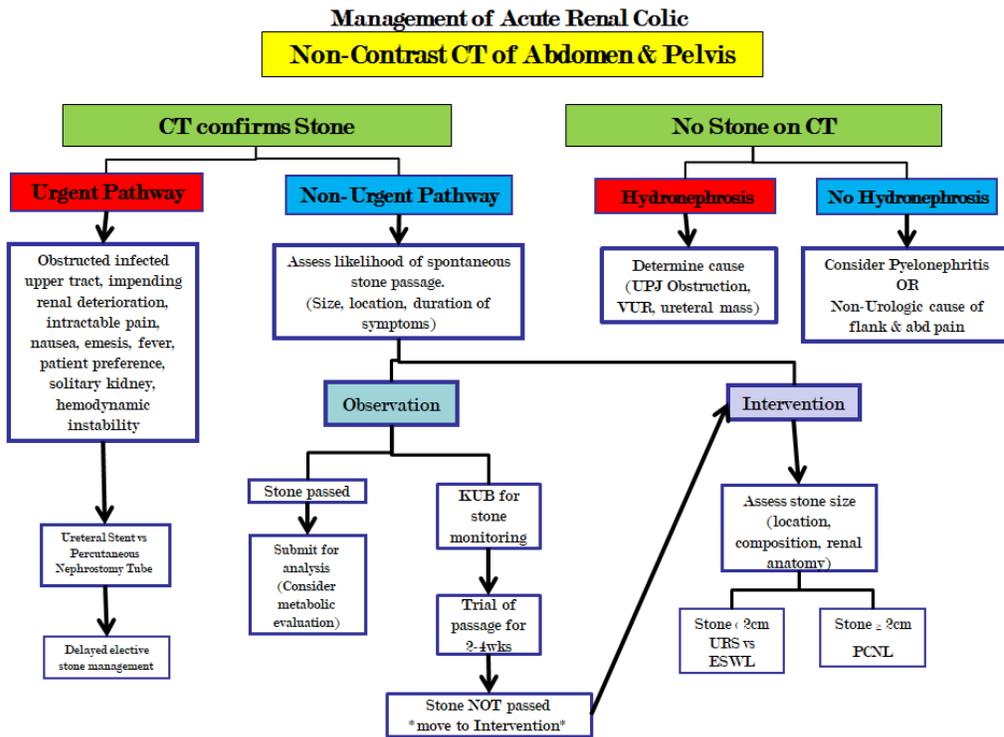
High-grade obstruction (moderate or severe hydronephrosis) in a solitary or transplanted kidney is an example of impending renal deterioration and requires rapid resolution of the blockage with drainage or surgery. Patient preference is a relative indication for urgent intervention.

Pain

Since most stone patients present with pain, analgesia must also be addressed. Narcotics and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain relief. In most randomized, blinded studies of NSAIDs versus narcotics, NSAIDs have shown equal or greater efficacy of pain relief and a shorter time to reach adequate analgesia with equal or fewer side effects. NSAIDs may pose a threat to renal function with decreased blood flow from obstruction, particularly if patients have pre-existing renal impairment. Also, if surgical intervention is warranted, NSAIDs cause platelet inhibition and risk increased surgical bleeding. Intractable renal colic pain is effectively controlled by decompressing the obstruction via percutaneous nephrostomy or ureteral stenting.

Expectant Management

When urgent intervention is unnecessary, the next clinical decision is whether patients may be followed expectantly in anticipation of passing their stone spontaneously versus elective intervention. Stone size and location are key determinants to predict spontaneous passage. The ureter is the smallest diameter structure of the urinary tract and is the area most prone to obstruction by a stone; especially the ureterovesical junction or UVJ. The majority of stones < 5 mm in diameter are likely to pass spontaneously but the likelihood of spontaneous stone passage decreases as stone size increases (Table 3).

TABLE 3: CHANCE OF PASSING URETERAL STONES

Stone size (mm)	Number of days to pass stone (mean)	% Likelihood of eventual need for intervention
2 or less	8	3
3	12	14
4-6	22	50
> 6	--	99%

Two-thirds of ureteral stones pass spontaneously within four weeks of the onset of symptoms. Spontaneous stone passage within the distal ureter may be facilitated with drugs that enhance expulsion and reduce ureteral spasm. Such medical expulsive therapy (MET) includes calcium channel blockers and alpha blockers like tamsulosin which are typically used in combination with NSAIDs. These medications work by inhibiting smooth muscle contraction (peristalsis) in

the distal ureter. MET is most effective for small, distal ureteral stones where it appears to shorten the duration of ureteral obstruction and increases the likelihood of spontaneous stone passage by about 30%.

