Nephrolithiasis refers to the condition of having stones (calculi) in the kidney or collecting system. Nephrolithiasis is a worldwide problem with prevalence rates of 1% to 5% in Asia, 5% to 9% in Europe, 13% in North America, and an annual incidence of 7 to 12 cases per 10,000 persons in the United States [1–3]. The prevalence of this disease in the United States is rising, especially in men and with increased age [3]. Recent data suggest that diet and lifestyle might account in part for changes in stone disease prevalence and the apparent increase of nephrolithiasis in women [4]. African-American women excrete less urinary calcium and have a higher urinary pH than Caucasian women [5] and have lower incidence of kidney stones. Rate of kidney stone recurrence is much higher in males. Within 1 to 2 years the recurrence rate is 10% to 20%, at 5 years 35%, and at 10 years 60% if left untreated. Nephrolithiasis accounts for $5 billion in U.S. health expenditures annually [6].

New information has become available regarding epidemiologic risk factors, diagnostic approach, and outcome of various therapeutic strategies. In this article, we review the pathophysiology of the various types of kidney stones and discuss the current evidence on epidemiology, treatment, and prevention.

**CASE STUDY**

**Initial Presentation**

A 45-year-old man presents to the emergency department (ED) with a 6-hour history of colicky pain in the right lower quadrant radiating to the right testicle. Physical examination shows that he is in distress, afebrile, and has tenderness of the right costovertebral angle and lower quadrant. Urinalysis shows microhematuria. Helical computed tomography (CT) of the abdomen and pelvis shows a 6-mm calculus of the right proximal ureter and mild hydroureteronephrosis.

**What are the symptoms of kidney stones?**

**Clinical Presentation**

Most patients present with moderate to severe colicky pain caused by a stone entering the ureter. Stones in the proximal ureter can cause pain in a flank or anterior upper abdomen [6]. As the stone moves further down the ureter toward the bladder, the pain often radiates in the groin and in...
the ipsilateral testicle or labia. Less often, patients present with persistent urinary tract infection (UTI), or painless hematuria, usually with nonobstructive stones. However, the absence of hematuria does not exclude urolithiasis. The differential diagnosis in a patient with symptoms suggesting renal colic include musculoskeletal pain, herpes zoster, diverticulitis, cholecystitis, pyelonephritis, renal infarct, renal papillary necrosis, appendicitis and gynecologic disorders [6].

**What are aspects of the diagnostic workup if a kidney stone is suspected?**

**History and Physical Examination**
The history should include total number of stones, evidence of residual stones, number and types of procedures, previous preventive treatments, family history, and related medical illnesses (malabsorptive conditions, Crohn’s disease, colectomy, sarcoidosis, hyperparathyroidism, renal tubular acidosis (RTA), recurrent UTIs, neoplasms). An inquiry into diet (volume intake, relative protein intake, high oxalate foods, salt, and calcium intake) and medications (acetazolamide, salicylic acid, acyclovir, indinavir, methyldopa, triamterene) should also be made [7]. The physical examination may reveal evidence of bone loss and subcutaneous calcifications; however, most patients with asymptomatic kidney stones will have little or no findings that are specific. The initial workup of a patient with suspected kidney stones should include urinalysis for blood.

**Imaging Studies**
Helical CT without contrast is the preferred imaging study in patients with suspected nephrolithiasis. It requires no radiocontrast material, it shows the distal ureters, and it can detect radiolucent stones (uric acid stones), stones as small as 1 to 2 mm, hydronephrosis, and intra-abdominal disorders other than stones. In a study of 100 patients presenting to an ED with flank pain, helical CT had a sensitivity of 98% and a specificity of 100% for the diagnosis of ureteral stones [8].

