

MODULE 6: KIDNEY STONES

KEYWORDS: Nephrolithiasis, urinary stones, kidney, calciuria, oxaluria

LEARNING OBJECTIVES

At the end of this clerkship, the medical student will be able to:

1. List risk factors for the most common types of kidney stones
2. Contrast differences between the clinical presentation of acute renal colic versus an acute abdomen
3. Name 4 kidney stone chemical compositions
4. Describe the best imaging study to diagnose kidney or ureteral stones
5. Describe 3 types of medications effective for relief of renal colic pain
6. List 3 clinical situations that warrant urgent decompression of a ureteral stone
7. List 2 types of medications that may help medical expulsion therapy of a distal ureteral stone
8. Describe two medical prophylaxis options for hypercalciuria
9. List 2 common surgical techniques to manage a renal stone and a ureteral stone that fails to pass with observation

INTRODUCTION

Urinary stone prevalence is estimated at 3% in all individuals, and it affects up to 12% of the population during their lifetime. Urinary stone recurrence rates approach 50% at 10 years and white males have the highest incidence in the U.S. There is traditionally a high incidence of urinary stones in the southeastern and central southern United States, termed the "Stone Belt", which probably reflects water and soil content as well as hot weather and dehydration that occur in these areas. Currently mortality from stone disease is rare, although there is still a significant rate (28%) of renal deterioration with certain stone types. Prior to the development of modern urologic techniques for treatment, mortality from untreated staghorn calculi was 27%.

PATHOPHYSIOLOGY

Urinary calculi may have various compositions which include, in order of decreasing frequency: calcium oxalate (monohydrate or dihydrate), uric acid, struvite (magnesium ammonium phosphate), calcium phosphate, and cystine. There are other less common stones, including xanthine and drug-related stones as well. Stones are

solutes that occur in amounts too high to stay dissolved (supersaturated) in urine. As a result of supersaturation, the solutes precipitate and aggregate to form concretions or stones.

Calcium oxalate stones

It is thought that the majority of calcium oxalate stones form from an initial calcium phosphate concretion that originates near the renal calyx epithelium in the highly concentrated environment of the terminal collecting duct. The calcium phosphate concretion (called a Randall's plaque) erodes through the urothelium, is exposed to urine, and forms a nidus for calcium oxalate deposition with time (Figure 1).

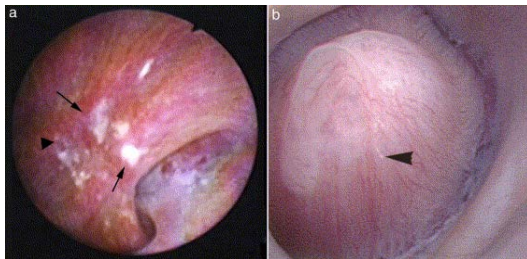


Figure 1: Intrarenal view of renal papillae. (A) stone former showing many Randall's plaques (arrows), and (B) non-stone former with far fewer lesions. (From: Matlaga et al. J Urol 2007; 177: 31-38)

The calcium oxalate deposition grows until the stone becomes large enough to break free of its urothelial "anchor" and then may pass through the collecting system. Factors that promote calcium oxalate supersaturation (and calcium oxalate deposition) are dehydration, hypercalciuria, hyperoxaluria, hypernatrituria, and hyperuricosuria. Urinary citrate is a strong complexing agent of calcium. It therefore is an important inhibitor of calcium oxalate formation and hypocitraturia is a risk factor for stone formation.

Uric acid stones

Uric acid is a product of purine metabolism. Uric acid is 100 times more soluble at a pH > 6 compared to a pH < 5.5. Other than dehydration, the most common risk factor for uric acid lithiasis is persistently acidic urine including the lack of a normal postprandial alkaline tide. Likewise, patients with persistent acidosis (e.g., distal renal tubular acidosis) are also at risk for developing uric acid stones. Less commonly, gout (hyperuricemia) is associated in approximately 20% of cases with hyperuricosuria and uric acid lithiasis. Hyperuricosuria is also seen in patients with lymphoma or leukemia that are treated with chemotherapy. With such treatment, the sudden lysis of millions of cells releases a large quantity of purines into the circulation and urine that may precipitate in the renal tubules and cause uric acid stones.

