in the clinic

Nephrolithiasis

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The content of In the Clinic is drawn from the clinical information and education resources of the American College of Physicians (ACP), including PIER (Physicians' Information and Education Resource) and MKSAP (Medical Knowledge and Self-Assessment Program). Annals of Internal Medicine editors develop In the Clinic from these primary sources in collaboration with the ACP's Medical Education and Publishing Division and with the assistance of science writers and physician writers. Editorial consultants from PIER and MKSAP provide expert review of the content. Readers who are interested in these primary resources for more detail can consult http://pier.acponline.org and other resources referenced in each issue of In the Clinic.

The information contained herein should never be used as a substitute for clinical judgment.

CME objective: To review the screening and prevention, diagnosis, acute and preventive treatment, and practice improvement for nephrolithiasis.

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What factors increase the risk for nephrolithiasis?

Genetic and environmental influences cause kidney stones. More than 50% of patients in kidney stone clinics have a first-degree relative with stones. The most common urinary phenotype in patients with stones and with family histories of stones is hypercalciuria. Kidney stones in both members of a twin pair occur at twice the rate in monozygotic twins versus dizygotic twins (5). Calculations based on twin studies estimate that 56% of the stone phenotype is accounted for by genetic factors and the rest is environmental. The genes responsible for these genetic effects, however, have not been identified.

Environmental factors or acquired traits are presumably responsible for the increase in stone prevalence observed in the past 20 years. For example, stones are strongly associated with weight gain, diabetes, obesity, and the metabolic syndrome, which are occurring more frequently. Diabetes is a strong risk factor for both calcium and uric acid stones. Whether, hypertension is a risk factor for stones is unclear. Increases in dietary salt, oxalate, and animal protein have been implicated in altering urine composition to favor stone formation. Decreased dietary calcium content has been associated with the risk for stones, probably because dietary calcium can precipitate intestinal oxalate and prevent its absorption from the intestine, thus reducing oxalate excretion in the urine. Low urine volume leads to increased concentration of stone-forming calcium salts and uric acid, so lifeguards, athletes, soldiers (especially those deployed to hot climates), and others with increased sweating have reduced urine volume and increased rates of stones. Drivers and teachers have lower fluid intake and excrete more concentrated urine. Oxalobacter formigenes is an intestinal bacterium that metabolizes oxalate. Colonization with Oxalobacter may reduce oxalate absorption from the colon, reduce urinary oxalate, and protect against stones. Antibiotics may eliminate this organism, thus increasing oxalate absorption from the intestine and oxalate excretion into the urine (6). However, it is not clear if Oxalobacter preparations, which are not yet available commercially, can prevent kidney stones by reducing urinary oxalate levels. Urinary tract infections associated with high urine pH,
particularly with urease-producing organisms, such as *Proteus* species, are important risk factors for struvite stones. Bowel disorders, such as inflammatory bowel disease or the short-bowel syndrome, are associated with enteric hyperoxaluria and calcium oxalate stones, and low urine pH due to bowel fluid loss is associated with uric acid stones. Bariatric surgery causes hyperoxaluria and stones (7). Some medications can cause stones, including calcium supplements (8) (as opposed to increased dietary calcium [9]); high-dose vitamin C; and poorly soluble drugs, such as triamterene or feldane. Carbonic anhydrase inhibitors like acetazolamide, which is used for glaucoma, or topiramate, which is used for epilepsy and migraine, also cause kidney stones by increasing urine pH and decreasing citrate excretion.

**Should clinicians screen patients for asymptomatic stones if they are at increased risk for nephrolithiasis?**

No evidence supports the screening of patients for asymptomatic stones unless they have recurrent stones unresponsive to usual therapy.

**What measures should clinicians recommend to prevent nephrolithiasis in patients at increased risk?**

Increased fluid intake dilutes the urine and decreases urinary supersaturation of poorly soluble salts, such as calcium oxalate and uric acid. Increased fluid intake is safe and inexpensive and can be recommended to patients at increased risk. Although no trials of primary prevention have been performed, increased fluid intake has been shown effective in 1 trial of secondary prevention.

Higher fluid intake with higher urine volume as secondary prevention was associated with a lower rate of stone recurrence in calcium oxalate stone-forming patients. Patients with calcium stones were advised to increase fluid intake, whereas a control group was not given this advice. After 5 years, the group with high fluid intake had a mean daily urine volume of 2.6 L compared with 1.0 L in the control group, and 12% of the group with high fluid intake had a recurrent stone compared with 27% of the control group (8).

Changes in diet are best reserved for secondary prevention.

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**Screening and Prevention...** Genetic factors increase the risk for stones, but most stones cannot be linked to a specific genetic defect. Increased dietary salt, oxalate, and animal protein are associated with stone formation, as are specific medical conditions and some drugs. Patients should not be screened for asymptomatic stones even if they are at increased risk. Patients at increased risk for stones should be encouraged to increase fluid intake to more than 2 to 2.5 L/d (68 to 85 oz/d) to maintain urine volume greater than 2 L/d.

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**CLINICAL BOTTOM LINE**

**What is the spectrum of presentation for patients with nephrolithiasis?**

Most patients have flank pain that radiates downward and anteriorly into the abdomen and then into the pelvis and genitals as stones progress down the ureter. Stones lodged at the ureteropelvic junction (10.6%) produce flank pain, stones lodged between the ureteropelvic junction and the iliac vessels (23.4%) produce flank pain with radiation to the genitals, and stones lodged at the ureterovesical junction (60.6%) produce voiding...
urgency and suprapubic discomfort (10). Stones may less frequently lodge at the bladder neck and cause suprapubic discomfort and anuria. Patients with a history of renal colic usually make the diagnosis correctly themselves. The pain often starts rapidly and waxes and wanes. Nausea and vomiting are often present, and fever is absent. Gross or microhematuria may be present. Smaller stones that only partially obstruct the ureter may present with mild discomfort. Stone passage is associated with dramatic and sudden cessation of pain. Struvite stones often do not cause flank pain, because they remain intrarenal and may not cause obstruction, and a struvite stone can remain asymptomatic until the urinary tract infection that caused it becomes symptomatic. Asymptomatic stones are often detected during imaging studies for unrelated indications.