Compared with helical CT as a gold standard, ultrasonography has a sensitivity of 24% and a specificity of 90% [9]. Ultrasonography can image only the kidney and the proximal ureter and also may miss stones smaller than 3 mm in diameter. Ultrasonography is preferred in pregnant women with suspected calculi to minimize radiation exposure [10]. However, due to the high rate of false-negative results, if nephrolithiasis is not confirmed in pregnant women, and if symptoms suggestive of renal calculi persist, single-shot intravenous pyelography (IVP) should be performed. Radiography (kidney-ureter-bladder [KUB] view) is inadequate for diagnosis and provides no information about possible obstruction. IVP has few advantages, exposes the patient to the risk of radiocontrast, and gives less information than noncontrast CT.

**What is appropriate therapy for renal colic?**

**Management of Renal Colic**
Most stones are smaller than 5 mm and readily pass without interventions in 90% of patients. The patient can be allowed to try to pass a stone as large as 1 cm spontaneously, if it is in the distal ureter, within 4 weeks [6]. All patients presenting with possible kidney stones should be instructed to strain their urine and recover any stone that passes. The patient can be sent home with oral analgesics and instructions to return for fever or uncontrollable pain. After 4 weeks, intervention is indicated, as the risk of complications and kidney deterioration increases.

Randomized controlled trials suggest that parenteral nonsteroidal anti-inflammatory drugs (NSAIDs) are as effective as narcotics for controlling the pain [11]. Oral intake of at least 2 to 3 L of fluids per 24 hours can induce high urine flow and hasten stone passage. Tamsulosin (Flomax) increases the likelihood of spontaneous stone passage [12]. Patients who are unable to take oral fluids or medications and patients with signs of early hemodynamic instability should be treated intravenously.

Patients with UTI, stone greater than 6 mm in size, localized obstruction, or intractable pain require urgent intervention. A cystoscopically placed ureteral stent is typically used but requires anesthesia and commonly causes gross hematuria. The cystoscopy or stent placement can push the stone back up into the renal pelvis, thus relieving the obstruction [6,13].

**Case Continued**
The patient was treated in the ED with intravenous fluids and his pain was controlled with NSAIDs. He was evaluated by a urologist and had cys-
Nephrolithiasis

toscopy with a right ureteral stent placed to relieve an obstruction. Patient was discharged home with oral NSAIDs and recommendations to increase oral fluid intake.

The patient remained asymptomatic. He was seen by a urologist 3 weeks later. Renal ultrasonography showed a 6-mm stone in the right proximal ureter.

• What are treatment options for this patient?

Interventions for Nephrolithiasis

The surgical treatment of small, nonobstructing lower pole stones is controversial. Approximately 32% of patients with asymptomatic renal stones can develop symptoms in the next 2.5 years, increasing to 49% at 5 years [14]. Half of the symptomatic patients will require a procedure to remove stones, while half will pass the stone spontaneously [14]. A recent prospective study suggested that observation should be considered for patients with asymptomatic lower pole stones; however, patients should be informed about the 33% chance of progressive increase in stone size and the likelihood of the need for intervention in one-third of patients with enlarged stones [15]. All stone fragments need to be removed during the intervention to prevent stone growth or recurrence. For this reason, most renal stones should be treated or at least followed for the signs of progression with imaging studies. Stone size, location, and composition, urinary tract anatomy, and experience of the urologist determine the method of stone removal.

Extracorporeal Shock Wave Lithotripsy

Extracorporeal shock wave lithotripsy (ESWL) is a non-invasive outpatient procedure generally indicated for renal stones smaller than 2 cm, especially those located in the renal pelvis (proximal), and least effective for lower pole stones (distal) [15,16]. ESWL can cause bleeding, perforation, and cardiac arrhythmias during the treatment. Long-term concerns regarding ESWL include development of diabetes and hypertension [17]. ESWL is contraindicated in pregnancy and coagulopathy and is less effective in obese patients.

Cystoscopy

Cystoscopic stone removal, either by basket extraction or fragmentation, is invasive but effective, and allows removal of stones even in the kidney [13,15]. Usually, cystoscopy is a preferred procedure for proximal stones larger than 2 cm and distal ureteral stones.