Struvite stones

Struvite stones are caused by urinary infections with 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 NH_3 to produce NH_4 , yielding OH^- from water making urine more alkaline. Phosphate is less soluble at alkaline versus acidic pH, so phosphate precipitates onto the insoluble ammonium products, yielding magnesium ammonium phosphate. As the bacteria that produce urease remain in urine and within the stone, they continue to produce urease, and continue to cleave urea, and so large (staghorn shaped) stones may develop quite rapidly and fill the calyceal spaces of the kidney (Figure 2).



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

Cystine stones

Cystine stones are produced in patients with a homozygous recessive gene for cystine transport, producing excess urinary cystine. Cystine is an amino acid of cysteine-S-S-cysteine. (The four dibasic amino acids are cystine, ornithine, lysine, and arginine, hence the mnemonic: COLA.) Normal individuals generally excrete into urine <100 mg cystine/day whereas the majority of homozygous cytinurics excrete > 200 mg/day. There are no known inhibitors of cystine. Cystine is more soluble at a pH of 9.6 and higher compared to lower pHs, but it is practically impossible to achieve such a high urine pH by oral alkali agents (and not without risk of calcium phosphate stone formation).

Renal Physiology with Obstruction

All stones may produce obstruction and pain. Pain is thought to occur from ureteral obstruction and renal capsular distension. With acute unilateral obstruction, in the setting of a normal contralateral kidney, the affected kidney responds in 2 phases to obstruction:

- Initial 2 hours: There is increased renal pelvic pressures and renal blood flow. As renal pelvic pressure increases, glomerular filtration (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,
- >24 hours: Renal pelvic pressures trend down towards baseline (but remain elevated) and renal blood flow continues to diminish. If persistent, the obstruction leads to renal ischemia.

Thus, obstruction from urinary stones threatens GFR, renal blood flow, and if obstruction is not relieved, renal ischemia leads to irreversible renal impairment. In general, with high-grade obstruction, renal impairment will occur within 2 weeks.

CLINICAL PRESENTATION

The classic presentation of a renal stone is acute, colicky flank pain radiating to the groin or scrotum. As the stone descends in the ureter, pain may localize to the abdomen overlying the stone. Renal and ureteral colic are often considered among the most severe pain experienced by patients, and many female stone patients describe the pain as 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, while trying to find a comfortable position. In contrast, patients with an acute abdomen typically have board-like abdominal rigidity and do not want to move. Costovertebral angle or lower quadrant tenderness may be present. A large distal ureteral calculus at the ureterovesical junction in a woman may be palpated on vaginal exam. Gross or microscopic hematuria is present in approximately 90% 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
 - 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)
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DIAGNOSTIC EVALUATION

The current gold standard for confirming urinary stones in the setting of acute flank pain is an unenhanced, 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. A prospective trial of 106 adult patients with acute flank pain imaged all patients with both an unenhanced helical CT and IVP. CT and IVP showed a ureteral stone in 96% vs. 87% of patients, respectively, which was significantly different. Of patients without stones, the CT and IVP were negative in 100% versus 94% of cases, also significant. Thus, the positive and negative predictive values for CT were 100% and 91%, and for IVP, 97% and 74%, respectively. In ambulatory settings where CT is not available a plain abdominal radiograph (KUB) is useful as approximately 75-90% of urinary stones are radiopaque. Ultrasound appears to be vastly inferior to unenhanced CT for stones and is insensitive for ureteral calculi. However, in the case of pregnancy, ultrasound should be the first imaging test when a urinary calculus is suspected in a pregnant woman.

MANAGEMENT

The most pressing issue in managing patients with urinary stones is whether or not urgent intervention is needed. Table 2 outlines the indications for immediate intervention.

TABLE 2: INDICATIONS FOR URGENT INTERVENTION WITH URINARY STONES

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- Obstructed upper tract with infection
 - Impending renal deterioration
 - Pain refractory to analgesics
 - Intractable nausea/vomiting
 - Patient preference
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In addition, Figure 3 presents a clinical algorithm for patients with urinary stones. In general, fully obstructed or infected collecting systems are decompressed either by percutaneous nephrostomy or ureteral stent placement. Infection is suggested by fever and elevated WBC count and a urinalysis showing pyuria and bacteriuria.