How should clinicians use history and physical examination to evaluate patients with suspected nephrolithiasis?

The history should concentrate on establishing risk factors for stones, including the family history, occupational status, diet, medications, supplements, and other medical conditions. A history of other kidney or urologic conditions, such as polycystic kidney disease or urinary tract infection, should be elicited. Past bowel disease, sarcoidosis, and hyperparathyroidism are also risk factors.

The physical examination is most important for ruling out other conditions. Kidney stones have no specific manifestations on examination.

What other disorders should clinicians consider in patients with suspected nephrolithiasis?

Patients with conditions associated with peritonitis have fever, abdominal tenderness, guarding, and rebound. Pyelonephritis may cause flank pain, but fever is expected. Pyelonephritis and stones sometimes coexist, however. In women, a pelvic examination may suggest ovarian torsion, cysts, or ectopic pregnancy. In men, a rectal examination may identify prostatic hypertrophy, prostatitis, or prostate cancer with lower urinary tract symptoms that may be mistaken for obstructing stones.

What imaging studies and laboratory tests should clinicians use to confirm the diagnosis of nephrolithiasis?

Computed tomography (CT) is the gold standard for the diagnosis of renal colic. It has superior sensitivity and specificity to ultrasonography and intravenous pyelography (IVP). Calcium stones are radiopaque, cystine and struvite stones are often but not always radiopaque, and uric acid stones are never opaque unless they include a calcium component. Therefore, noncalcium stones may be missed by plain radiography and visualized by CT. Computed tomography is also better at making alternative diagnoses when ureteral stones are not present. Because CT does not require contrast, it is faster and safer than IVP. Although the price has fallen in recent years, CT is still more expensive than other modalities, particularly because pelvic and abdominal studies are usually billed separately. Plain radiography of the abdomen is inexpensive, usually detects calcium stones 5 mm or bigger, identifies some nonstone diagnoses, and has a low dose of radiation. Magnetic resonance imaging is a poor tool for visualizing stones.

In a prospective evaluation of radiologic imaging in renal colic, 168 patients had both noncontrast helical CT and IVP (11). Comparison of CT findings with the final diagnosis of stone showed 98% sensitivity, 95% specificity, 98% positive predictive value, and 95% negative predictive value. Intravenous pyelography had inferior results, with 83%
Some stone-forming patients receive repeated doses of radiation. In 1 retrospective study, 108 patients with a primary acute stone episode underwent an average of 4 radiographic examinations during a 1-year period. Studies included a mean of 1.2 plain abdominal films, 1.7 abdominal and pelvic CTs (range 0 to 6), and 1 IVP (range 0 to 3) during the first year of follow-up (12). In an attempt to minimize radiation exposure for these patients, new protocols and imaging techniques for low-dose CT are being developed and have become the standard of care at many institutions. Low-dose stone-protocol CT seems nearly as effective as standard helical CT for detection of stones and abdominal pathology in patients who are not morbidly obese (13, 14).

When evaluating acute renal colic, obtain a complete blood count, a urinalysis, and serum chemistry. Complete blood count and urinalysis are useful for detecting concomitant infection, but hematuria may be absent in acute stone disease. Serum chemistries are important for detecting underlying renal dysfunction associated with urinary tract obstruction or alterations in extracellular volume associated with vomiting.

Although not recently updated, the National Institutes of Health consensus statement suggested routine laboratory analyses for first-time stone-forming patients to identify risk factors for recurrent stones (15). More recent guidelines from the European Association of Urology are not substantially different (16). In the elective office-based setting, this evaluation should include serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, and uric acid. Hypercalcemia suggests sarcoidosis or primary hyperparathyroidism, and chest radiography and measurement of parathyroid hormone may be appropriate. A low serum bicarbonate concentration with a urine pH of 6.0 or more suggests renal tubular acidosis (RTA). Hypophosphatemia is seen in some patients with a renal phosphate leak and calcium stones. High urine pH or pyuria should lead to urine cultures and consideration of struvite stones.

**How and when should clinicians use specialized laboratory testing to determine the cause of nephrolithiasis?**

More detailed analyses, such as 24-hour urine collections for measurement of chemistries, are usually reserved for patients with recurrent stones, children with stones, and perhaps patients whose first stones are larger and require urologic intervention. Clinicians can use these 24-hour urine collections to identify risk factors for recurrent stone formation that are then used to prescribe specific diet and pharmacologic interventions, although no randomized, controlled trials (RCTs) have shown that this approach is superior to others (17). Use a laboratory that calculates supersaturation, which is a ratio of the patient’s ion activity product to the known solubility product for the crystal-forming solute in question. Higher values are associated with greater stone-forming tendency. Supersaturation combines urine volume with concentrations of calcium, oxalate, citrate, and other variables into a single value that suggests the likelihood of recurrence, correlates well with stone composition (18) and is intuitively understandable by patients. Determining stone composition by infrared spectroscopy or X-ray crystallography is inexpensive, aids in understanding the pathophysiology of the stone formation, and helps plan prevention. About 80% of stones contain calcium, and about 80% of calcium stones are composed of:

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mostly of calcium oxalate. The rest are calcium phosphate. Uric acid stones account for up to 10%, with a higher proportion in obese patients and patients with diabetes, and struvite stones are more common in women. Cystine stones account for about 1% of stones.