Patients rarely have complete obstruction and thus the risk of renal deterioration from observation for a small stone is presumed low. However, a ureteral stone that has not passed or moved within 1 - 2 months is unlikely to pass spontaneously with further observation alone. An observation period of 2 - 4 weeks is reasonable in most circumstances even in symptomatic patients. With observation, close follow-up is needed to ensure stone passage, to follow stone growth and to watch for new infections. Asymptomatic patients who have stones < 10 mm in size may be followed unless symptoms, infection, impending renal deterioration or stone growth warrant intervention. As precise stone chemical composition is typically not known on initial presentation, it is important to encourage patients to strain their urine for stone passage and collect and submit their stone or fragments for chemical analysis. Recurrent stone episodes may be more efficiently managed with knowledge of prior stone composition.

MEDICAL AND SURGICAL MANAGEMENT

All patients presenting with newly diagnosed kidney or ureteral stones warrant screening evaluation consisting of a detailed medical and dietary history, serum chemistries, and urinalysis. Medical conditions that contribute to an increased risk of stone formation include hyperparathyroidism, inflammatory bowel disease and other malabsorption disorders, RTA type I, and diabetes. These as well as common medications with a known link to kidney stones can be found in table 4. Common dietary discrepancies that may contribute to stone formation include low dietary calcium intake, low fluid intake, high sodium intake, low fiber diet, low fruit and vegetable intake, and high intake of animal proteins.

Table 4: Risk Factors for Kidney Stone Formation	
Anatomic	- Urinary obstruction leading to urinary stasis
Urine Composition	- pH, hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, hypomagnesiuria, xanthinuria
Low urinary volume	- Poor dietary fluid intake
Dietary Factors	- High potential renal acid load (PRAL): cheese, egg yolks - High sodium intake - Low fiber - High oxalate - Carbonated drinks with phosphoric acid

Hypokalemia	- Intracellular acidosis promotes stone formation
Chronic Diseases	- Obesity - Diabetes Mellitus - Hypertension - Gout - Metabolic acidosis - Renal Tubular Acidosis (type 1) - Sarcoidosis - Cystinuria - Inflammatory bowel disease - Primary hyperparathyroidism - Chronic diarrhea - Medullary sponge kidney
Recurrent UTI	- Specifically with urease producing organisms (proteus mirabilis, klebsiella pneumoniae, pseudomonas aeruginosa)
Medications	- Topiramate, indinavir, vitamin C, vitamin D, triamterene, furosemide, acetazolamide, probenicid

For those in whom intervention is warranted, treatment is based on stone characteristics such as chemical composition (based on Hounsfield units of the stone on CT and patient associated risk factors), intra-renal location, number and size of stones, and upper tract anatomy. Other factors such as patient co-morbidities, patient size and body habitus, equipment availability, surgeon's judgment and patient preference are also important in determining the approach for intervention.

TABLE 5: OPTIONS FOR STONE INTERVENTION
Oral stone dissolution (Uric acid stones only) Extracorporeal Shock Wave Lithotripsy (ESWL) Ureteroscopy Percutaneous Nephrolithotomy (PCNL) Open or Laparoscopic Lithotomy

Presumed uric acid calculi, as suggested by CT Hounsfield units of <500 and/or history of prior uric acid stones, are unique in that they may be completely managed and dissolved medically. Urinary alkalinization with potassium citrate (or alternatively sodium citrate or sodium bicarbonate) will dissolve uric acid stones. Sufficient alkalinization therapy should be given to increase the pH to at least 6.5. Maintaining the pH at this level usually results in dissolution of pure uric acid stones in 2 - 6 weeks. Progress can be followed with ultrasound. Potassium citrate can have significant side effects including nausea, vomiting, and diarrhea that limit its use in some patients. These patients may be indicated for intervention.