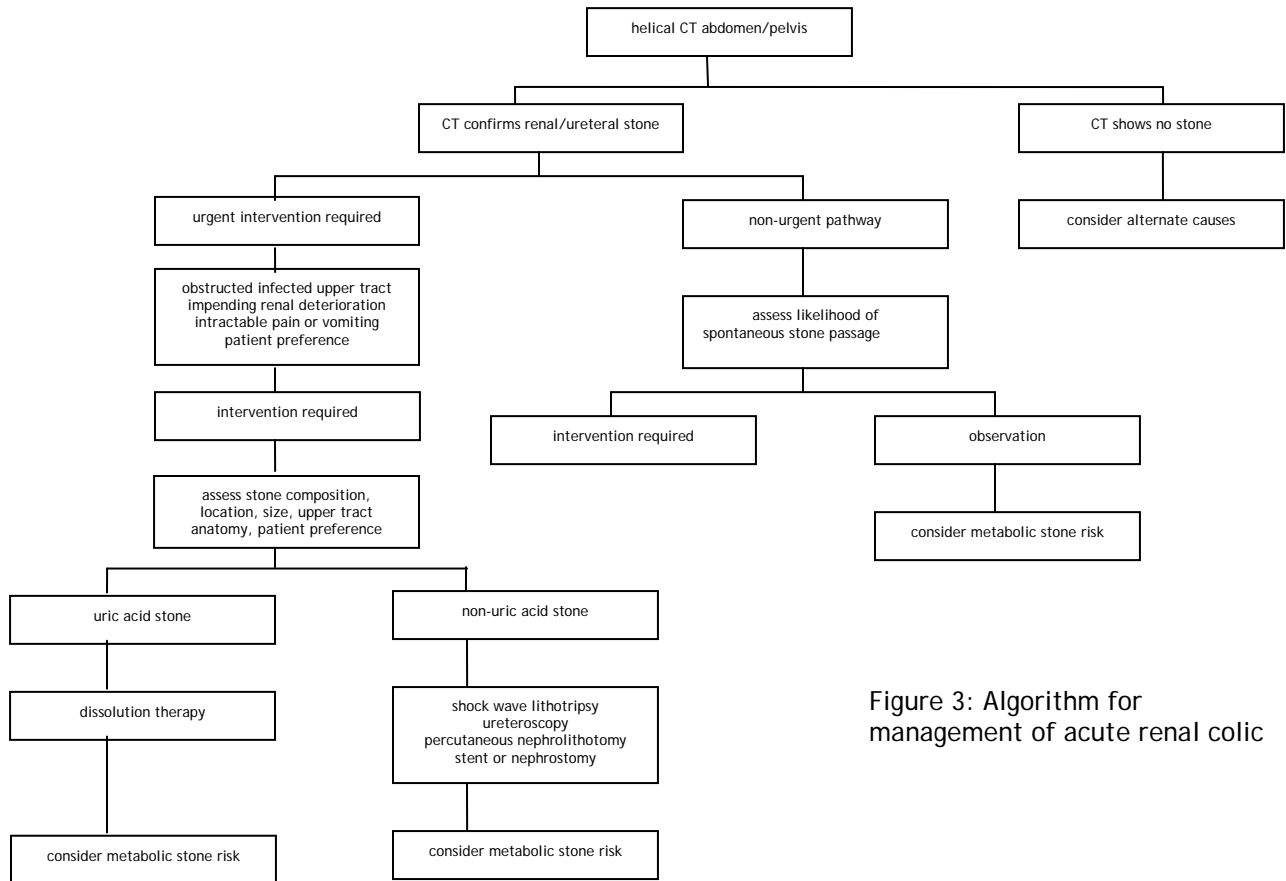


Figure 3: Algorithm for management of acute renal colic

Infection proximal to an obstructing stone differs from an infection (struvite) stone. In the absence of obstruction, most struvite calculi may be temporized with antibiotics without decompression, pending definitive treatment. High-grade obstruction (moderate or severe hydronephrosis) in a solitary or transplant kidney is an example of impending renal deterioration. Patient preference may also impact urgent intervention.

