Management and Prevention of Nephrolithiasis

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Introduction

Nephrolithiasis (also termed *kidney stones*, *renal stones*, *urinary stones*, *urolithiasis*, and *renal calculi*) affects a great number of patients in the United States. Twelve percent or more of the country's population develop a stone at some point in their lives.[1] Approximately 350,000 patients experience the excruciating pain of nephrolithiasis annually,[2] resulting in 100,000 inpatient hospital visits per year.[3]

An understanding of the disorder's epidemiology is important to allow effective preventive efforts. White men are particularly affected by nephrolithiasis, and the incidence of renal stone formation is highest among white men between ages 30 and 60 years. The incidence of renal stones in men is three times the incidence in women,[3] and 50% of all patients who experience a stone experience a recurrence within 5 to 10 years.[3] Further, patients with a family history of stone formation have a 25-fold higher incidence of stone formation compared with patients without a family history of nephrolithiasis. The northeast, southeast, and southwest areas of the United States have the highest incidence of nephrolithiasis. Hot weather and hydration status have been connected to an increased frequency of stone formation; summer in both the northern and southern hemispheres has been associated with greater nephrolithiasis incidence.[4,5] Sunlight, which increases vitamin D production and calcium absorption, is also related to nephrolithiasis formation.[4]

Because of the large number of patients with nephrolithiasis, the disorder's associated costs are concomitantly high: a total greater than $2 billion annually.[1] General treatment modality costs alone are high; and the costs of surgical treatment, extracorporeal shock wave lithotripsy (ESWL), and fiberoptic techniques have risen to approximately $20,000, $12,000, and $3,500, respectively.[6]

Since the mid-1980s, however, noninvasive medical-oriented methods such as lithotripsy have vastly improved the treatment of nephrolithiasis.[7] For example, more than 500,000 patients have undergone lithotripsy and avoided surgical intervention in treatment of their nephrolithiasis.[7] Management of nephrolithiasis has been revolutionized since the mid-1980s not only by non-surgical methods such as lithotripsy, but also by improvements in fiberoptic technology and laser techniques, which also provide therapy alternatives to surgery. Other technologies, such as the use of electrical sparks, have been developed that effectively break up kidney stones.[2] Thus, the need for surgical intervention has virtually been eliminated.[8] Through such advances, postprocedural pain, the need for hospitalization, and convalescent time have all been reduced.[7] This result is important as procedures and treatments are shifted to the outpatient setting; also, the risks associated with anesthesia and nosocomial infections can be greatly reduced by treatment in an outpatient rather than inpatient setting.[9]

Yet as cost continues to be the focus of the United States health care delivery system, advances in nephrolithiasis treatment may become less pronounced. Although academic centers have researched renal stone treatment and provided significant, cost-efficient results in the treatment of this disorder, concern in the academic setting continues regarding treatment

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costs of nephrolithiasis and its related conditions.[10,11] Large discounts on the part of specialized nephrolithiasis treatment centers make it difficult for academic centers to compete for managed care patients with this disease.[12]

Prevention of nephrolithiasis is critical because of the significant morbidity associated with this disorder as well as the potentially high costs for treatment, which include presentation to the emergency department (ED) as in this case study. Primary care physicians must be cognizant of the established epidemiology of this disorder and must vigilantly note new causes of nephrolithiasis (eg, kidney stones are a potential severe side effect of antiretroviral drugs[13]). With regard to effective intervention techniques, the treatment of nephrolithiasis has generally been a success story. However, if at all possible, the paramount approach to nephrolithiasis is to prevent occurrence. Successful prevention relies on a partnership between the physician and the patient: The physician must provide education to the patient, and the patient must understand the appropriate methods to avoid stone formation.

CASE PRESENTATION

Initial Presentation

A 37-year-old man presents to his primary care physician for evaluation of a kidney stone that was diagnosed during a recent visit to the ED. He passed the stone 2 days before presentation and brought it with him, as instructed in the ED.

History

The patient presented to the ED with severe colicky flank pain. A diagnosis of renal colic was considered after a urinalysis revealed hematuria. Laboratory evaluation showed normal serum calcium, phosphate, uric acid, and creatinine levels. An intravenous urogram (IVU) confirmed the presence of a 5-mm radiopaque stone in the left ureter. After treatment with intravenous fluids and analgesics, the patient was discharged with instructions to increase his fluid intake and to make an appointment with his primary care physician. He was given a urine strainer and told to void through the strainer.

The patient has a negative family history for kidney stones and other renal disorders, and his only medication is one multivitamin pill per day. He is married and employed as an elementary school teacher. He is a cycling enthusiast who enjoys long bicycle rides in the country. He adheres to no specific dietary regimen and describes his diet as "normal."

Physical Examination

Physical examination reveals a normal body habitus (5 ft, 8 in, 165 lb), a blood pressure of 122/78 mm Hg, and moist mucous membranes. A cardiopulmonary examination is completely normal. No abdominal masses are noted and no flank or suprapubic tenderness is present. No tophi or arthritic changes are observed.

QUESTIONS

- **What is the pathogenesis of nephrolithiasis?**
- **What are the major types of renal calculi?**

DISCUSSION

Pathogenesis of Stone Formation

Stone formation is the end result of a multistep process in which the balance of factors that promote crystallization of urinary salts and factors that inhibit crystallization is perturbed.[14] When the urinary concentration of certain salts exceeds their solubility product, the urine becomes supersaturated for that salt. In a state of supersaturation, nuclei of salt crystals are formed in a process called *nucleation*. Often there is another nidus of nucleation, such as the injured surface of renal tubular epithelial cells or a different solute (eg, uric acid) that causes crystal formation (heterogeneous nucleation). Low concentrations of crystallization inhibitors (citrate, nephrocalcin, uropontin, magnesium) may promote the nucleation of salts in saturated but stable solutions. If the nuclei begin to aggregate, crystals begin to form. These crystals continue to aggregate and eventually grow into stones. Retention within the kidney appears to be important for the crystals to grow: If not retained, crystals are passed in the urine. Locations of prior injury, such as renal papillae, are hypothesized to be sites where crystals are retained. Low urine flow or stasis from genitourinary abnormalities or volume depletion also may promote crystallization.[15] Stones tend to reside either at the area of prior injury or in gravity-dependent locations, such as the lower pole calices.