Patients should have a screen to urinate through in the hospital or at home to capture stones or fragments for analysis. Instruct patients to urinate into a cup with a 4 × 4 gauze pad if a screen designed for the purpose of capturing stones or fragments is not available.

**Diagnosis...** Computed tomography without contrast is the best method for diagnosing the cause of renal colic. Repeated episodes lead to repetitive exposure of patients to radiation, and ultrasonography is preferred for serial follow-up. Many stones can be diagnosed by plain radiography, and ultrasonography is good for demonstrating hydronephrosis, although ureteral stones below the kidney are often missed. When evaluating acute renal colic, obtain a complete blood count; urinalysis; and levels of serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, and uric acid to manage the acute episode and to evaluate the patient for preventive therapy. To guide the choice of preventive therapy, measure stone composition in all patients and measure urine supersaturation in 24-hour urine collections of patients with recurrent stones, children with stones, and perhaps patients whose first stones are large and require urologic intervention.

**How should clinicians treat pain in patients with renal colic?**

Opiates or nonsteroidal anti-inflammatory drugs are used alone or in combination for moderate-to-severe pain. Ketorolac provides effective pain relief with less sedation than opiates and, therefore, is preferred for patients who are discharged from the emergency department before a stone has passed. Among opiates, meperidine causes more nausea and vomiting and is contraindicated in the presence of decreased kidney function.

In a double-blind RCT of ketorolac, 60 mg intramuscular, versus meperidine, 100 to 150 mg intramuscular based on weight, in 70 patients with renal colic, ketorolac gave better pain relief and led to slightly quicker discharge from the emergency department (19). In another RCT of 130 patients with renal colic, patients received either intravenous morphine, 5 mg and then another 5 mg after 20 minutes; intravenous ketorolac, 15 mg and then another 15 mg after 20 minutes; or a combination of both. The combination was superior to either drug alone for pain relief, required less “rescue analgesia,” and had fewer adverse effects (20).

**Which drugs aid the passage of renal stones?**

Patients with distal ureteral stones less than 10 mm in diameter can be treated with tamsulosin, an α1-adrenergic antagonist usually used for benign prostatic hypertrophy, to aid stone passage. Tamsulosin is well-tolerated but infrequently lowers blood pressure, leading to lightheadedness or dizziness. A second choice is nifedipine, a calcium-channel blocker that presumably causes ureteral dilatation and relaxation, although this drug is more often associated with undesirable lowering of blood pressure. These 2 drugs have not been compared with each other. The trials that used nifedipine for this indication also used concomitant glucocorticosteroids, such as methylprednisolone. Steroids and non-steroidal anti-inflammatory drugs may reduce stone-induced
When should clinicians hospitalize patients with nephrolithiasis?
Consider hospitalization for patients with stones larger than 5 mm if parenteral therapy is required to manage pain. Admit patients with stones of any size if pain or nausea and vomiting cannot be managed in the outpatient setting. Smaller stones (<5 mm) are likely to pass without surgical intervention, whereas larger stones are more likely to be associated with a prolonged course, more pain, and a lower likelihood of spontaneous passage.

A meta-analysis of 327 studies by the Ureteral Stones Clinical Guidelines Panel convened by the American Urologic Association (AUA) found that 98% of smaller stones (<5 mm) passed spontaneously. Distal ureteral stones passed more frequently than proximal ureteral stones (21).

An obstructed and infected urinary tract is an absolute indication for emergent intervention, because this condition can lead to urosepsis and irreversible renal parenchymal damage. Concomitant urinary tract infection is suggested by fever or pyuria (>5 to 20 leukocytes per high-powered field) or substantial leukocytosis. Also, admit patients with bilateral obstruction or obstruction in a solitary kidney if decreased kidney function is evident. Administer antibiotics promptly on the basis of local sensitivity patterns.

When should clinicians consult a urologist or other specialist?
Consult a urologist for stones larger than 5 mm or those that prevent patients from conducting their normal activities. Consult a urologist for stone removal when the likelihood of spontaneous passage is low or when complications occur. Urinary tract infection with obstruction is the most urgent indication for hospitalization and urologic consultation.

When should clinicians consider lithotripsy, surgery, or other interventions in the acute management of patients with nephrolithiasis?
Usually, urologists will decide whether a procedure will be done and which procedure will be used. The choice often depends on the urologist’s assessment and skills and the patient’s preference. The AUA’s Ureteral Stones Clinical Guidelines Panel and the European Association of Urology (22) recommend extracorporeal shock wave lithotripsy (ESWL) as first-line treatment for stones no larger than 1 cm in diameter in the proximal ureter; ureteroscopy and percutaneous nephrolithotomy are acceptable alternatives, especially if ESWL is inappropriate or fails. For stones larger than 1 cm in diameter in the proximal ureter, consider percutaneous nephrolithotomy or ureteroscopy. For distal ureteral stones no larger than 1 cm in diameter, choose ESWL or ureteroscopy instead of blind basketing without fluoroscopy. For distal ureteral stones greater than 1 cm, perform ESWL or ureteroscopy; although for larger stones, ureteroscopy may be more appropriate because ESWL must fragment stones into smaller pieces to be successful. Ureteroscopy may lead to better clearance of stone fragments, which minimizes stone recurrence. For patients with stones who are undergoing ESWL, consider subsequent treatment with tamsulosin to aid passage of stone fragments. The AUA recommendations regarding the management of staghorn calculi suggest that percutaneous nephrolithotomy should be the first treatment used for most patients, and that ESWL monotherapy should not be used for most patients.