Pain

Since most stone patients present with pain, analgesia must also be addressed. Traditionally, narcotics and now 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 for pain relief, shorter duration to pain relief, with equal or fewer side effects. NSAIDs may pose a threat to renal function with decreased blood flow from obstruction, particularly if patients have preexisting renal impairment. Also, if surgical intervention is warranted, NSAIDs

might lead to platelet inhibition and lead to increased surgical bleeding. Intractable pain is effectively controlled by decompressing the obstruction (percutaneous nephrostomy or ureteral stent).

Expectant management

When urgent intervention is unnecessary, the next clinical decision is whether the patients may be followed expectantly in anticipation of passing their stone spontaneously versus elective intervention. The stone size and location are key determinants to predict spontaneous stone passage. The ureter is the smallest diameter structure of the urinary tract and is the area most prone to obstruction by a stone. The majority of stones < 5 mm in diameter are likely to pass spontaneously and 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 that pass spontaneously pass within 4 weeks of the onset of symptoms.

Spontaneous stone passage within the distal ureter may be facilitated with drugs that enhance expulsion. Such medical expulsion therapy (MET) includes alpha-blockers and calcium channel blockers, typically used in combination with NSAIDs. MET shortens the duration to stone passage and increases the likelihood of stone passage. Corticosteroids (e.g., prednisone) have also been studied in combination with alpha blockers and may help with stone expulsion; however, anecdotal reports of avascular necrosis of the hip may limit its use in the future.

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 within 1-2 months is unlikely to pass spontaneously with further observation. An observation period of several weeks is reasonable in most circumstances in symptomatic patients. With observation, close follow-up is needed to insure stone passage or to follow stone growth and to watch for new infections. In asymptomatic patients who have stones < 5 mm in size, they may be followed, unless symptoms, infection, impending renal deterioration or stone growth warrant intervention. As stone composition is typically not known on presentation, it is important to encourage patients to catch and submit their stone for analysis, so that

recurrent stone episodes may be more efficiently managed with knowledge of prior stone composition.

Medical and Surgical Management

For those in whom intervention is warranted, treatment is based on stone composition, stone location and size, upper tract anatomy, and patient preference (Table 4).

TABLE 4: OPTIONS FOR STONE INTERVENTION

- Oral stone dissolution
- Extracorporeal shock wave lithotripsy (SWL)
- Ureteroscopy
- Percutaneous nephrolithotomy (PCNL)
- Open or laparoscopic lithotomy

Uric acid calculi, which comprise 5-10% of urinary calculi, are unique in that they may be managed medically. Urine alkalization with potassium citrate (or alternatively sodium citrate or sodium bicarbonate) will dissolve uric acid stones.

For other urinary calculi < 3 cm in maximal diameter, they are generally best treated by shock wave lithotripsy (SWL) (Figure 3) SWL generates shock waves extracorporeally, focuses them and fragments the stone. The patient then passes smaller fragments in their urine. Success varies based on SWL machine, stone size, composition, and location. SWL is less successful for renal calculi located in the lower pole compared to all other renal locations, likely from the effects of gravity on fragment clearance. Patients with lower pole stones are more likely to be stone-free if treated by percutaneous nephrolithotomy (PCNL) than by SWL (Figure 4). Renal calculi in all locations > 3 cm are best treated by percutaneous nephrolithotomy (PCNL), with or without adjunctive SWL.