Percutaneous Nephrolithotomy

Percutaneous nephrolithotomy is a more invasive approach requiring the placement of a nephrostomy tube, but it is necessary for large stone burdens or staghorn calculi, or stones that cannot be removed cystoscopically [13,15]. Open surgeries such as ureterolithotomy or nephrolithotomy are rarely needed now and indicated only in situations in which lithotripsy or ureteroscopic treatment is expected to fail [13,15].

Case Continued

The patient underwent successful ESWL, and follow-up renal ultrasonography showed no evidence of residual stone fragments. The patient was advised to perform 2 consecutive 24-hour urine collections in 6 weeks and come back in 8 weeks for a follow-up appointment to discuss results of metabolic evaluation and therapeutic management.

• What is the pathogenesis of nephrolithiasis?

Nephrolithiasis begins with urinary supersaturation [1,6]. Saturation is the point at which crystals in solution are in equilibrium with the salt of that crystal in solution. Increased excretion of urinary crystals and decreased urine volume will both increase free ion activity and favor stone formation and growth. High urine flow rates (more than 2 L in 24 hours) will decrease supersaturation and might prevent calculi formation. This is true for all stone types, and it is a very effective therapy for stones. Uric acid stone formation is a pH-mediated phenomenon rather than uric acid excretion problem [1,6]. People with very low urine pH (less than 5.5), normal uric acid excretions, and normal urine flow rates will be highly supersaturated with uric acid. Nucleation is usually heterogeneous with a mixture of substances and leads to crystal growth, and then to crystal aggregation. Tendency to form kidney stones is based on the presence of promoters and inhibitors of crystallization. Promoters include hydrogen ion, sodium, and magnesium. Crystal inhibitors are protein crystal inhibitors (uropontin, nephrocalcin), glycosaminoglycans, citrate and pyrophosphate. Presently, citrate is the only
naturally occurring inhibitor that is routinely measured in urine [18]. Crystals most likely are retained in sites of prior injury such as renal papillae or in the lower pole calices. Nearly 7 decades ago, Randall described plaque-like lesions in the renal papillae, which were invariably present in patients with calcium oxalate stones, although sometimes also present in individuals who did not form stones [19]. Now called Randall's plaques, these lesions were believed to be the nidus upon which calcium oxalate stones arose and grew. Attached to renal tissue in the renal papillae, and of crystalline composition, they seem an ideal site on which overgrowths of calcium oxalate or calcium phosphate could grow into stones.

**Stone Composition**

Most stones are calcium-based [1,6]. Other types of stones, such as cystine, pure uric acid, and struvite, are much less common [1,6] (Table 1).

**Calcium-Based Stones**

Approximately 70% of all kidney stones contain calcium and may consist of calcium oxalate (26%), calcium phosphate (7%), or both (35%). Once a patient forms a calcium-containing stone, another stone will generally form in less than 7 years, with a shortening time interval to subsequent stone events. Calcium calculi may form in urine that is supersaturated secondary to excess calcium, oxalate, or uric acid excretion, or they may form without an apparent cause. Calcium-based stones have a multifactorial etiology. Several risk factors for calcium-based stones have been identified (Table 1) [7].