Preventive Treatment

What is the role of fluid intake and diet in the preventive treatment of patients with nephrolithiasis?

Advise patients at high risk for recurrent stone disease to drink at least 2 to 2.5 L/d (68 to 85 oz) to maintain urine volume of at least 2 L. Emphasize higher intake to achieve the same urine output in people who are physically active (for example, athletes), work in hot climates (for example, lifeguards), have diseases associated with stone formation (for example, distal RTA, medullary sponge kidney, polycystic kidney disease), or have increased bowel fluid losses (for example, from ileostomy or other bowel disorders). Increased fluid intake leads to urine dilution and a decrease in urine supersaturation of poorly soluble salts, such as calcium oxalate, calcium phosphate, and cystine. Urine volume may be less important in uric acid stone-forming patients who successfully alkalinize the urine. Increasing fluid intake may be especially difficult for men with benign prostatic hypertrophy or for other persons with bladder disorders. These patients may benefit from dietary alteration and drug therapy.

Diet is an attractive therapy to many patients with stones who may be reluctant to take medications for an episodic condition that is not usually life-threatening. Despite ample epidemiologic data linking diet and stones, only 1 RCT with positive results has been published. Few data are available regarding the willingness and ability of stone-forming patients to adhere to a diet. Epidemiologic evidence demonstrates that men and women with greater calcium intake have fewer stones (23, 24). This effect is most likely due to the ability of dietary calcium to bind oxalate in the intestine and prevent its absorption.

These observational data were supported by 1 RCT. Italian men (n = 120) with hypercalciuria and recurrent calcium oxalate stones were randomly assigned to 1 of 2 regimens. One regimen restricted calcium intake to 400 mg/d, and the other recommended a "normal" calcium intake of 1200 mg/d and restricted animal protein (52 g) and salt intake (50 mmol) (Table 1). In both groups, participants were counseled to restrict oxalate intake. At the end of 5 years, the group on the high-calcium, low-salt, low–animal-protein diet had a 50% lower rate of stone recurrence when compared with the group on the low-calcium diet. The effect was attributed to increased calcium ingestion leading to reduced urinary oxalate excretion while sodium restriction limited urinary calcium excretion. Protein restriction may have also played a part by increasing citrate excretion and contributing to the reduction of calcium excretion (both of which may occur with less net acid excretion, suggested by the modest decrease in urine sulfate excretion) (9).
Although bone mineral density was not measured, one would anticipate that the group on the higher calcium intake would have had less demineralization than the other group. This possibility is another reason not to restrict calcium in patients with hypercalciuria, who have reductions in bone mineral density and more frequent bone fractures (25).

Patients with uric acid stones should limit animal protein intake, which reduces the amount of alkali needed to increase urine pH, but diet alone has not been shown to prevent uric acid stones. People with cystine stones should limit animal protein and salt intake to increase urine pH and reduce cystine excretion.

**What drug therapy should clinicians consider to prevent recurrent nephrolithiasis, and how does it differ in patients with different types of stone disease?**

Table 2 lists drug therapy for stone prevention. The effectiveness of this or other diets in patients with other risk factors for stones, or other types of stones, has not been tested. Thiazides lower urinary calcium excretion in patients with hypercalciuria, and several RCTs have demonstrated that thiazides prevent recurrent calcium stones. At 3 years, stones recurred in 50% to 60% of patients receiving placebo and 15% to 30% of patients receiving thiazide. Studies with less than 2 years of treatment did not show benefit (26, 27). Thiazides include chlorthalidone, indapamide, and hydrochlorothiazide. The first 2 are usually taken once a day, whereas hydrochlorothiazide is best taken twice a day. Thiazides reduce urinary calcium by stimulating renal calcium reabsorption and may stimulate bone to incorporate calcium. Because hypercalciuria is linked to decreases in bone mineral density (BMD), it is useful that thiazides are also associated with increases in BMD (28). Because thiazides can cause hypokalemia, which lowers citrate excretion, most patients receiving thiazides should be supplemented twice a day with potassium citrate or given potassium-sparing drugs, such as amiloride or spironolactone. Avoid triamterene, because it is poorly soluble.

Citrate is an inhibitor of the crystallization of calcium oxalate and calcium phosphate. Use citrate supplementation for secondary prevention.

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**Table 1. Composition of the Normal-Calcium, Low-Protein, Low-Salt Diet**

<table>
<thead>
<tr>
<th>Daily Intake</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calories, kcal</td>
<td>2540</td>
</tr>
<tr>
<td>Total protein, g</td>
<td>93†</td>
</tr>
<tr>
<td>From meat or fish, g</td>
<td>21</td>
</tr>
<tr>
<td>From milk and derivatives, g</td>
<td>31</td>
</tr>
<tr>
<td>From bread, pasta, and vegetables, g</td>
<td>41</td>
</tr>
<tr>
<td>Lipids, g</td>
<td>93 (837 kcal, or approximately 33% of total calories)</td>
</tr>
<tr>
<td>Carbohydrates, g</td>
<td>333 (1332 kcal, or approximately 52% of total calories)</td>
</tr>
<tr>
<td>Fiber, g</td>
<td>40</td>
</tr>
<tr>
<td>Sodium chloride, mmol</td>
<td>50</td>
</tr>
<tr>
<td>Potassium, mmol</td>
<td>120</td>
</tr>
<tr>
<td>Calcium, mmol</td>
<td>30</td>
</tr>
<tr>
<td>Phosphorus, mmol</td>
<td>48.8</td>
</tr>
<tr>
<td>Magnesium, mmol</td>
<td>14.5</td>
</tr>
<tr>
<td>Oxalate, mmol</td>
<td>Approximately 2.2</td>
</tr>
<tr>
<td>Water in foods, mL</td>
<td>1550</td>
</tr>
</tbody>
</table>

*The data were obtained from the composition tables issued in 1989 by the Italian National Institute for Nutrition. The values are based on direct chemical analyses of the foods available in Italian markets. Reprinted with permission from reference 24. Copyright 2002 Massachusetts Medical Society. All rights reserved.