Composition of Stones

Seventy percent of all renal stones primarily contain calcium, and approximately 26% of calcium stones are composed of pure calcium oxalate, 35% are composed of calcium oxalate and calcium phosphate, and approximately 5% to 10% are composed of calcium crystallized around a uric acid core.[16] Approximately 5% to 10% of renal stones are composed of pure uric acid. Magnesium ammonium phosphate or struvite stones account for approximately 10% to 15% of stones and are more commonly found in women than in men. These stones are formed in urine infected with urease-producing

organisms such as *Proteus* or *Morganella*. Cystine stones account for 1% to 2% of kidney stones and are found in patients who suffer from autosomal recessive cystinuria.

QUESTION

- **What risk factors predispose a patient to nephrolithiasis?**

DISCUSSION

Risk Factors

Renal stones are known to occur with increased frequency in a variety of clinical disorders. Conditions that appear to increase risk include hyperparathyroidism, inflammatory bowel disease, prior bowel resection, strong family history of stone disease, urinary tract abnormalities leading to recurrent infections, and nephrocalcinosis.

Several other risk factors also need to be identified.[17] Low urine volumes increase urine stasis and also increase the saturation of urine. Diarrhea and hot climates frequently cause volume contraction and may contribute to uric acid and calcium-based stone formation. Certain medications increase the likelihood of nephrolithiasis. Loop diuretics cause increased calcium excretion, whereas triamterene, acyclovir, and indinavir may precipitate as crystals given the proper conditions. Use of nonprescription medications also should be reviewed. Antacids bind phosphate in the intestine, leading to increased availability and absorption of calcium and predisposing to calcium stones. Vitamins A and D taken in excess can lead to hypercalcemia and hypercalciuria: Vitamin A increases bone resorption, and vitamin D promotes calcium absorption from the gut. Although not convincingly proven, vitamin C may increase urine oxalate levels in some patients.[17]

Certain lifestyles may predispose to stone formation. Soldiers on active duty in desert conditions have been shown to have an increased incidence of nephrolithiasis. Long-distance runners, bicycling enthusiasts, and traveling sales people may limit their fluid intake avoid frequent urination and thus are also at increased risk.

QUESTIONS

- **Based on initial risk assessment, what is an appropriate approach to the workup of this patient presenting with a first kidney stone?**
- **Is an extensive metabolic evaluation needed?**

DISCUSSION

Approach to Workup

Often, a kidney stone is diagnosed in the ED based on clinical features, the presence of hematuria, and radiographic findings. Patients are treated with analgesics and asked to follow up with their personal physician. The primary care physician then must decide on a course of action, including the need for further evaluation.

Traditionally, the natural history of nephrolithiasis has been used by physicians to both justify an extensive evaluation and defend a more minimalist approach. The average cumulative risk of developing a second stone is approximately 14% at 1 year, 35% at 5 years, and 52% at 10 years.[18] An argument could be made that this long-term risk is relatively high and thus testing that might reveal an underlying and treatable metabolic abnormality should be pursued. Parks and Coe[19] have suggested that waiting for a second stone to form before evaluating the patient and possibly initiating therapy may further increase the risk of subsequent stones by leaving residual crystals to serve as a nidus for nucleation. Other investigators have suggested avoiding an extensive metabolic evaluation in all patients and using ESWL because of its low attendant risks to treat patients with recurrent stones.[18]

Most physicians do not perform an extensive evaluation after the first stone because a symptomatic stone may merely reflect anatomic activity (ie, movement of a previously formed stone down the ureter) rather than metabolic activity. Metabolically active stone disease is characterized by the formation of new stones, enlargement of an old stone, or passage of gravel. A patient who has a stone (or stones) that is not new and not changed in size (metabolic quiescence) would be unlikely to benefit from a detailed metabolic evaluation because the patient's risk of recurrent disease is likely to be low.[17]

There is a paucity of reliable prospective data that can be used to formulate a definitive outcomes-based approach to managing the patient who has had one kidney stone. Several authors suggest that minimal investigations be performed in patients with their first stone provided no signs of infection or obstruction are present.[20–22] A reasonable approach in a patient of average risk, such as the patient in this case study, would include a thorough history and physical examination (although specific clues are seldom noted on physical examination), selected laboratory tests, urinalysis and culture, review of any radiographs, and stone analysis (**Table 1** and **Figure 1**). For patients at high risk, an extensive evaluation is advised.

QUESTION

- **What laboratory and imaging studies are useful in evaluating patients with a first kidney stone?**

DISCUSSION

Laboratory Testing

The objective of laboratory testing in patients with a history of a solitary kidney stone is to identify possible uncommon, but treatable, secondary causes of nephrolithiasis and to uncover coexisting problems that may have an impact on management. It is important to ensure that the initial workup excludes the presence of urinary infection and renal insufficiency because these complicating factors may indicate the need for urgent intervention. Measurement of serum electrolytes, creatinine, and calcium is useful to make an initial assessment of renal function, to identify renal tubular acidosis (RTA, or non-anion gap metabolic acidosis), and to diagnose hypercalcemia (found in primary hyperparathyroidism or sarcoidosis). The examination of urine is also important and may provide clues to the composition of stones and their etiology. An alkaline urine pH may indicate distal RTA or an infection with a urease-producing organism. An acidic urine is associated with uric acid stones. Certain crystals in the urine can be pathognomonic, as in cystinuria. The presence in the urine of a significant quantity of crystals other than cystine (eg, calcium oxalate), although not pathognomonic, almost always reflects a pathologic process in this setting.

