Update on Kidney Stones

Once acute surgical conditions have been ruled out, pain control is a mainstay of ED treatment of this condition.

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Nephrolithiasis, or *kidney stone disease*, is relatively common, with a lifetime risk of approximately 5% for both sexes.[1] The prevalence of this disease has been increasing among males and females of all ages, indicating a possible environmental cause in addition to genetic predisposition. Furthermore, the incidence of stone disease is increasing worldwide.[2] The lifetime risk of kidney stones is 6% for women and 12% for men.[1] For those with untreated stones, the risk at 5 years for forming another stone is 30% to 40%; however, treatment comprising diet modification or medication has reduced the rate of recurrence by as much as 50% in some studies.[3,4] Disease prevalence varies by race, with the highest prevalence in white men, followed by Asian, Hispanic, and African American men.[5]

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Kidney stone disease is costly; in 2000, this condition led to an estimated $2.1 billion in expenditures.[6] This has been attributed to both an increase in population as well as an increase in prevalence.[6]

CLINICAL SYNDROME

Renal colic, or the pain associated with kidney stones, is typically defined not only by pain but also by its acute onset. It classically involves a unilateral severe pain—described as a spasm—that may wax and wane in intensity. It may begin either as a vague discomfort that intensifies or in its most severe state. Regardless of intensity or character, the pain usually starts abruptly and, depending on the location of the stone within the ureter, may be found in the flank (if near the ureteropelvic junction), anterior abdomen (if within the midureter), or lower quadrants (if near the ureterovesicular junction). Patients with renal colic often cannot find a comfortable position (leading to the "stone dance"). The pain may migrate to the groin, the ipsilateral tes-

ticle in the male, and the ipsilateral labium majus in the female. Given the location of the ureter, the pain tends to refer medially and caudally.[7] Due to the pain's colicky nature, it is assumed that there is at least some ureteral obstruction that activates stretch receptors and leads to discomfort. Furthermore, because the renal capsules and intestines share innervations via the celiac plexus, the patient may manifest visceral symptoms, including nausea and vomiting.[8]

The classic pain as described, coupled with costovertebral angle tenderness and microscopic hematuria, is highly predictive of kidney stone disease, with a sensitivity of 84% and a specificity of 99%.[9]

PATHOPHYSIOLOGY

The underlying pathophysiology of stone formation is urinary supersaturation. When urine contains a concentration of calcium salts above their nascent solubility, precipitation of the salts is inevitable.[10]

Researchers have studied various substances that directly affect not only the formation of crystals but also their aggregation and growth. Some are causative, while others may actually prevent the formation of crystals, as evidenced by the lack of significant crystallization in urine that is supersaturated with these agents.[11]

RISK FACTORS

The multiple risk factors for kidney stone disease can be classified in various ways.

Anatomic

Numerous anatomic abnormalities may lead to the formation of renal stones. These include vesicoureteral reflux and ureteral strictures, as well as any other condition that causes urinary stasis.[8]

Family History

Having a family member with nephrolithiasis is a well-known risk factor for stone formation. In fact, a person with a positive family history is three times more likely to have a stone develop.[12] This increased risk is most likely due both to genetic similarities within families and to shared environmental exposures.[12]

Systemic Disorders

Systemic disorders have recently come to the forefront as a cause of renal stones. In fact, as many as 5% of those with primary hyperthyroidism will develop stones.[13] Other systemic conditions associated with an increased risk for stone formation include Crohn's disease, renal tubular acidosis, and hyperparathyroidism.[14] The infectious stone–causing staghorn calculus has been thought to be a major cause of stone disease linked to chronic renal failure.[15]

Furthermore, the formation of kidney stones has been associated with the metabolic syndrome, which is also associated with chronic kidney disease and nephrolithiasis. Recent studies have also indicated a link between type 2 diabetes mellitus and elevated serum triglyceride levels in persons with uric acid stones compared to those without, and retrospective studies have indicated a link between obesity and uric acid stone formation that appeared to increase along with body mass index.[16] Other studies have shown a link between stone formation and hypertension.[17]

Metabolic and Dietary

A multitude of metabolic and dietary factors affect urine saturation or composition, increasing the likelihood of stone formation. Among the metabolic conditions are hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria.[18]

Hypercalciuria is the most common metabolic abnormality in patients with calcareous stones, occurring in 35% to 65% of this population.[18]

The major mechanisms of hypercalciuria are *absorptive* (intestinal sensitivity to vitamin D is increased, resulting in increased absorption of calcium and ultimately in an increased calcium load filtered by the kidney), *renal* (the renal tubule is impaired in its absorption of calcium, resulting in increased urinary calcium), and *resorptive* (usually occurring as an end result of primary hyperparathyroidism and causing bone demineralization).