† 372 kcal, or approximately 15% of total calories.
Table 2. Drug Treatment of Stone Prevention

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Benefits</th>
<th>Side Effects and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>Stimulates renal calcium reabsorption; may inhibit bone resorption</td>
<td>25 to 50 mg qd to bid</td>
<td>Prevents stones, lowers blood pressure, increases bone density</td>
<td>Most patients require potassium citrate supplementation in conjunction with thiazides, either for hypokalemia or decreased citrate excretion. The latter occurs with potassium depletion even with normal serum potassium concentration. Hypokalemia is also associated with hypocitraturia. Hypotension is occasionally a problem in young, normotensive persons. For secondary prevention of kidney stones, chlorthalidone may be slightly more potent in reducing calciuria but may also cause more potassium loss. Indapamide is also effective. Concomitant sodium restriction maximizes effect on calciuria. Avoid poorly soluble triamterene as potassium-sparing combination. Amiloride is preferable as a potassium-sparing agent. Sodium restriction also minimizes potassium losses.</td>
</tr>
<tr>
<td>Potassium citrate</td>
<td>Citrate forms soluble complexes with calcium; inhibits crystal growth and aggregation. For uric acid and cystine stones, citrate increases urine pH after metabolism to bicarbonate by liver</td>
<td>20 to 30 mEq bid to tid. Once-daily dosing may be effective for some patients if citrate excretion or urine pH increases adequately. Dosing tid may be appropriate for dissolution of uric acid or cystine stones.</td>
<td>Increases urinary citrate excretion and prevents calcium stone recurrence. Increased urine pHe dissolves uric acid crystals and solubilizes cystine. At urine pH values &gt;7.0, solubility of cystine in urine increases dramatically.</td>
<td>GI intolerance, especially in elderly patients or patients with GERD (heartburn, nausea). Potential for hypokalemia in patients with renal insufficiency or taking ACE inhibitors. For secondary prevention of kidney stones. Comes in longer-acting tablets or dissolvable crystal forms. Sodium citrate preparations may have better GI tolerance for some but are not clearly effective in preventing stone recurrence.</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Xanthine oxidase inhibitor reduces urinary uric acid excretion</td>
<td>300 mg qd, reduce with decreased GFR</td>
<td>Prevents stone recurrence in patients with hyperuricosuria and normocalciuria. Prevents gout. Adjunctive to potassium citrate for uric acid stones.</td>
<td>Rare allergy, eosinophilia, interstitial nephritis, the Stevens–Johnson syndrome. For secondary prevention of kidney stones. For uric acid stones, urinary alkalinization with citrate supplementation is usually more important than reducing uricosuria.</td>
</tr>
<tr>
<td>Organic marine hydrocolloid (Ox-Absorb)</td>
<td>Seaweed-derived hydrocolloid binds oxalate in intestinal lumen and prevents absorption</td>
<td>9 tablets per day</td>
<td>Well-tolerated nutraceutical agent for treatment of hyperoxaluria. Useful for enteric or dietary hyperoxaluria.</td>
<td>Only anecdotal reports exist of efficacy for reducing urinary oxalate excretion. Decreased urinary oxalate in patients with bowel disorders. No trials demonstrating decreased stone recurrence. Both calcium citrate and cholestyramine may have some effect to reduce intestinal oxalate absorption.</td>
</tr>
<tr>
<td>Sodium cellulose phosphate</td>
<td>Ion-exchange resin which binds dietary calcium in intestinal lumen and reduces urinary calcium excretion</td>
<td>10 g/d in divided doses</td>
<td>Reduction of hypercalciuria</td>
<td>Causes negative calcium balance and decreased bone mineral density, similar to dietary calcium restriction. Can reduce urinary magnesium excretion and increase urinary oxalate. No randomized trials have been performed with stone formation as an outcome, and questions about long-term safety because of risk for osteoporosis have led to very infrequent use of this preparation.</td>
</tr>
<tr>
<td>Orthophosphate</td>
<td>Reduces serum 1,25-dihydroxyvitamin D concentration and intestinal calcium absorption; increases urinary excretion of pyrophosphate, an inhibitor of calcium oxalate crystal formation</td>
<td>4 tablets bid. Each tablet contains phosphate, 155 mg, and potassium, 8 mEq.</td>
<td>Neutral potassium phosphate may directly inhibit bone resorption while reducing calcium absorption and urinary excretion</td>
<td>Associated acid and sodium loads limit efficacy in reducing calciuria and protecting bone density. Rapid-release forms are associated with abdominal cramping and diarrhea. Slow-release potassium phosphate may be better tolerated. A randomized, controlled trial of phosphate acid did not prevent stones. A slow-release preparation of neutral potassium phosphate was safe and effective in improving urinary chemistries and preventing bone resorption in a short randomized trial, although efficacy in preventing stones was not studied. It may overcome the disadvantages of acid and sodium phosphate preparations, but is not yet commercially available.</td>
</tr>
</tbody>
</table>

(continued on next page)
Table 2. Drug Treatment of Stone Prevention (continued)