Stone Analysis

The analysis of a retrieved stone can be pivotal in the evaluation process because the composition of the stone may suggest a specific cause. When patients are sent home from the office or the ED, they should be given a urine strainer and instructions to void through the strainer. Any collected stones or gravel should be placed in a specimen cup and sent to the laboratory for analysis to allow planning for therapy. In a patient who has not retrieved a stone and in whom there is no radiographic confirmation of the presence of a stone or signs suggesting recent passage of a stone (eg, ureteric edema or stranding), the diagnosis of nephrolithiasis is not ruled out.

Imaging Studies

Plain abdominal films. In the initial evaluation, a plain radiograph of the abdomen using a technique to image the kidneys, ureters, and bladder (KUB) is generally ordered to look for the presence of a kidney stone. Approximately 90% of kidney stones contain some calcium, and if the stone is 1 to 2 mm, it can usually be seen on the KUB radiograph. The KUB radiograph is simple to perform and results in minimal radiation exposure. Radiography performed without a bowel preparation, however, may be suboptimal because of the presence of fecal and gas shadows. Unfortunately, the plain KUB radiograph is not sensitive or specific enough to confirm or exclude the diagnosis of nephrolithiasis. The finding of a calcification is not diagnostic for a kidney stone because there are many other causes of calcifications in the areas of interest on the KUB radiograph. These causes include but are not limited to pelvic phleboliths, fecaliths, and renal calcifications.

When a patient whose stone disease has been diagnosed presents for follow-up, the physician may order a KUB radiograph to determine if the stone has either passed in the urine or relocated to an area that would not cause any symptoms (renal pelvis). If a KUB radiograph was not performed in the ED, as might be the case in a patient whose diagnosis was made by spiral computed tomography (CT) scan, a baseline KUB radiograph should be obtained by the primary care physician because this modality can be used to follow the patient's stone disease for metabolic and anatomic activity.

Intravenous urography. The initial diagnosis of renal stone disease generally requires additional radiologic procedures. Traditionally, an IVU is performed to confirm that a kidney stone is responsible for the patient's symptoms and to confirm the location of a calcific density within the urinary tract. An IVU can also identify radiolucent stones (stones composed of uric acid) lying within the urinary tract. In a patient who has had a kidney stone diagnosed solely on the basis of a KUB radiograph in the ED, an IVU is useful

Table 1. Evaluation of a Patient with a First Kidney Stone

Complete history, with emphasis on:
Family history
Occupation and hobbies that may predispose to dehydration
Dietary history
Fluid intake (types and volumes of fluids ingested)
Nonprescription medications (calcium supplements, vitamins, antacids)
Infection/systemic disease/abdominal surgery
Physical examination
Laboratory evaluation
Stone analysis (if retrieved)
Urinalysis/culture
Serum electrolytes, calcium, phosphate, uric acid, and creatinine levels
Abdominal radiograph (kidney, ureter, and bladder)

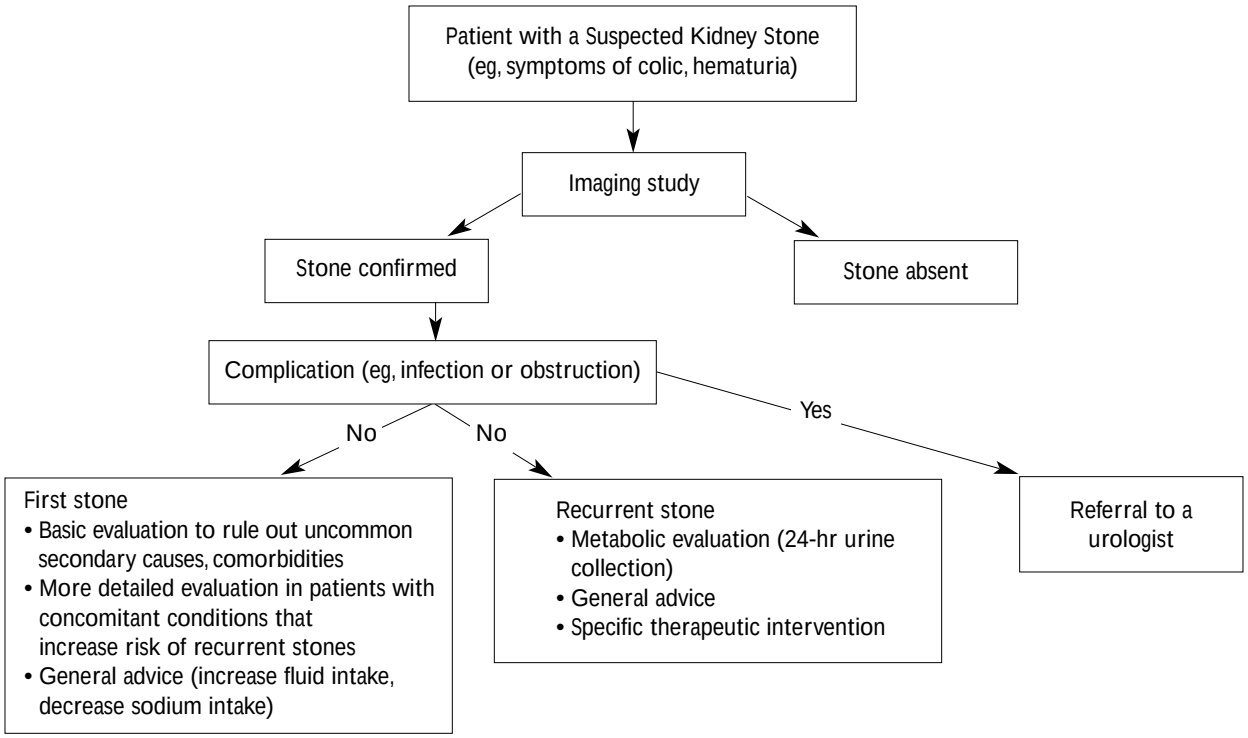

Figure 1. Evaluation and management of a patient with kidney stones.

for diagnosing obstruction and other abnormalities that may predispose the patient to stone formation (eg, medullary sponge kidney).