Hyperoxaluria is believed to cause formation of kidney stones by increasing urinary saturation of calcium oxalate. As with hypercalciuria, it has multiple distinct mechanisms. *Primary hyperoxaluria* is a disorder in biosynthetic pathways, caused by an inborn error of metabolism. *Enteric hyperoxaluria* in persons with kidney stones is most commonly caused by either intestinal disease or resection leading to malabsorption. Bariatric surgery has been implicated in significant hyperoxaluria and hypocitraturia. Chronic diarrhea has also been shown to decrease the level of calcium required to bind oxalate; oxalate is therefore

bound at a lower level of calcium.[19] *Oxalobacter formigenes* degrades intestinal oxalate; decolonization has been shown to increase intestinal oxalate levels.[20] *Dietary hyperoxaluria* is associated with a high intake of foods that increase urinary concentrations of oxalate (eg, spinach, nuts, chocolate). Dietary oxalate contributes 10% to 50% to urinary oxalate, and its role in calcium oxalate nephrolithiasis is controversial.[21] In addition to dietary oxalate, endogenous metabolism of certain substances, including some amino acids, contributes to urinary oxalate concentration.

As stated, hypocitraturia contributes to stone formation. One of the most abundant anions found in urine, citrate protects against stone formation through several mechanisms. Citrate binds with calcium, forming a soluble entity that inhibits not only the formation of stones but also the further crystallization of these complexes. Additionally, it provides a buffering capacity, causing only slight rises in urine pH in the presence of an alkali load.[22]

Acid-base status determines urinary citrate. Diseases associated with systemic acidosis, including renal tubular acidosis, ultimately cause hypocitraturia and increase the risk for stone formation. Other processes associated with hypocitraturia include chronic diarrhea, which leads to acidosis due to alkali loss, a high-protein/low-carbohydrate diet, chronic use of thiazide diuretics, and lactic acidosis.[23-26]

>>FAST TRACK<<

CT has numerous advantages, including significantly faster study time, the ability to diagnose other serious conditions such as abdominal aortic aneurysm, and the avoidance of IV contrast.

In addition, hyperuricosuria can lead to increased calcium oxalate levels and contribute to uric acid stone formation by either direct crystallization or an inhibitory effect. Monosodium urate crystals provide a nidus for calcium oxalate stone formation. In the presence of low urine pH, poorly soluble uric acid precipitates, leading to uric acid or calcium oxalate stone formation. Having a higher urine pH can also lead to increases in the urinary concentration of monosodium urate, again forming a nidus for calcium oxalate stone formation.[27,28]

Fluid Intake and Urinary Volume

Low urine volume increases the saturation of stone-forming materials and is a risk factor for kidney stone formation. Studies have shown that a urine output of less than 1 L per day is associated with a higher risk for stone formation.[29] Among persons with first-time stone formation, 12% to 25% exhibit low urine output.[30] While beverages such as sodas and coffee were previously discouraged for stone formers, observational studies have shown that consumption of any beverage, including wine, tea, soda, and coffee, actually reduces risk for nephrolithiasis.[31,32]

CLASSIFICATION

Kidney stones are classified as *calcareous* or *noncalcareous* and radiographically as *radiopaque* or *nonradiopaque*. Within these broad categories are the most common types of stones, including calcium oxalate, phosphate, or both; struvite (triple phosphate); uric acid; and cystine. Urate stones are radiolucent, while the others are radiopaque.