Most patients with calcium oxalate stones have hypercalciuria (defined as 24-hour urinary calcium excretion > 300 mg in men and > 250 mg in women, or > 4 mg/kg in men or women). Hypercalciuria can occur in primary hyperparathyroidism, sarcoidosis, vitamin D excess, glucocorticoid excess, RTA, hyperthyroidism, malignant neoplasms, and patients taking loop diuretics. Idiopathic hypercalciuria is the most common cause of hypercalciuria and is sometimes associated with a strong family history and genetic basis for the disease. Pak and colleagues propose subdividing individuals with hypercalciuria into 3 categories: (1) absorptive (increased gastrointestinal absorption of ingested calcium), typically poorly responsive to dietary modifications, and associated with elevated serum calcium and 1,25 vitamin D, and slightly decreased parathyroid hormone (PTH), (2) resorptive (increased bone resorption caused by hyperparathyroidism), and (3) renal (increased urinary excretion of filtered calcium due to kidney defect), associated with mild hypocalcemia and secondary hyperparathyroidism, occurring in 5% to 10% of kidney stone formers [19–21]. Patients with severe absorptive and resorptive hypercalciuria are advised to avoid excessive calcium intake (more than 2 g per day) [19–21]. Increased urinary oxalate may result from either enhanced gastrointestinal absorption, due to high dietary oxalate intake or increased fractional oxalate absorption, or increased endogenous production. Malabsorptive states such as Crohn’s disease are associated with increased urinary oxalate excretion. With fat malabsorp-

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<th>Composition</th>
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| Calcium oxalate or calcium phosphate | 7%–80% | Hypercalciuria  
High dietary sodium and protein intake  
Hypercalcemia  
Idiopathic  
Chronic metabolic acidosis  
Low urine volume  
Hyperuricosuria  
High-purine, high-protein diet  
Hyperoxaluria  
Low dietary calcium, high-oxalate diet  
Genetic hyperoxaluria  
Hypocitraturia  
Chronic metabolic acidosis  
Inflammatory bowel disease  
Idiopathic |
| Uric acid | 10%–15% | Low urine pH  
Chronic metabolic acidosis  
Hyperuricosuria |
| Magnesium ammonium phosphate (struvite) | 10%–15% | Urinary tract infection (urea-splitting bacteria) |
| Cystine | < 1% | Cystinuria  
Autosomal recessive disorder of cystine, ornithine, arginine, and lysine |
| Other | < 1% | Antiretroviral therapy for HIV  
Potassium-sparing diuretic |
tion, calcium is bound in the small bowel to free fatty acids, leading to an increased amount of unbound oxalate available for absorption in the colon.

Hypocitraturia (24-hour urinary citrate excretion < 434 mg in men and < 500 mg in women) plays an important role in inhibiting calcium crystal [18,22]. Hypocitraturia is usually seen in conditions that cause chronic metabolic acidosis, such as inflammatory bowel disease and RTA – all of which are associated with increased occurrence of kidney stones. Acetazolamide also increases the risk of developing calcium oxalate and calcium phosphate kidney stones.

Diet plays an important role in the pathogenesis of calcium-based stones. Recent epidemiologic studies support the beneficial role of the normally recommended levels of dietary calcium [23–25]. Evidence suggested that dietary calcium inhibits the absorption of oxalate in the intestinal tract, reducing urinary oxalate excretion. In a study of the effect of taking calcium supplements with meals compared with at bedtime, urinary excretion of calcium was significantly elevated when taking calcium supplement both with meals and at bedtime [26]. Urinary oxalate excretion, however, was decreased significantly when calcium supplement was taken with meals only. The authors concluded that calcium supplements should be consumed with meals if reduction in the risk of stone formation is a goal of therapy.

High-protein, low-carbohydrate diets for weight reduction deliver a marked acid load to the kidney and enhance the risk for stone formation, decrease calcium balance, and may increase the risk for bone loss [27].

Uric Acid Stones

Uric acid stones occur mostly in patients with low urine pH (< 6.0) and hyperuricosuria. Kramer et al using data from a cohort of 51,529 health care professionals confirmed the independent association between gout and incident kidney stones [28]. The tendency to form uric acid stones is reported to be higher in patients with metabolic syndrome, including diabetes mellitus, hypertension, obesity, and hypertriglyceridemia, probably because of the defect in ammonia production by the kidney as a result of insulin resistance leading to highly acidic urine [29].