Computed tomography. Since its introduction into practice**,** more patients with nephrolithiasis are being diagnosed by ultrafast spiral CT scans. Spiral CT avoids the risk of exposure to intravenous contrast without compromising sensitivity or specificity, and the dose of radiation from the spiral CT is only slightly greater than the radiation exposure from an IVU. An additional advantage to using the spiral CT, besides being able to complete the scan within minutes, is the ability to investigate for other possible causes of pain that may simulate renal colic, such as ovarian torsion. Despite the advantages of the spiral CT scan, no cost-effectiveness analysis has been performed to date and the choice of procedure may depend on availability of the modality and an individual institution's experience with a particular technique.

Ultrasonography. Ultrasonography has been previously utilized to look for nephrolithiasis, particularly in patients at high risk for complications caused by contrast exposure. Ultrasonography generally should not be the first radiologic technique implemented when searching for renal stones. This technique is operator-dependent, and the ability to visualize the collecting system may be impaired by a large body habitus or loops of bowel filled with gas. The inability of ultrasonography to detect mid- and distal ureteric stones also limits its usefulness. In contrast, ultrasonography is an excellent modality to detect urinary tract obstruction and to follow patients with radiolucent stones. The advantages and disadvantages of the different imaging modalities are summarized in **Table 2.**

RESULTS OF LABORATORY ANALYSIS AND KIDNEY, URETER, BLADDER ASSESSMENT

Initial laboratory testing of the patient reveals normal serum calcium, phosphate, uric acid, and creatinine levels; urinalysis shows a pH of 5.5, 50 to 100 erythrocytes per high-power field, and no crystals. A repeat KUB radiograph in the physician's office does not reveal any residual stones. Analysis of the passed stone indicates that the stone is composed primarily of calcium oxalate.

QUESTIONS

- **What underlying disorders are associated with calcium-based calculi?**
- **What do the test results indicate in this patient?**

DISCUSSION

Causes of Calcium-Containing Stones

Approximately 90% of calcium stones are idiopathic in origin. The most common underlying metabolic

Table 2. Imaging Studies for the Evaluation of Nephrolithiasis

Study	Advantages	Disadvantages
Abdominal radiography (kidney, ureter, and bladder)	Easy to obtain Minimal radiation exposure Useful for following stone activity	Sensitivity decreases without bowel preparation Provides no functional information Misses radiolucent stones
Intravenous urography	Good sensitivity and specificity Detects obstruction Diagnoses anatomic abnormalities of urinary tract Entire urinary tract visualized Easy to perform	Exposure to radiocontrast Radiation exposure Time-consuming
Ultrafast spiral computed tomography	Excellent sensitivity and specificity Rapidly performed Detects all types of stones Helps diagnose other causes of symptoms Noninvasive and requires no contrast	Not universally available Expensive (although costs are decreasing) Radiation exposure
Ultrasonography	Noninvasive Can detect radiolucent stones Detects obstruction No radiation exposure	Decreased ability to detect mid- and lower ureteral stones Highly operator-dependent

abnormality is idiopathic hypercalciuria, seen in approximately 40% to 50% of patients with calcium-containing stones. Up to 5% of patients with calcium-containing calculi have associated diseases (distal RTA or primary hyperparathyroidism) that result in nephrolithiasis as an added complication (**Table 3**). Pure calcium phosphate stones are seen in primary hyperparathyroidism and distal RTA but may also be idiopathic, especially in women. In addition to hypercalciuria, calcium-based stones may be the result of other alterations in urinary constituents. Hyperoxaluria, either idiopathic or caused by gastrointestinal disorders such as Crohn's disease, may be responsible for calcium oxalate stones. Relatively minor increases in the level of urinary oxalate have more influence on stone formation than an equivalent rise in urinary calcium levels.[16] Urinary citrate is an inhibitor of stone formation and low urinary citrate levels, as seen in idiopathic hypocitraturia, distal RTA, or chronic diarrhea, also may predispose to nephrolithiasis. Finally, elevated urinary uric acid excretion usually is the result of high dietary purine intake, which may lead to calcium stones, mixed stones in which calcium oxalate surrounds a nucleus of uric acid crystals, or pure uric acid stones.

Results of Testing in This Patient

The clinical data in this patient suggest no obvious secondary cause of calcium stone formation, such as primary hyperparathyroidism or Crohn's disease.

QUESTION

- **What is appropriate therapy for a first stone of idiopathic origin?**

DISCUSSION

General Observations

The management of a patient presenting with their first, idiopathic stone is controversial. Scott and Lewi[23] prospectively treated 172 patients presenting with a first stone with bendrofluazide (a thiazide diuretic) if the patient was hypercalciuric or allopurinol if the patient was not hypercalciuric. When compared with a group of 129 patients treated with advice to increase fluid intake and to avoid dietary excess (exact advice not outlined), the group treated with medications had a decrease in the rate of stone recurrence during a follow-up period averaging 5 years. The decrease in stone recurrence achieved statistical significance during the third year and beyond, but not in the first 2 years. This study was not randomized, and details of adverse

Table 3. Common Underlying Causes of Calcium-Containing Calculi

Hypercalciuria (50%)
Idiopathic hypercalciuria (90%)
Primary hyperparathyroidism
High-sodium diet
High-protein diet
Medications (loop diuretics, calcium supplements)
Hyperoxaluria (10%–20%)
Crohn's disease
Chronic pancreatitis
Celiac sprue
High vitamin C intake (in some patients)
Calcium restriction
Primary hyperoxaluria
Hypocitraturia (10%–40%)
Idiopathic (90%)
Metabolic acidosis (diarrhea)
Distal renal tubular acidosis
Potassium depletion
Hyperuricosuria (10%–20%)
Excessive dietary purine intake
Other
Genitourinary abnormalities (medullary sponge kidney)

effects related to medical therapy were not described. Given the paucity of reliable randomized and prospective data and concerns regarding adverse effects of medical therapy, the current approach to the treatment of a first stone of idiopathic origin involves increased fluid intake and dietary modification.