<table>
<thead>
<tr>
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<th>Dosage</th>
<th>Benefits</th>
<th>Side Effects and Notes</th>
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</thead>
<tbody>
<tr>
<td>Magnesium supplementation</td>
<td>Magnesium inhibits calcium oxalate crystal formation and growth in vitro. Hypomagnesemia may reduce urinary citrate excretion.</td>
<td>250 mg bid for 3 to 4 weeks; if tolerated, increase dose to 250 mg tid</td>
<td>Patients with bowel disease often have decreased urinary magnesium excretion, which might contribute to stone formation.</td>
<td>Diarrhea. Efficacy of magnesium supplementation in randomized, controlled trials is lacking. It should probably be reserved for patients with low urinary magnesium excretion.</td>
</tr>
<tr>
<td>Acetohydroxamic acid</td>
<td>Inhibits activity of urease, the bacterial enzyme responsible for causing struvite stones</td>
<td>500 to 1000 mg/d, occasionally up to 3000 mg/d</td>
<td>Inhibition of urease decreases urinary alkalization and precipitation of struvite.</td>
<td>Headache is a frequent side effect to limit long-term use. 20% to 30% of patients are unable to tolerate use of the drug. Other side effects include mild hemolytic anemia, GI upset, tremulousness, dysgeusia, anxiety. Surgical removal of all struvite stone fragments is the most effective therapy and preferable to this drug. Acetohydroxamic acid does reduce stone growth but not necessarily stone events. Adequate urinary levels of the drug are not achieved if serum creatinine is &gt;176.8 mmol/L (2 mg/dL). ¶</td>
</tr>
<tr>
<td>Tiopronin (α-mercapto propionylglycine)</td>
<td>Thiol drug reduces the disulfhydryl bridge of cystine to form the more soluble drug–cysteine complex</td>
<td>1000 to 2000 mg/d</td>
<td>Solubilizes cystine</td>
<td>Rash, proteinuria, GI intolerance, pruritus, intrahepatic cholestasis, wrinkling and friability of the skin, hypoguesia, vitamin B6 deficiency. Limited sources suggest a somewhat better side effect profile than D-penicillamine. Administer vitamin B6, 50 mg/d. Check LFTs and CBC every mo when initiating therapy, then every 3 mo.**</td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>Thiol drug reduces the disulfhydryl bridge of cystine to form the more soluble drug–cysteine complex</td>
<td>500 to 1000 mg/d, occasionally up to 3000 mg/d</td>
<td>Solubilizes cystine</td>
<td>Bone marrow depression with leukopenia, thrombocytopenia, Agranulocytosis, aplastic anemia, pancytopenia, and sideroblastic anemia can be fatal. Proteinuria, dysgeusia, fever, rash, vitamin B6 deficiency, aphthous stomatitis. Give vitamin B6, 50 mg/d. Check LFTs and CBC every mo when initiating therapy, then every 3 mo.**</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; bid = twice daily; BID = twice daily; CBC = complete blood count; GERD = gastroesophageal reflux disease; GFR = glomerular filtration rate; GI = gastrointestinal; LFT = liver function tests; qd = once daily; tid = three times daily.


Patient per year in the treated group compared with no change in the placebo group (29). Potassium citrate supplementation might also be useful in “unselected” calcium stone-forming patients regardless of urinary citrate excretion. Citrate supplementation is associated with an increase in urine pH. In calcium stone disease, this increase in urine pH might lead to an increase in urine supersaturation of calcium of calcium stones in patients with reduced urinary citrate. Low urine citrate occurs with chronic metabolic acidosis, which can be caused by bowel disease, RTA, and high protein intake but is often idiopathic. In an RCT of potassium citrate in patients with calcium stones and low urinary citrate, treatment with potassium citrate, 30 to 60 mEq/d in divided doses, led to reduction of stone formation from 1.2 to 0.1 per patient per year in the treated group compared with no change in the placebo group (29). Potassium citrate supplementation might also be useful in “unselected” calcium stone-forming patients regardless of urinary citrate excretion. Citrate supplementation is associated with an increase in urine pH. In calcium stone disease, this increase in urine pH might lead to an increase in urine supersaturation of calcium.

phosphate with subsequent calcium phosphate stones (30). Adequate fluid intake is, therefore, more important in this setting, and thiazide use to lower urinary calcium excretion may be indicated if urine pH is increasing and calcium phosphate stone formation occurs. Orange juice and lemonade increase urine citrate excretion (31, 32), and drinking lemonade has been associated with fewer stone recurrences in observational studies (33).

In 1 placebo-controlled trial, at 3 years stones formed in 63.6% of participants receiving placebo and 12.9% of participants receiving a combination of potassium and magnesium citrate (34). The drug was effective regardless of whether urine citrate was low.

The potassium–magnesium citrate preparation may be better tolerated than the potassium salt alone but is currently not available. Magnesium supplementation has not been shown to be effective in patients without bowel disease (35), so reserve it for patients with inflammatory bowel disease, diarrhea, or ileostomy.

Calcium phosphate stones suggest hyperparathyroidism or RTA. Treat hyperparathyroidism with surgery, and treat RTA with potassium citrate therapy. Use potassium citrate to increase urine pH and dissolve uric acid. Use allopurinol only in patients with hyperuricosuria in whom alkalinization is difficult, poorly tolerated, or not completely effective.

Most patients with uric acid stones have a low urine pH as the major risk factor, rather than hyperuricosuria.

Even intermittent urinary alkalinization, once a day or every other day, may suffice to prevent recurrent uric acid stones (37). In the presence of low pH, reducing urinary uric acid excretion with allopurinol is relatively ineffective, whereas if pH is increased, uric acid stones will not form even in patients with substantial hyperuricosuria (38). No randomized trials have been done on urinary alkalinization for uric acid stone prevention, because of the perceived efficacy of potassium citrate therapy.

The low urine pH seen in patients with uric acid stones may be due to an abnormality in renal ammonia- genesis associated with increased body mass index and insulin resistance (39).