Struvite Stones

Struvite stones are the result of chronic upper urinary tract infection with urease-producing bacteria (Proteus sp, Haemophilus sp, Klebsiella sp, and Ureaplasma urealyticum) and occur more often in women and in patients who have chronic urinary obstruction [30]. Ammonia and persistently alkaline urine promote the formation of stones composed of magnesium ammonium phosphate, struvite. Struvite stones can grow to fill all or part of the renal pelvis and branch into several or all of the calyces (branched or “staghorn” stones). Cystine stones, although much less common, may also develop into staghorn calculi.

Cystine and Other Stones

People with certain rare inborn errors of metabolism have a propensity to accumulate crystal-forming substances in their urine. Cystinuria is a relatively common autosomal recessive gastrointestinal and renal transport disorder of 4 amino acids—cystine, ornithine, arginine, and lysine [31]. Cystine is insoluble in normally acidic urine and thus precipitates into stones. People afflicted with xanthinuria often produce stones composed of xanthine [6,21]. People with adenine phosphoribosyltransferase deficiency may produce 2,8-dihydroxyadenine stones [6,21], alkaptonurics produce homogentisic acid stones, and iminoglycinurics produce stones of glycine, proline and hydroxyproline. Urolithiasis has also been noted to occur in the setting of therapeutic drug use, with crystals of drug forming within the renal tract in some people currently being treated with agents such as indinavir, sulfadiazine, and triamterene [7].

What laboratory analysis is indicated?

Laboratory (Metabolic) Evaluation

The diagnostic evaluation of a first stone includes a chemistry panel (electrolytes, creatinine, calcium, and uric acid), urinalysis, and urine culture. In patients with high serum calcium or high urine calcium, parathyroid hormone level should be measured. However, there is lack of agreement on the appropriate workup after the first kidney stone. The evaluation we propose should be cost-effective, since single stone formers have high recurrence rate and the same incidence of metabolic derangements as patients with recurrent calculi. The decision to proceed with a metabolic evaluation in a single stone former should depend on the patient’s willingness to make lifestyle modifications to prevent recurrent stone formation [19,21].

The keystone of the evaluation is the 24-hour urine collection. Two consecutive 24-hour urine collections...
should be done while the patient follows his or her usual diet. Because individuals frequently change their dietary habits immediately after an episode of renal colic, a patient should wait at least 6 weeks before performing 24-hour urine collections. Two collections are needed because of substantial day-to-day variability in the values; 2 collections have about 92% sensitivity [19–21]. The variables that should be measured in the 24-hour urine collections are total volume, calcium, oxalate, citrate, uric acid, sodium, potassium, phosphorus, pH, and creatinine. Collections need to be sent to a reference laboratory specializing in kidney stone evaluations. Relative supersaturation of the urine factors can be calculated and be used to monitor the impact of therapy.

- **What are recommendations to prevent recurrent stone formation?**

**Dietary Recommendations**

In preventing recurrent stones, some principles apply to all patients and some are specific to the type of stone (Table 2) [7]. Increasing daily fluid is the most important recommendation in preventing recurrent stones regardless of their type. Patients should be encouraged to drink 2 to 3 L of fluid, ideally water, per day, to maintain a daily urinary volume of more than 2 L [32].

Hypercalciuria is worsened by a diet high in sodium [33] and animal protein [34]. There is no evidence that dietary calcium restriction is beneficial in preventing stone formation and substantial evidence that it is harmful [24–26]. Dietary calcium restriction can lead to a negative calcium balance. It is also thought that with less calcium to bind to dietary oxalate, more unbound oxalate can be absorbed in the colon and excreted in the urine, increasing the likelihood of calculi formation. Avoidance of excess dietary calcium (more than 2 g per day) is recommended to patients with severe absorptive and resorptive hypercalciuria [24].

Hyperuricosuria is associated with formation of calcium oxalate stones [27] and, in conjunction with low urine pH, with uric acid stones. Decreasing purine intake (meat, chicken, and seafood) will reduce urine uric acid [19,20,32].