Increased Fluid Intake

The most important intervention in a patient who has developed an idiopathic kidney stone is instituting increased fluid intake because this intervention reduces the risk of recurrent stone formation. A recent Italian study examined patients with idiopathic hypercalciuria after their initial presentation and randomized them either to drinking water to increase their daily urine output to more than 2 L/day or to no intervention.[24] Interestingly, all of the patients who formed stones had an average baseline urine output of 1 L/day. Over a 5-year follow-up period, the incidence of recurrent stones was only 12.1% in the group that successfully increased their daily urine output to more than 2 L/day versus a recurrence rate of 27% for the group that did not increase their daily urine volume. Additionally, the time interval to recurrence was longer in the group with higher urine volumes (38.7 months versus 25.1 months). No dietary interventions were implemented in either group.

Some intriguing studies have recently been published that analyze the risk of nephrolithiasis based on the types of fluids ingested. Curhan et al[25] originally demonstrated that men without a prior history of stone formation who drank apple juice had a 35% increased risk of stone formation and that men who drank grapefruit juice had a 37% increased risk. In a more recent study involving prospective data from a large sample of women, also without a prior history of stone formation, the increased risk of stone formation with grapefruit juice intake was confirmed. In contrast, several other beverages including cranberry juice, tea, coffee, beer, and wine were all shown to reduce the risk of nephrolithiasis.[26] Although these studies involved people who had no prior history of stone formation, the results may be relevant to the management of patients with nephrolithiasis.

Dietary Modification

Urinary calcium excretion is increased by high-sodium diets. By restricting the sodium in the diet to 2 to 3 g/day, urinary calcium excretion can be significantly lowered. Some studies have demonstrated an increased incidence of nephrolithiasis in people who consume diets with a high animal-protein content.[27] Although no prospective studies confirm the benefit of the intervention, it may be prudent to recommend modification of sodium and animal-protein intake in patients with calcium stones and hypercalciuria.

Follow-up

After initial evaluation of a patient with nephrolithiasis, a follow-up appointment should be scheduled in 3 to 6 months to determine if the patient is experiencing any recurrent problems and to assess if the patient has been following the treatment plan. General advice for patients who form calcium stones is given in **Table 4**. Even in the absence of recurrent symptoms, a KUB assessment should be ordered at the follow-up visit to screen for the development of any new stones. Determination of metabolic activity requires examination of serial abdominal (KUB) radiographs—analogous to following a pulmonary nodule by serial chest films.

PRESCRIPTION OF THERAPY AND CLINICAL COURSE

The patient is prescribed to drink at least two 8-oz glasses of fluid (predominantly water) every 4 hours

while awake. Additionally, he is instructed to drink another glass of fluid upon awakening at night. The physician also instructs him to collect his urine in a volumetric container to ensure that he maintains a urine output exceeding 2 L/day. The physician instructs the patient to call if symptoms of renal colic recur or if he passes gravel or stones in his urine. A follow-up appointment is scheduled for 4 months later.

The patient fails to keep his scheduled follow-up appointment because of the lack of any symptoms. Three years later, however, the patient returns to his primary care physician approximately 8 weeks following another episode of renal colic, which occurred while he was traveling. The recent episode was similar in clinical presentation to the previous incident (flank pain and hematuria). The diagnosis of recurrent nephrolithiasis was confirmed by an IVU in the ED. A stone was subsequently retrieved in the urine strainer, and again the analysis showed that the stone was composed primarily of calcium oxalate. A review of the IVU reveals three radiopaque stones in the right renal pelvis. Two stones are 4 mm in diameter and one is 9 mm. No other genitourinary abnormalities are seen on the IVU.

The physician schedules the patient for tests to look for metabolic abnormalities that may be causing the kidney stones. Pending the results of this evaluation, the patient is told to increase his fluid intake as before and is referred to a dietitian to help him with modifying his sodium and protein intake.

QUESTIONS

- **What assessments are helpful in evaluating a patient with recurrent stone formation?**
- **Is a detailed assessment necessary for instituting therapy?**

DISCUSSION

Evaluation of Patients with Recurrent Stones

When new stones are found in patients with recurrent stones, most physicians begin an extensive metabolic evaluation with the goal of categorizing the stone disease and prescribing specific therapy to prevent further stones. This approach is based on the assumption that identifying abnormalities in urinary composition and then selecting the appropriate intervention aimed at correcting this abnormality will result in decreased stone recurrence. Unfortunately, no evidence reliably indicates that this cumbersome approach is more efficacious than the nonselective approach of treating patients with an intervention without identifying specific metabolic abnormalities. Many of the agents that have been used to decrease stone recurrence have been shown to be efficacious independent of the metabolic profile. Some authors have demonstrated the efficacy of potassium-magnesium citrate in reducing the risk of stone recurrence in a group of patients with a history of recurrent nephrolithiasis who were already being treated with a low-sodium, low-oxalate, animal-protein–restricted diet.[28] In a randomized placebo controlled trial, potassium-magnesium citrate was shown to decrease the risk of recurrent stone formation by 50.7% when compared with placebo. Some specialists may choose to treat patients with recurrent stones with this salt or with thiazides without pursuing a detailed metabolic evaluation. This approach remains controversial.

Table 4. General Advice for Patients who Form Calcium Stones*

Fluid intake
Drink at least 10 glasses of fluid/day (at least five glasses should be water)
Avoid grapefruit juice and apple juice
Goal is urine output exceeding 2 L/day
Sodium intake
Restrict to 2 to 3 g/day
Animal-protein intake
Restrict to 1 g/kg body weight/day
Oxalate-restricted diet (for hyperoxaluric patients)
Avoid cocoa, beets, spinach, rhubarb, chard, kale, okra, sweet potatoes, endive, peanuts, chocolate
Low-purine diet (for hyperuricosuric patients)
Avoid kidney, liver, sweetbreads, herring, salmon, sardines, mussels, scallops
Limit all meat, poultry, seafood, beans, lentils, spinach

*Also may apply to patients with other types of stones.