For cystine stones, prevention starts with high fluid intake to maintain urinary cystine concentrations less than 250 mg/L. Dietary restriction of protein and salt limits cystine excretion (40). Citrate supplementation to increase urine pH to 7.0 or more helps solubilize cystine, but a urinary pH of 7.5 or higher may be necessary to see clinical benefit. Thiol-binding drugs tiopronin and D-penicillamine reduce urinary cystine to the more soluble cystine–drug complex (41).

For struvite stones, successful treatment requires stone removal, because infected stones cannot be sterilized with antibiotics. The AUA Nephrolithiasis Clinical Guidelines Panel has recommended that struvite stones are best treated with percutaneous nephrolithotomy (21).
removal is often followed by long courses (4 to 6 months) of suppressive low-dose antibiotics, such as nitrofurantoin or sulfamethoxazole–trimethoprim. If residual stone material is left in place, use acetohydroxamic acid to inhibit bacterial urease activity and decrease rates of stone growth. In 1 double-blind, placebo-controlled study, the drug was evaluated in 94 patients with chronic urinary tract infection. Stone growth occurred in 17% of the acetohydroxamic acid group and in 46% of the placebo group. "Intolerable" side effects were experienced by 22.2% of patients in the acetohydroxamic acid group (42). Evaluate patients with struvite stones for underlyiing metabolic abnormalities, such as low urine volume, hypercalcicuria, and hypocitraturia, which occur in as many as 40% of patients, and treat these abnormalities.

What are the complications of nephrolithiasis and how should clinicians treat them?

Patients with calcium stones and hypercalcicuria have been shown to have decreased bone density (43) and a higher rate of bone fracture (25). Thiazides put patients with hypercalcicuria into positive calcium balance and increase bone mineral density (BMD) (28). Stones are associated with chronic kidney disease, although the nature of this relationship is not clearly understood (44).

How should clinicians follow patients with nephrolithiasis?

Consider screening patients with multiple episodes of asymptomatic stone disease every 6 to 12 months initially and then less frequently with serial ultrasonography, or in the case of calcium stones, with plain abdominal radiography. Computed tomography is more sensitive, but the cumulative dose of radiation may not be acceptable. The potential value of screening is that it may aid decisions about intensifying preventive therapy, motivate patients to adhere to recommendations, and allow elective scheduling of urologic interventions instead of during or after episodes of renal colic, but no data exist on the effectiveness of screening.

In 1 study of 107 patients with asymptomatic stones with a mean follow-up of 31.6 months, 68.2% remained asymptomatic. A symptomatic event developed in 31.8%. Of these, almost one half had spontaneous passage, whereas the rest required urologic intervention. Cumulative 5-year probability of a symptomatic event was 48.5% (45).

In a retrospective study of 76 patients with asymptomatic stones, the cumulative probability of an episode of renal colic was 39% at 5 years and 51% at 10 years. Fourteen patients (18.4%) required ESWL or other urologic interventions (46).

One study suggested that a policy of observation was associated with a greater risk for requiring more invasive procedures. In 1 RCT, 228 patients with small (<15 mm total diameter) asymptomatic calyceal stones were randomly assigned to ESWL or observation. With a mean follow-up of 2.2 years, 28% of the patients in the ESWL group were stone-free, compared with 17% in the observation group. Ten patients in the observation group required invasive procedures, compared with none in the ESWL group. Prophylactic ESWL, therefore, had a slight advantage (47).

Preventive Treatment...

Prevent recurrent stones with a stepped approach. Increased fluid intake is always appropriate because it is effective, safe, and inexpensive. Dietary changes may be added if recurrence continues. Pharmacologic therapy is appropriate for patients unable to adhere to dietary changes or if dietary therapy is ineffective. If recurrence continues, consider screening for asymptomatic stones with ultrasonography or plain radiography for calcium stones, recognizing that little evidence supports the value of screening.

CLINICAL BOTTOM LINE
What do professional organizations recommend regarding the care of patients with nephrolithiasis?

The National Institutes of Health last published a consensus document in 1980 (14). The recommendations made at that time have not evolved substantially (48). Surgical therapy has improved dramatically, radiologic imaging is vastly superior, but medical therapy has not advanced very much, with the exception of not restricting calcium intake in calcium stone–forming patients. The AUA guidelines address surgical management rather than preventive therapy (20, 49). In 2007, the American Urological Association and the European Association of Urology cooperated to create joint recommendations for managing patients with suspected kidney stones (21, 50).

How should clinicians educate patients with nephrolithiasis?

Patients can be referred to the Web resources listed in the Toolkit. A useful book about preventing stones, written for lay people and co-authored by a nephrologist, a urologist and a dietician, is available (51).
WHAT YOU SHOULD KNOW ABOUT KIDNEY STONES

What is a kidney stone?

- A kidney stone is a solid piece of material that forms in a kidney from substances in the urine.
- A stone may stay in the kidney or break loose and move down the urinary tract. A small stone may pass all the way out of the body without too much pain.
- A larger stone may get stuck. It can block the flow of urine and cause great pain.

What can my doctor do about a large stone?

- If you have a stone that does not pass by itself, your doctor may need to remove it. Your doctor may choose one of the following ways to do this.

**Shock Waves**

- A machine sends shock waves to the kidney stone. This breaks the stone into small pieces that pass out of your body with your urine. This method is called extracorporeal shock wave lithotripsy (ESWL). Lithotripsy is a Greek word that means stone crushing.
- With one type of shock machine, you sit in a tub of water. With the other type, you lie on a table. A technician directs the sound waves to the stone.