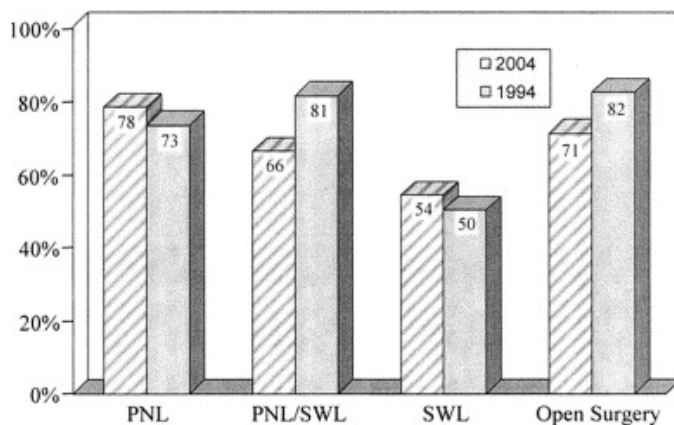


Figure 4. Stone-free rates after various urological procedures. Note: PNL-percutaneous nephrolithomy; SWL-shock wave lithotripsy. (From: Preminger et al, J Urol 2005;173:1991-2000).

PCNL involves initial placement of a small caliber nephrostomy catheter under radiographic guidance through the flank into the renal collecting system. The tract is then dilated and a larger sheath is placed to allow passage of a rigid or flexible

nephroscope into the collecting system. Working instruments may be passed through the nephroscope to fragment the stone, evacuate fragments, or grasp and remove fragments. PCNL is generally more invasive (and morbid) than SWL, with higher likelihood of narcotic use, higher narcotic equivalents required for pain control, significant bleeding, and transfusion rates.

It is also feasible to use retrograde ureteroscopy (i.e., passing a flexible ureteroscope from the bladder, up the ureter and into the renal collecting system) to treat renal calculi. With sophisticated laser lithotripsy devices, most stones can be fragmented into tiny pieces (< 1 mm) and stone-free outcomes result in over 90% of cases of ureteral calculi after a single procedure. Performing nephroscopy with this technique for renal calculi is technically more challenging, with stone-free outcomes at 60-84% after a single procedure. In general, the success rate diminishes as stone size increases, and multiple procedures are usually required for renal calculi >2 cm.

The optimal surgical treatment of ureteral calculi is with SWL or ureteroscopy. Proximal ureteral calculi are generally treated by SWL, but ureteral calculi located over the bony pelvis may be problematic for SWL as they are difficult to image and target with shock waves. For distal ureteral calculi, the preferred treatment is controversial as a randomized study comparing SWL with ureteroscopy found no difference in stone-free rates but many variables, including patient preference, are considered when treating individual patients. As flexible ureteroscopes improve in development and functionality, ureteroscopy will probably become more popular as first line surgical management.

STONE PROPHYLAXIS

A patient with recurrent stones warrants metabolic evaluation as renal deterioration is more likely to occur from recurrent compared to solitary stone episodes. The typical metabolic evaluation includes stone composition analysis, 24-hour urine collection and serum studies as described in Table 5.

TABLE 5: METABOLIC STONE EVALUATION

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- 24 hr 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), 1,25-di-OH-vitamin D₂ (optional)
 - Stone composition analysis
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The most common metabolic factors identified are low urine volume, hypercalciuria, and hypocitraturia. Low urine volume increases urinary supersaturation. A simple means to reduce supersaturation is to instruct patients to increase fluid intake. Dietary calcium restriction alone is no longer recommended. Fewer stone recurrences occur with dietary restriction of animal protein (oxalates) and salt when compared to

calcium restriction. It is unclear whether dietary management alone, pharmacologic management alone, or combined dietary and pharmacologic management is the best for stone prophylaxis. In the setting of hypercalciuria, dietary calcium restriction is not warranted, but dietary restriction of animal protein and salt, with or without additional use of thiazide and citrate therapy may be beneficial. When other metabolic abnormalities are uncovered (hypocitraturia, distal renal tubular acidosis, primary hyperparathyroidism, hyperuricosuria, sarcoidosis) specific therapy is warranted. Regardless, patient compliance with long-term stone prophylaxis therapy is no better than 70-80%. Moreover, medical prophylaxis may not be cost-effective for all patients with a first stone episode.

SUMMARY

- Urinary calculi typically present with renal colic and hematuria.
- The unenhanced helical CT is the best initial diagnostic test.
- Clinicians should assess the need for urgent intervention and the likelihood for spontaneous stone passage.
- Urologic intervention must be individualized.
- Metabolic risk of stone recurrences should be addressed in repeat stone formers, and in some first-time stone formers.

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