The history should be specifically focused on compliance with previously suggested interventions. All radiographic tests should be reviewed and a KUB radiograph repeated. The urine should be reexamined. If a stone is available for analysis, which is not usually the case, the stone composition may help direct further evaluation. A screening serum chemistry panel of creatinine, electrolytes, calcium, phosphate, and uric acid levels should be obtained.

Metabolic testing of the urine should not begin until at least 6 to 8 weeks after stone passage because the passage of a stone may alter urine composition.

Table 5. Selected Therapeutic Interventions for Nephrolithiasis

Metabolic Abnormality	Type of Stone	Therapeutic Intervention
Hypercalciuria	Calcium	Thiazide diuretics, amiloride, moderate daily calcium intake, neutral orthophosphate
Hyperoxaluria	Calcium	Adequate dietary calcium intake, avoid oxalate-rich foods, magnesium supplements
Hypocitraturia	Calcium	Oral citrate supplements (potassium citrate, sodium citrate)
Hyperuricosuria	Calcium	Low-purine diet, allopurinol
Hyperuricosuria	Uric acid	Low-purine diet, allopurinol
Acid urine	Uric acid	Urinary alkalinization, oral citrate supplements, sodium bicarbonate, acetazolamide

After this time has elapsed, a 24-hour urine collection is obtained for measurement of volume and daily excretion of sodium, calcium, phosphate, uric acid, oxalate, citrate, creatinine, urea nitrogen, and magnesium. The addition of nitroprusside to the urine allows cystinuria screening. If this test is not available, measuring urinary cystine is still reasonable because elevated levels may provide for heterogeneous nucleation of calcium stones. The 24-hour collection of urine should be performed while patients are maintaining their usual diet and daily activity routine.[22] Measurement of urinary creatinine excretion helps determine adequacy of collection; the test may need to be repeated if the collection is deemed inadequate.

METABOLIC TESTING AND RESULTS

Laboratory testing reveals normal values for serum calcium, phosphate, uric acid, and creatinine; urinalysis shows a pH of 5.5, 50 to 100 erythrocytes per high-power field, and no crystals. Results of a 24-hour urine collection are as follows: creatinine, 20 mg/kg (normal for men, > 15 mg/kg/day); calcium, 250 mg/day (normal for men, < 300 mg/day); uric acid, 600 mg/day (normal for men, < 800 mg/day); oxalate, 30 mg/day (normal, < 40 mg/day); and citrate, 200 mg/day (normal, > 320 mg/day).

QUESTIONS

- **What are the implications of these test results, particularly the finding of hypocitraturia?**
- **What specific interventions may be instituted to prevent further stone formation?**

DISCUSSION

The patient has isolated hypocitraturia. Hypocitraturia may occur in the setting of chronic metabolic acidoses including RTA and hypokalemia of any etiology, or hypocitraturia may be idiopathic. Because citrate is an inhibitor of stone formation in the urinary tract, the low citrate excretion is likely to be responsible for this patient's nephrolithiasis. In the absence of any other abnormalities, this patient is likely to have idiopathic hypocitraturia.

Selective Therapy for Calcium Stones

Selective interventions tailored to specific metabolic abnormalities are outlined in the following discussion and in **Table 5**. In addition, general advice for patients who form calcium stones (Table 4) should be reviewed with these patients.

Hypercalciuria. In hypercalciuric patients, thiazide diuretics can reduce urinary calcium excretion by increasing proximal and distal tubular absorption of calcium. Thiazides are extremely effective at decreasing recurrent stone formation but the frequency of side effects is variable.[29,30]

Contrary to popular belief, dietary calcium should not be restricted in most hypercalciuric patients. In a recent analysis of the Health Professionals Follow-up Study,[31] a decreasing incidence of renal calculi with increasing content of dietary calcium was demonstrated in individuals without a prior history of kidney stones. In contrast, ingestion of calcium supplements was associated with an increased risk of stone formation.[32] This increase may have been caused by between-meal ingestion of the calcium supplements. It has been postulated that dietary calcium may bind oxalate in the gut, thereby lowering oxalate absorption and hence urinary excretion of oxalate. However, when calcium supplements are not taken with food, a greater amount of the calcium is absorbed and can contribute to hypercalciuria. Calcium restriction may also induce a negative mineral balance predisposing to osteoporosis and fractures[16] and thus must not be lightly recommended as an intervention for preventing nephrolithiasis. These authors recommend two to three daily dietary servings

of calcium, even in patients who form hypercalciuric stone.

Neutral orthophosphate has also been used to reduce calcium excretion and inhibit stone formation. This agent works by reducing calcium absorption and excretion as well as by increasing levels of urinary pyrophosphate, a potent inhibitor of stone formation.

Hyperoxaluria. In patients with enteric hyperoxaluria, increased urinary oxalate excretion is the result of enhanced absorption of oxalate from the intestines. Treatment consists of addressing the underlying problem (Crohn's disease) and possibly the addition of calcium supplements to bind intestinal oxalate and prevent its absorption. Lowering the level of dietary oxalate is difficult because oxalate is present in most foods, a low-oxalate diet is not palatable, and evidence suggests that the urinary excretion of oxalate is not significantly different in patients who are compliant with this diet.[16] Nevertheless, these authors educate patients regarding foods that are rich in oxalates. Magnesium supplementation in the form of magnesium oxide 400 mg twice daily may be useful in patients with idiopathic hyperoxaluria.