Hypocitraturia can be caused by high-protein, low-carbohydrate diets that lead to intracellular acidosis, leading to decreased urinary excretion of citrate. Increased intake of fruits and vegetables, which are high in citrate, and reduced animal protein intake is recommended [19–21].

Hyperoxaluria may be a result of high dietary oxalate intake (black tea, chocolate, soy milk, nuts, berries, beans, carrots, celery) or low-calcium diet; therefore, low-oxalate diet and adequate dietary calcium intake is recommended. High vitamin C intake may increase urine oxalate excretion [19–21].

**Medical Therapy to Prevent Further Stone Formation**

**Calcium-Based Stones**

For patients who have elevated urinary calcium but not have an excessive calcium intake (more than 2 g/day), a thiazide diuretic (hydrochlorothiazide, chlorthalidone) has been demonstrated to decrease urine calcium excretion and also to help maintain bone density [35]. Adequate sodium restriction (less than 2 g/day) is needed to achieve maximum benefit from the thiazides. In 1 randomized trial [36], giving allopurinol (Zyloprim) decreased the recurrence rate by 50% among patients with a history of calcium oxalate stones and isolated hyperuricosuria. Treatment with sodium bicarbonate (100 to 200 mg/kg/
day in divided dosages) or potassium citrate (10–20 mEq twice a day) to maintain urinary pH between 6.5 and 7 corrects the metabolic acidosis, reduces the loss of calcium from bone, and increases urinary citrate in patients with hypocitraturia [6,19,21].

**Uric Acid Stones**

Alkali supplementation with oral sodium bicarbonate or potassium citrate is the most effective prevention and treatment of uric acid stones. Maintaining urine pH at or above 6.5 can dissolve pure uric acid stones [6,19,21]. Allopurinol is the second-line choice if the patient has hyperuricemia or marked hyperuricosuria and/or is unable to maintain a urine pH of 6.5 or higher.

**Cystine Stones**

Cystine stones also form in acidic urine and require alkalinization of urine to a pH higher than 6.5 with oral sodium bicarbonate or potassium citrate [37,38]. If these measures fail, D-penicillamine (Depen) and tiopronin (Thiola) may be given to increase the solubility of the filtered cysteine [37,38].

**Struvite Stones**

Struvite stones are the result of chronic upper urinary infections with urease-producing bacteria, and dietary factors do not directly influence these stones’ formation. Struvite stones are often large and branched (staghorn stones) and may fill the renal pelvis. Treatment requires eradicating the infection with antibiotics and complete removal of stones and all residual fragments. Prevention of urinary tract infections is most important for preventing recurrence [6,19,21]. Acetohydroxamic acid inhibits urease, but it has frequent and severe adverse effects [39].

**Case Follow-up**

Analysis of 2 consecutive 24-hour urine collections while the patient was not receiving medications revealed a calcium level of 450 mg (hypercalciuria), an oxalate level of 35 mg (hyperoxaluria), and a volume of 1.45 L; the urine pH was 5.5 (acidic). The patient started treatment with 20 mEq of potassium citrate twice daily and was advised to increase fluid intake to at least 2 L daily and reduce sodium intake to 2300 mg and protein intake to 0.8 to 1 g per kg of body weight per day. A follow-up 24-hour urine collection performed 8 weeks later showed a calcium level of 300 mg, an oxalate level of 20 mg, and a volume of 2.2 L with urine pH of 7.0. The patient has remained asymptomatic.

**CONCLUSION**

Kidney stone disease remains a major health and economic burden worldwide. In the United States, the prevalence of kidney stones has risen over the past 30 years. Early recognition and treatment initiation for kidney stones will benefit patients acutely, and the use of prophylactic measures will prevent future recurrences and complications. Improved awareness and education in both the general population and among health care providers about modifiable risk factors has the potential to improve general health and decrease morbidity and mortality secondary to kidney stone disease.

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