Renal or ureteral stones <2cm in maximal diameter may be treated by ureteroscopy (URS) or Extracorporeal Shock Wave Lithotripsy (ESWL). Patients with signs of obstruction and infection require a period of decompression with a ureteral stent or percutaneous nephrostomy tube prior to intervention to treat the stone. Additionally, infections must be appropriately treated with culture appropriate antibiotics prior to intervention. Ureteroscopy involves passing a flexible or semirigid ureteroscope from the bladder into the ureter and renal collecting system. Using laser lithotripsy devices and endoscopic baskets, stones can be located and removed or fragmented into tiny pieces that will pass painlessly. Ureteroscopy has a greater stone-free rate in a single procedure and is recommended especially for patients with mid or distal ureteral stones or stones in the lower pole of the kidney. Ureteroscopy is also the preferred treatment for patients with cysteine or uric acid stones who fail MET or desire intervention.

For patients who are unwilling to undergo ureteroscopy, ESWL may be offered for stones that are visible on KUB. This technique focuses shock waves on the stone to fracture it into small fragments, which then must pass through the urinary tract. ESWL may be used for renal stones or proximal ureteral stones. ESWL is less successful for lower pole renal stones due to the effects of gravity on fragment clearance.

Renal stones >2cm in maximal diameter are best treated by percutaneous nephrolithotomy (PCNL). This procedure involves placement of a small caliber nephrostomy catheter, under radiographic guidance, through the flank into the renal collecting system. This catheter can be placed either by interventional radiology or by the urologist. The catheter is then used to dilate a tract into the kidney to allow placement of a larger sheath to drive either a rigid or flexible nephroscope into the collecting system. Various working instruments and graspers including lasers, ultrasonic probes, and pneumatic devices may then be passed through the nephroscope to fragment the stone, evacuate fragments, or grasp and remove them. PCNL is more invasive and morbid than ESWL and ureteroscopy, and has a higher risk of significant bleeding.

Table 6: Overview of Surgical Management for Stone Disease				
Procedure	Stone Size and Location	Approximate Stone-Free Rate	Complications	Contraindications
Ureteroscopy (URS)	- Any renal or ureteral stone up to 1.9cm - Recommended first line for mid and	- 85-97% for any stone up to 1cm	- Ureteral perforation - Ureteral avulsion - Sepsis - Post operative lower urinary tract symptoms and flank	- Active urinary tract infection

	- distal ureteral stones - Cystine or uric acid stones	- 79% for proximal ureteral stones >1cm	pain (likely due to use of ureteral stent) - Ureteral stricture (long-term)	
Extracorporeal Shockwave Lithotripsy (ESWL)	- Proximal ureteral or non-lower pole renal stone up to 1.9cm - May offer for lower pole stones <1cm	- 70-75% for any stone up to 1cm - 74% for proximal ureteral stones >1cm	- Bleeding/hematoma formation - "Steinstrasse" – obstruction by multiple passing stone fragments - Sepsis - Intraoperative arrhythmias	- Stone not visible on KUB - Active urinary tract infection - Coagulopathy - Lower pole stone >1.9cm - Stones resistant to ESWL (cystine, matrix)
Percutaneous Nephrolithotomy (PCNL)	- Single stone >2cm or total stone burden > 2cm - May also be offered for	- 80-90% for renal calculi - 86% for	- Bleeding - Need for blood transfusion - Sepsis - Intraperitoneal injury - Bowel injury - Lung injury (pneumotho	- Active urinary tract infection - Coagulopathy - Therapeutic anticoagulation - Pregnancy

	lower pole stone >1cm in size - Staghorn stones	proximal ureteral calculi	rax, hydrothorax)	

METABOLIC STONE EVALUATION AND STONE PREVENTION

Any patient with recurrent stones warrants metabolic evaluation as renal deterioration is more likely to occur from recurrent compared to solitary stone episodes. Metabolic stone evaluations are also recommended for all stone formers with high risk factors such as solitary or transplanted kidneys, GI bypass surgery or significant medical co-morbidities. It is also recommended for all children with kidney stones. The typical metabolic evaluation includes stone composition analysis, 24-hour urine collection and serum studies as described in Table 5.