Hypocitraturia. Urinary citrate is a key inhibitor of stone formation. Decreased urinary citrate excretion is often secondary to chronic diarrhea or distal RTA, but this decrease may be idiopathic. Treatment of low urinary citrate requires the use of oral citrate supplements. Potassium citrate is preferred to sodium citrate because sodium salts enhance natriuresis, which in turn worsens the hypercalciuria. It is important to realize that the dose of alkali needed to restore urinary citrate levels in patients with RTA is often as high as 3 to 4 mEq/kg body weight versus 1 to 2 mEq/kg body weight in patients without RTA. In one prospective trial involving patients with calcium stones, 72% of patients given potassium citrate over a 3-year period were free of recurrent stone formation versus 20% of patients given placebo and increased fluids.[33]

Hyperuricosuria. Ten percent to 20% of calcium oxalate stones are formed as a result of heterogeneous nucleation from increased urinary uric acid levels. Decreasing dietary purine intake is recommended and referral to a nutritionist is useful. In one prospective study, the addition of allopurinol to an increased fluid intake reduced the recurrence of calcium oxalate stones by 27% over a 3-year period.[34]

Therapy for Noncalcium Stones

Uric acid stones. Only 20% of patients with uric acid stones are hyperuricosuric. The majority of patients with uric acid stones (80%) have decreased urinary uric acid solubility as a result of an acidic urine pH and low urine volume. Persistently acidic urine is the result of a poorly understood defect in ammonia production. Uric acid is 10 to 20 times more soluble when urine pH exceeds 7 than when urine pH is 5. In addition to increasing the urine volume, alkalinization of the urine is probably the most important intervention in the treatment of uric acid stones. Effective alkalinization of urine may also lead to dissolution of previously formed stones. Pak[35] has shown that alkalinization of the urine with potassium citrate decreased stone formation from 1.2 stones per year to 0.01 stones per year. The goal is to keep the urine pH between 6 and 7, and a daily urine pH log should be maintained to assess efficacy of the treatment. Patients who have high levels of daily uric acid excretion or who cannot comply with alkali intake can also be placed on a low-purine diet or allopurinol.

Struvite stones. As previously mentioned, struvite stones are usually the result of urinary tract infection by urease-producing organisms. Struvite stones are considered to be infected, and medical therapy alone has a limited ability to eradicate them and the infections associated with them. Early referral to a urologist for ESWL (for stones < 2 cm) or alternative intervention (for stones > 2 cm) is recommended.[36] It is important to remove all stone fragments because any remaining fragment serves as a nidus for future infections and recurrent stone formation.

Cystine stones. Cystine stones are uncommon stones that are the result of the excessive excretion of the amino acid cystine. These stones may be pure or mixed in composition. Initial therapy is to increase the urine volume to improve the solubility of cystine. Alkalinization of the urine has a limited role because the urine pH must be greater than 7.5 to appreciably improve the solubility of cystine, and this high pH is difficult to maintain. Chelating therapy using penicillamine or tiopronin may be needed for patients with greater than 500 g/day of cystine or for patients who have had a recurrence despite increased fluid intake. Cystine stones are not susceptible to ESWL and either percutaneous or open nephrolithotomy is needed if surgical intervention becomes necessary.

QUESTION

- **What are the cost implications of treating patients with nephrolithiasis?**

DISCUSSION

Cost Implications

Parks and Coe[37] recently published a cost analysis of the evaluation and medical treatment of a large cohort of

patients with recurrent stones. Assuming that the medical intervention was responsible for the decrease in stone recurrence in the study's patient population, these researchers proposed that the evaluation and medical treatment of patients reduced costs by $2158 per patient/year compared with the costs of caring for patients with recurrent nephrolithiasis without metabolic evaluation and medical intervention. The protocol used by this research group to evaluate the patients required three separate samplings of blood and three 24-hour collections of urine to measure the excretion of various constituents as outlined previously. Identical tests were performed each time. This study, given its limitations and assumptions, suggests that the approach of evaluating and medically treating patients with recurrent nephrolithiasis is less expensive in the long term when compared with the strategy of expectantly waiting for recurrent stone formation and treating patients as needed.

INITIATION OF CITRATE SUPPLEMENT

In addition to recommending increased fluid intake and dietary changes for this patient, the physician prescribes potassium citrate 40 to 60 mEq/day to increase urinary citrate excretion. A follow-up appointment is scheduled in 4 weeks to assess compliance, response to initial therapy, and possible modification of therapy.

QUESTION

- **How should patients being treated for recurrent stones be monitored?**

DISCUSSION

Initial Follow-up

Initially, response to treatment and compliance with recommendations should be monitored at intervals of 4 to 6 weeks. The patient needs a 24-hour urine collection for sodium and volume (to assess compliance with sodium restriction and fluid intake) and creatinine (to assess completeness of the collection) in addition to the urinary constituents that are being manipulated.

Patients with calcium stones. In patients with hypercalciuria, urinary calcium should be decreased by approximately 50% if the patient has been compliant with a low-sodium diet and thiazides, if prescribed. Lack of a decrease in calcium excretion after thiazides are prescribed is often the result of excessive sodium intake. The dose of the thiazide diuretic may be increased if needed, but avoiding hypokalemia is important (through the use of supplements such as potassium citrate) because this condition decreases urinary citrate excretion by causing intracellular acidosis. Triamterene should not be used because this substance can precipitate in the urine and promote stone formation. For patients diagnosed with idiopathic hypocitraturia, the dose of potassium citrate must be titrated upward until normal urinary citrate levels are achieved. Measurement of 24-hour urinary urea nitrogen excretion is helpful in identifying those patients who are consuming an excessive quantity of protein, and results can be used to counsel patients.

Patients with uric acid stones. For monitoring patients being treated for uric acid stones, in addition to measuring urinary uric acid excretion, 24-hour urinary urea nitrogen measurement is helpful to assess compliance with reducing dietary protein, an important source of purines. The physician also should review the patient's urine pH log to ensure adequate urinary alkalinization.

Future Follow-up Visits

The frequency of further follow-up visits with the physician is determined by the need to reassess metabolic activity, patient symptoms, and the efficacy of interventions. Patients who have had the appropriate metabolic responses to therapy should be seen a minimum of once per year, with yearly abdominal radiography or ultrasound (for cystine or uric acid stones) to monitor the metabolic activity of their disease. No reliable studies confirm the cost-effectiveness of this approach. Also, no data are available to guide the length of time that patients should be treated. Although medications are often stopped after several years, dietary changes and increased fluid intake should be continued indefinitely.