Calcium-Containing Stones

Accounting for 75% to 80% of stones, calcium-containing stones are the most common, with calcium oxalate predominating.[33] Mixed calcium stones, a mixture of calcium phosphate and calcium oxalate, are also found frequently.[34] As stated previously, hypercalciuria is a major factor in the formation of calcium oxalate stones.

Uric Acid Stones

These comprise 5% to 10% of stones.[8] Excessive uric acid in the urine, low urine volume, and acidic urine predispose one to formation of these stones.

Struvite Stones

These stones result from infection with urea-splitting bacteria. They represent only about 15% to 20% of all kidney stones but cause significant morbidity that belies their relatively small number.[35] A crystalline substance composed of magnesium ammonium phosphate, struvite forms and leads to stones when urease-producing gram-negative bacteria split urea, ultimately raising urine pH.

Most struvite stones are caused by *Providencia* or *Proteus* spp, with *Proteus mirabilis* accounting for 50% of urease-positive infections. Other species of urease-producing bacteria include *Klebsiella*, *Pseudomonas*, *Serratia*, and *Staphylococcus*.[30]

Management of these stones differs from that of the other types, as the bacteria hide within the crevices of the stone, and antibiotics alone do not sterilize the urine. Therefore, management includes complete

stone removal, as well as antibiotics and close follow-up. Aggressive treatment of recurrent infections is necessary to prevent recurrence of struvite stones.[35]

Cystine Stones

These stones form as a result of cystinuria, an autosomal recessive disorder involving a transport defect of certain amino acids, including cystine, ornithine, lysine, and arginine. While the concentration of these amino acids all increase in the proximal tube in patients with this syndrome, only cystine is not soluble at normal urine pH; thus, it is the only amino acid that potentially becomes a stone.[36]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for renal colic is broad and includes catastrophic entities, such as ruptured abdominal aortic aneurysm, torsion of testicle or ovary, and other acute surgical conditions such as appendicitis. Furthermore, medical emergencies such as pneumonia or pyelonephritis may present with flank pain but can typically be differentiated from renal colic with the judicious use of laboratory testing.

Abdominal aortic aneurysm often presents as flank pain and is sometimes accompanied by hematuria on urinalysis. Typically, patients with a leaking aneurysm are older, have hypotension, and present with other signs and symptoms such as diaphoresis, pallor, and syncope. Abdominal CT is useful to distinguish between abdominal aortic aneurysm and nephrolithiasis.

DIAGNOSIS

Laboratory Studies

Basic laboratory studies are of some utility in the diagnosis of stone disease but do not in themselves make the diagnosis.

Urinalysis: This is perhaps the most important of the screening tests for patients presenting with flank pain. Although hematuria has been used as an indicator for the presence of urinary calculi in patients

presenting with flank pain, approximately 10% of patients with diagnosed kidney stones do not have this symptom.[37] Most authors define microscopic hematuria as more than 3 to 5 red blood cells per high-power field. Another method of identifying hematuria is dipstick testing, which is very sensitive but not specific.[37] When urinalysis results are considered, the clinical gestalt and underlying medical history of the patient are critical factors. Furthermore, the time from onset of pain to examination must be taken into account: Kobayashi and colleagues showed in a retrospective study of 450 patients who had stone disease documented on CT that hematuria was present in 95% on day 1 but only in 65% to 68% on days 3 and 4.[38] In addition, the magnitude of hematuria does not correlate with the degree of obstruction.[37]

When a stone is diagnosed, urinalysis provides information on urine pH that may help determine the type of stone. For example, uric acid stones are usually formed in acidic urine, while infectious stones are typically produced in alkaline urine. The shape and presence of crystals may also help clarify the type of stone. For instance, calcium oxalate stones have envelope-shaped crystals; brushite has a long, tubular shape; and cystine is hexagonal. Since there is irritation of the ureter during stone passage, some white blood cells are typically seen in the urine. However, the presence of bacteria should always raise questions concerning concomitant infection.

>>FAST TRACK<<

For patients who do not have complete obstruction, pain management is essential. Relaxation of ureteral smooth muscle may allow spontaneous passage of the stone.