TABLE 7: METABOLIC STONE EVALUATION FOR RENAL STONES
• 24 hour urine for total volume, pH, calcium, oxalate, sodium, uric acid, citrate, phosphate, magnesium, sulfate, creatinine, quantitative cystine (optional). • Serum calcium, phosphorus, uric acid, HCO3, BUN, creatinine, albumin, alkaline phosphate, intact PTH (optional but recommended in hypercalcemia) and 1.25-dihydroxyvitamin D3 (optional). • Stone composition analysis.

The most common metabolic factors identified are low urine volume, hypercalciuria, hyperoxaluria, hypocitraturia and hyperuricosuria. We will also briefly review hypercystinuria.

Low Urine Volume increases urinary supersaturation. A simple way to reduce urinary supersaturation is to instruct patients to increase their oral fluid intake sufficiently to generate a 24 hour urinary volume of at least 2.5L.

Hypercalciuria can occur by multiple mechanisms, including increased dietary absorption of calcium, poor reabsorption of calcium by the kidneys, or by calcium release from bone resorption such as happens in primary hyperparathyroidism. Patients with a history of calcium stones should be advised to consume a normal amount of dietary calcium (1000-2000mg per day), and to limit dietary sodium intake to less than 2g per day. They should also be advised to increase fluid intake. Patients with primary hyperparathyroidism should be referred to an endocrine surgeon for appropriate management. Medications used to manage hypercalciuria include thiazide diuretics, which increase calcium reabsorption from the distal tubule. Patients on thiazides should be monitored for hypotension, dizziness, and hypokalemia.

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Hyperoxaluria is often caused by increased dietary intake of oxalate rich foods, including dark leafy greens like spinach, chocolate, nuts, and tea. Vitamin C is a precursor to oxalate, and high dietary intake of vitamin C can also lead to hyperoxaluria. Another form of hyperoxaluria, called enteric hyperoxaluria, can be seen in Crohn's disease or cases of intestinal bypass surgery that leads to fat malabsorption. The presence of fat in the intestinal lumen binds with calcium, leaving oxalate to be more freely absorbed. Preventive treatment usually consists of dietary oxalate restriction. Vitamin B-6 can help some hyperoxaluric patients by modifying hepatic oxalate metabolism. Oral calcium supplementation (calcium citrate is preferred) given with any high oxalate meal (usually lunch and/or dinner) can be effective in increasing intestinal oxalate binding which limits GI absorption of free oxalate thereby reducing urinary oxalate excretion which otherwise can be difficult to manage with dietary oxalate reduction alone.

Hypocitraturia is an important risk factor for both calcium and uric acid stone disease. This can occur in patients with chronic acidosis or hypokalemia (which creates an intracellular acidosis). Distal renal tubular acidosis, enteric hyperoxaluria, chronic diarrheal states and the use of carbonic anhydrase inhibitors like topiramate (Topamax) and acetazolamide (Diamox) lead to metabolic acidosis and hypocitraturia, but the specific cause of low urinary citrate in most stone formers is unknown. Dietary methods to increase urinary citrate require very large intake of lemonade or other citrus drinks, and can be hard for patients to sustain long term. These patients are usually best treated with citrate supplementation sufficient to reach optimal 24-hour urine levels of 500 - 600 mg and/or urine pH of 6.5 if possible. Potassium citrate is usually the preferred citrate supplement and urinary alkalinizing agent, but serum potassium and urine pH levels should be monitored periodically when giving significant potassium citrate supplementation.

Hyperuricosuria contributes to both calcium oxalate and uric acid stones. Dietary recommendations include increasing fluid intake, decreasing sodium intake, and decreasing intake of animal proteins including red meat, poultry, and fish. Patients with hyperuricosuria, normal urinary calcium, and recurrent calcium oxalate stones may be treated with allopurinol. Allopurinol should not be used first-line to treat patients with uric acid stones. Probenicid, a commonly used medication for gout, should be discouraged in stone formers as it increases urinary uric acid excretion which increases both uric acid and calcium stone production.