QUESTION

- **What urologic interventions are available for the treatment of nephrolithiasis, and when are they indicated?**

DISCUSSION

Urologic Intervention

General observations. Advances in technology have significantly increased the variety of surgical interventions for removal of kidney stones. These advances include noninvasive approaches such as ESWL, percutaneous nephrolithotomy, and endoscopic procedures. These procedures are performed by a urologist and are primarily indicated for the amelioration of intractable pain, to prevent worsening infection, and to prevent renal damage caused by obstruction(**Table 6**).[38,39]

The probability that a renal stone will pass spontaneously depends on the size of the stone. The likelihood of spontaneous passage is about 80% for stones smaller

Table 6. Indications for Urologic Intervention

Intractable pain
Persistent hydronephrosis
Anuria in bilateral obstruction or in a solitary kidney
Infection
Chronic ureteral stone
Staghorn calculus
Transplant kidney
Occupation (eg, airline pilot)

Table 7. Complications of Extracorporeal Shock-Wave Lithotripsy

Ecchymosis
Perinephric hematoma (may result in hypertension)
Pancreatitis (rarely)
Renal colic
Ureteral obstruction
Sepsis

Adapted with permission from Lingemen JE: Lithotripsy and surgery. *Semin Nephrol* 1996;16:487–498.

than 4 mm, 59% for stones between 4 and 6 mm, and 21% for stones larger than 6 mm.[40] Stones smaller than 5 mm may generally be managed with fluids and analgesics. A patient who has intractable pain requiring frequent visits should be referred to a urologist, even if the stone is likely to pass spontaneously. Hydronephrosis, which is commonly seen, is not an indication for immediate intervention but must be followed closely. Persistent hydronephrosis, even if asymptomatic, is an indication for intervention by a urologist. If a urinary tract infection is evident, an obstructed stone requires immediate removal because the risk of urosepsis and irreversible renal injury is exceedingly high.

A vast majority of patients who require surgical intervention can be managed without the need for open surgical procedures (nephrolithotomy). The choice of a specific type of intervention depends upon the size, location, and type of stone as well as the clinical features of the patient (eg, body habitus, infection).

Caliceal stones. A stone that is smaller than 2 cm can be treated with ESWL. ESWL results in greater than 90% of patients being stone-free and an overall complication rate of less than 5% (**Table 7**). Percutaneous nephrolithotomy should be utilized when the stone is larger than 2 cm, when the stone has failed to respond to ESWL, in patients who have a large body habitus or abnormal renal anatomy, and when the stone composition is cystine. Ninety percent of patients with a stone larger than 2 cm who are treated with percutaneous nephrolithotomy become stone-free compared with 43% of patients treated with ESWL.[41]

Ureteral stones. An upper ureteral stone is generally treated using ESWL, with a greater than 90% stone-free rate. Stone removal using retrograde ureteroscopy is reserved for cases in which ESWL has failed, for cystine stones, or for distally located stones causing obstruction. The ureteroscopic approach is preferred to percutaneous nephrolithotomy because this approach is less invasive and causes fewer complications (ie, bleeding). Stones located in the midureter are in close proximity to the pelvic bones. Bones absorb a significant amount of the energy of the shock wave, which makes ESWL less effective in managing stones at the pelvic location. Ureteroscopic stone removal is the preferred modality in this situation, particularly for stones larger than 10 mm or when stents are required to relieve intractable pain or obstruction or to treat infection. The management of distal ureteral stones is controversial. Both ureteroscopy and ESWL are accepted modalities, each with its own advantages and disadvantages. Ureteroscopy, for example, has a stone-free rate close to 100% versus 80% for ESWL, but this high rate is at the expense of the need for full anesthesia and a higher complication rate (sepsis and strictures). The preferred treatment varies depending upon the expertise of the urologist, access to ESWL, and patient occupation (in some occupations [eg, airline pilot], disabling renal colic may be dangerous to other people). Several cost analyses of these two techniques have been published, but these analyses have not settled the issue because of the criticism that these studies failed to consider outcomes such as the need for re-treatment in patients who have undergone ESWL and costs of contemporary machines.[38]

REFERRAL TO UROLOGIST

This patient's calcified, 9-mm stone is deemed not likely to pass spontaneously and he is referred to a urologist for possible intervention. Given the size of the stone (< 2 cm), the presumed composition (calcium oxalate), a relatively small stone burden, and the patient's desire to avoid recurrent symptoms, the urologist recommends ESWL. The patient successfully undergoes ESWL with an HM-3 lithotriptor.

QUESTIONS

- **What are some of the challenges in the long-term management of nephrolithiasis?**
- **When should a patient be referred to a specialist?**

DISCUSSION

Problems with Compliance

Long-term management of nephrolithiasis relies heavily on patient compliance with maintaining a low sodium intake, a high fluid intake, and a routine of citrate supplementation. The more recent the episode of renal colic, the more compliant patients are with their therapy. Patients tend to become less compliant once they have been asymptomatic for several months. Physicians must emphasize to the patient that the predisposition for recurrent nephrolithiasis, with its risks of renal failure, infection, and requirement for surgical intervention, remains very real. Specialists with expertise in stone disease may have a role in helping patients remain committed to their treatment.

Indications for Referral

No prospective studies compare patient outcomes based on provider (primary care physician versus subspecialist). Primary care physicians can easily perform the initial evaluation and follow-up of patients with a symptomatic stone. A patient who has demonstrated continued metabolic activity despite initial disease management efforts by the primary physician should be referred to a nephrologist with an interest in nephrolithiasis. Additionally, a specialist should see patients with concomitant problems such as RTA or renal insufficiency. Young adults, children, and possibly non-white patients, who do not constitute the usual demographic group at risk for nephrolithiasis, should be referred early in the course of disease because these patients are more likely to have atypical causes requiring more specific therapy. Recurrent passage of stones can cause significant morbidity in these patients and can be avoided with proper evaluation and treatment.

CONCLUSION

The patient continues to do well after the ESWL, with urine citrate levels remaining normal on the citrate supplements. He has only one episode of renal colic in 3 years, which occurs after a summer bike-a-thon; the episode resolves spontaneously with volume replacement and analgesics. **HP**

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