Complete blood count: This laboratory test is of limited use, as some patients will manifest leukocytosis due to the pain and spasm of renal colic, especially if the pain lasts for several hours. On the other hand, some authors have argued that the main utility of a complete blood count in the evaluation of a patient with flank pain is to ensure a normal hematocrit. This is especially important in older patients, in whom ruptured abdominal aortic aneurysm is one of the main concerns in the differential diagnosis.

Chemistry panel: Also nonspecific, a chemistry panel may be helpful in assessing for the sequelae of the stone, such as hypokalemia in an acutely vomiting patient. Furthermore, unless the patient has only one kidney or bilateral ureteral obstruction, blood urea nitrogen and creatinine levels should not be elevated.

Imaging

Plain abdominal radiography: Plain abdominal radiography has limited utility but may be considered if another etiology of flank pain (eg, calcified aorta of an abdominal aortic aneurysm) is identified.

Intravenous pyelography: Also called a *urography*, intravenous pyelography (IVP) shows the collecting system anatomy but is less efficacious than helical CT in detecting renal and ureteral calculi. Thus, IVP has been replaced in some institutions by the helical CT and is often difficult to obtain.[39] Initially, the advantages of IVP were thought to be the acquisition of physiologic information concerning the degree of obstruction;[40] however, modern management of nephrolithiasis is based on size and location of the stone and, in this regard, CT excels.

CT: The standard diagnostic technique in evaluating patients with suspected renal colic, CT has numerous advantages, including significantly faster study time, the ability to diagnose other serious conditions such as abdominal aortic aneurysm, and the avoidance of IV contrast.[41,42] CT has been shown to have a sensitivity ranging from 96% to 100% and a specificity of 92% to 100%.[43]

With the exception of stones produced in HIV patients taking the protease inhibitor indinavir, stones are detected on CT due to their higher attenuation compared to the surrounding soft tissue.[44,45] Stones commonly obstruct the ureter at sites of anatomic narrowing, including the ureteropelvic junction, the area where the ureter crosses the iliac vessels, and the ureterovesical junction. Some secondary signs of obstruction include ureteral dilation, inflammatory changes of the perinephric fat, hydronephrosis, and nephromegaly.[46,47] These secondary signs may be helpful in determining if a calcification seen on CT is a stone or phlebolith.

Ultrasound: This modality is becoming more readily available in the ED and is considered a core ultrasound competency by the American College of Emergency Physicians.[48] Researchers who have compared ultrasound and CT have found that ultrasound has a range of sensitivities (ie, 19% to 93%) and a specificity of 90%. The sensitivity and specificity for noncontrast CT is about 90%.[49] Ultrasound has a key role in diagnosis of patients in whom minimal radiation is preferable, including children and pregnant women.

The identification of stones using ultrasound depends on the size and location of the stone.[50] Since the size of the stone directly produces acoustic shadowing,

larger stones (>5 mm) are easier to detect; however, smaller stones may not show definitive shadowing, making diagnosis difficult. Furthermore, due to overlying bowel gas, ultrasound is unable to follow the entire course of the ureter, and thus mid-ureteral stones may not be visualized. Proximal and distal stones, however, are usually relatively easy to identify.[51] Secondary factors affecting stone visualization include stone composition, the presence of hydronephrosis, and technical matters, including transducer selection.

MRI: This modality can be used to evaluate the urinary tract, but its limitations include cost, poor ability to detect differences between urinary tract calcifications and air, and insufficient availability in the ED.[52]

EMERGENCY DEPARTMENT MANAGEMENT

Pain Control

The definitive method for alleviation of pain lies in passage of the stone. This can occur either spontaneously or by removal of the stone through stent placement or percutaneous nephrostomy. Because emergent urologic intervention often is not feasable in the ED, pain control remains a mainstay of therapy.

The pain of renal colic results from spasm of the smooth muscle of the ureter, local inflammation near the calculus, and back pressure proximal to the calculus. The inflammatory response produces prostaglandin release, ultimately leading to renal impairment if left untreated.

For patients who do not have complete obstruction, appropriate pain management is essential. Relaxation of ureteral smooth muscle may allow spontaneous passage of the stone. Pharmacologic treatment includes standard pain medications, including opioids and NSAIDs. Calcium channel blockers, such as nifedipine, and nitrates, such as isosorbide dinitrate, have been used with varying degrees of success and are also options.