Cystinuria patients are encouraged to increase their fluid intake enough to generate 3,000 mL of urine daily or more. This may require waking up in the middle of the night specifically to drink more water. Up to 1/3 of cystinuric patients can control their stone production with increased fluid intake alone. Citrate supplements are also recommended with the goal of reaching and maintaining a urinary pH of 7.5 if possible. Cystine solubility is generally 250 - 300 mg/liter at a pH of 6.5 - 7, but at a pH of 7.5, the solubility is doubled to 600 mg/liter which is reasonably obtainable in clinical practice with available oral urinary alkalinizers like potassium citrate and sodium bicarbonate. When these measures fail, tiopronin (Thiola) can be utilized. This medication forms a soluble complex with cystine and effectively reduces cystinuria, but it needs to be taken three times daily and has several potential side effects so its dosage should be titrated carefully.

Any patient who undergoes metabolic evaluation should undergo repeat evaluation with a 24-hour urine collection within 6 months of dietary changes or starting treatment to assess response to therapy.

When other metabolic abnormalities are uncovered (distal renal tubular acidosis, primary hyperparathyroidism, sarcoidosis) specific therapy is warranted. Regardless, patient compliance with long-term stone preventive therapy is no better than 70 - 80%. Moreover, medical prophylaxis may not be cost-effective for all patients with only a single stone episode unless they have high risk factors such as a solitary or transplanted kidney, or have significant co-morbidities making possible surgical intervention inadvisable. Patient motivation is critical to the success of any long-term preventive treatment plan.

SUMMARY

1. Urinary calculi typically present with renal colic and hematuria frequently accompanied by nausea and vomiting.
2. Gross or microscopic hematuria frequently accompanies renal colic but may be absent in 15% of cases.
3. The unenhanced CT is the single best initial diagnostic imaging test. If positive, an immediate KUB is very helpful for determining stone shape and density as well as for follow-up and tracking.
4. Clinicians should initially assess the need for urgent intervention as well as the likelihood of spontaneous stone passage.
5. Urologic intervention must be individualized.
6. Metabolic risk of stone recurrences should be addressed in repeat stone formers, children and in some motivated first-time stone formers.

REFERENCES

ACOG Committee Opinon. Number 72. Obstet & Gynecol 2017 Oct; 130(4): e210-e216

Assimos DG, Krambeck A, Miller NL, Monga M, Murad H, Nelson CP, Pace KT, Pais PM Jr, Pearle MS, Preminger GM, Razzvi H, Shah O, Matlaga BR:Surgical Manaement of Sotnes: AUA/Endourology Society Guideline. https://www.auanet.org/guidelines/stone-disease-surgical-(2016)

Dent CC, Rose GA. Amino acid metabolism in cystinuria. *Q J Med New Series*. 1974. 214: 507-12.

Hamm LL, Hering-Smith KS. Pathophysiology of hypocitraturic nephrolithiasis. Endocrinol Metab Clin North Am. 2002; 31: 885–893.

Leslie SW: Hypercalciuria. Emedicine/Medscape. 2013.
http://emedicine.medscape.com/article/2182757-overview

Masselli, G et al: The role of imaging in the diagnosis and management of renal stone disease in pregnancy. Clin Radiol 2015 Dec; 70(12):1462-1471

Masselli, G et al: Stone diseasei n pregnancy: image-guided therapy. Insights Imaging 2014;5:691-696

Matlaga BR, Coe FL, Evan AP, Lingeman JE: The role of Randall's plaques in the pathogenesis of calcium stones. J Urol 2007; 177: 31-8.

Miller OF, Kane CJ: Time to stone passage for observed ureteral calculi: a guide for patient education. J Urol 1999; 162: 688-91.

Ngo TC and Assimos DG: Uric acid nephrolithiasis: recent progress and future directions. Rev Urol 2007; 9(1): 17-27, PMID: 1831527

Pak CY, Resnick MI: Medical therapy and new approaches to management of urolithiasis. Urol Cl N Am 2000; 27: 243-53.

Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, Monga M, Penniston KL, Preminger GM, Turk TMT, White JR: Medical Management of Kidney Stones. https://www.auanet.org/guidelines/stone-disease-medical-(2014)

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: 1991-2000.

Preminger GM, Ferrandino MN, Haleblian GE, et al: Urology Core Curriculum: Surgical Stone Management. http://www.auanet.org/eforms/elearning/core/?topic=14 accessed May 7, 2011 – review updates to core curriculum

Segura JW, Preminger GM, Assimos DG et al: Ureteral stones clinical guidelines panel summary report on the management of ureteral calculi. J Urol 1997; 158: 1915.

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Disclosures: Urigen, Investment Interest.