NSAIDs: For controlling the pain of renal colic, NSAIDs and narcotic agents have nearly equal efficacy. NSAIDs are prostaglandin inhibitors that reduce ureteral spasm, local inflammation, and edema, as well as renal capsular distension and its associated pain. Additionally, NSAIDs prevent the increased vascular permeability that leads to greater pressure within the renal pelvis.

Numerous NSAIDs are available and differ primarily in adverse effects and cost. Ibuprofen and naproxen are

readily available over the counter, with ibuprofen producing fewer adverse effects but less therapeutic benefit than does naproxen. Naproxen and indomethacin have equal efficacy, but indomethacin has a higher incidence of adverse effects, especially gastrointestinal upset.

Ketorolac is available in a parenteral form, which is associated with faster relief, as well as a higher risk for adverse effects.

Opioids: This class of medication is highly effective in the management of acute renal colic. Intravenous administration may be preferred, especially if nausea and vomiting are present. Additionally, IV administration allows for titration of medication to clinical effect. The adverse effects of opioids include nausea and vomiting, possibly worsening the preexisting condition; pretreatment with an antiemetic may be beneficial. Larger opioid doses may lead to hypotension and respiratory depression. Although tramadol is associated with fewer adverse effects compared with traditional opioid agents, it appears to be less effective than morphine for severe acute pain.

Adjuncts

Alpha-2 antagonists: Recent literature supports the theory that alpha-1 antagonists can assist passage of stones by several mechanisms, including decreasing the frequency and force of ureteral contractions, as well as lowering the intrinsic tone of the ureter. Tamsulosin is an alpha-1-D selective adrenergic antagonist found in the distal ureter. A recent meta-analysis showed that tamsulosin was an effective adjunct to the treatment of uncomplicated distal ureteral stones, as it promoted the rate of stone passage and decreased the amount of analgesia required.[32,53]

Intravenous hydration: Formerly thought to worsen the pain of renal colic by increasing the back pressure caused from the obstruction of the stone within the ureter, IV fluids neither hasten passage of a stone nor increase the associated pain. Hydration is useful in patients with renal colic, as they may have emesis related to the visceral pain and a resultant component of dehydration.

Antiemetics: Helpful in controlling emesis caused by the pain of the stone as well as the potential vomiting secondary to opioid use, antiemetics are used in the treatment of kidney stones. Typically, the nausea abates when the renal colic is controlled.

Antibiotics: These agents should not be routinely given, unless the clinician suspects superimposed infection. In this case, an emergent urologic consultation should be obtained, as these infections are complicated and may lead to sepsis and renal failure. Intervention with either a nephrostomy tube or ureteral stent may be necessary. Without the removal of the stone, it may be difficult to completely eradicate the infection, as the bacteria may become integrated with the interstices of the stone.[54] Furthermore, infection control is required for stones produced by urea-splitting organisms to diminish or prevent crystal formation.

Antibiotic selection should cover typical gram-negative bacteria, such as *Escherichia coli*, as well as *Pseudomonas aeruginosa*, enterococci, and Enterobacteriaceae.[55] First-line antibiotics include penicillins and aminoglycosides; dual therapy should be considered. Fluoroquinolones and beta-lactams are also excellent and common choices.

DISPOSITION

Most patients with small stones can be discharged from the ED. Size of the stone is a determining factor for spontaneous passage. Stones smaller than 4 to 5 mm will typically pass within 1 to 2 weeks and usually require no intervention other than pain control, maintenance of hydration, and possibly an alpha-1 antagonist. Patients with stones and urinary tract infections may be safely discharged if they have no obstruction and are able to tolerate oral medications, including antibiotics. Urgent urologic follow-up, usually within 24 hours, should be obtained. Additionally, urine strainers should be provided to patients and stone composition should be analyzed.

Increasing or intractable pain, intractable vomiting, high-grade obstruction, obstruction with infection, renal failure, having a single kidney or a renal transplant, or signs of sepsis are all indications for admission and emergent urologic consultation. These factors may necessitate emergent intervention by either stent or nephrostomy tube. □

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