**Tunnel Surgery**

- The doctor makes a small cut on your back. A special instrument passes through a narrow tunnel to the stone and removes it. This method is called percutaneous nephrolithotomy.

**Ureteroscope**

- A ureteroscope looks like a long wire. The doctor puts it into the patient’s urethra through the bladder and up the ureter, and directs it to the stone. This is done using a camera that lets the doctor see the stone. A tiny cage catches the stone and pulls it out, or the doctor may be able to destroy it with a laser.
- Ask your doctor which method is right for you.

Points to Remember

- Most stones pass out of the body without a doctor’s help.
- See your doctor if you have severe pain in your back or side that will not go away.
- See your doctor if you have blood in your urine—the urine will look pink.
- In the future, after the stone is gone, drink lots of water to prevent more kidney stones from forming.
- Talk with your doctor about other ways to keep from getting more stones.

For More Information

kidney.niddk.nih.gov/kudiseases/pubs/stones_ez/index.htm
National Institute of Diabetes and Digestive and Kidney Diseases: What I Need to Know About Kidney Stones

kidney.niddk.nih.gov/spanish/pubs/stones_ez/index.htm
National Institute of Diabetes and Digestive and Kidney Diseases: What I Need to Know About Kidney Stones (Spanish)
1. In a patient with hypercalciuric nephrolithiasis, which of the following is associated with increased risk for stone formation?
   A. Low-sodium diet
   B. Low-calcium diet
   C. Low-oxalate diet
   D. Low-protein diet
   E. Low-purine diet

2. A 39-year-old male carpenter presents to the emergency department with a 4-hour history of gradually worsening right flank and right upper quadrant pain radiating to the right lower quadrant and into the right testicle. He vomits once shortly after arrival. He does not have fever or chills but has mild dysuria.

   On examination, the patient is restless and temperature is 37°C (98.6°F). Abdominal examination reveals mild right costovertebral angle tenderness, but no abdominal guarding. Genitalia are normal. The serum creatinine concentration is 79.56 µmol/L (0.9 mg/dL). Urinalysis reveals more than 50 erythrocytes/hpf, 3 to 5 leukocytes/hpf, and occasional calcium oxalate crystals. You suspect that a renal stone is causing the colicky pain and hematuria.

   What radiologic procedure will best confirm the diagnosis?
   A. Plain radiography of the abdomen
   B. Intravenous pyelography
   C. Renal ultrasonography
   D. Noncontrast spiral computed tomography

3. A 28-year-old woman presents for evaluation of recurrent kidney stones that she says “contain calcium.” She estimates that she has passed four stones during the past 4 years. She currently has no symptoms of renal colic. For several years, she has had dry eyes and dry mouth. She also describes symptoms of Raynaud’s phenomenon. Crohn disease was diagnosed 10 years ago; the patient is currently asymptomatic and passes 1 formed stool daily. She takes no medications. There is no family history of renal stone disease.

   On examination, the patient is alert and healthy. Blood pressure is 115/74 mm Hg, pulse rate is 72/min, and temperature is 37°C (98.6°F). The skin is clear, and the joints are normal. The lungs are clear. Cardiac examination shows regular sinus rhythm and no murmur. The liver and spleen are not palpable, and the abdomen is not tender.

   Plain abdominal radiography shows multiple calcifications overlying both renal shadows. Laboratory study results are as follows: hemoglobin, 13.2 g/dL; hematocrit, 39%; leukocyte count, 7.4 × 10^9 cells/µL; blood urea nitrogen, 6.4 mmol/L (18 mg/dL); serum creatinine, 79.56 µmol/L (0.9 mg/dL); serum sodium, 138 mmol/L; serum potassium, 2.8 mmol/L; serum chloride, 109 mmol/L; serum bicarbonate, 19 mmol/L; serum calcium, 2.3 mmol/L (9.1 mg/dL); serum phosphorus, 3.2 mg/dL; urinalysis: pH, 6.0, specific gravity, 1.020, trace hematuria, no proteinuria; arterial blood: pH, 7.29.

   What is the most likely cause of this patient’s renal stone disease?
   A. Idiopathic hypercalciuria
   B. Primary hyperparathyroidism
   C. Distal renal tubular acidosis
   D. Enteric hyperoxaluria

4. A 40-year-old man has recurrent nephrolithiasis due to idiopathic hypercalciuria. He has had more than 40 calcium oxalate stones in the past 5 years. He starts taking hydrochlorothiazide therapy and a low-sodium diet. During treatment, his 24-hour urinary calcium concentration decreases from 385 mg/d to 180 mg/d. No new stones have formed in the past 6 months; however, hypokalemia has developed (serum potassium level, 2.9 mmol/L).

   Taking the hypokalemia into account, what therapy should the patient receive for hypercalciuric stone disease?
   A. High-potassium diet plus hydrochlorothiazide
   B. Acetazolamide plus hydrochlorothiazide
   C. Magnesium oxide plus hydrochlorothiazide
   D. Amiloride plus hydrochlorothiazide

5. A 64-year-old woman comes for a follow-up visit after an episode of kidney stones 2 weeks ago. During the episode, she went to the emergency department and was treated with nonsteroidal anti-inflammatory drugs and fluids. Spiral abdominal CT performed at that time revealed a 3-mm nonobstructing calculus in the midleft ureter. She also has osteoporosis.

   Laboratory study results are as follows: blood urea nitrogen, 7.5 mmol/L (21 mg/dL); uric acid, 0.3 mmol/L; creatinine, 141.47 µmol/L (1.6 mg/dL); sodium, 137 mmol/L; potassium, 3.8 mmol/L; chloride, 105 mmol/L; bicarbonate, 24 mmol/L; albumin, 4.1 g/L; calcium, 2.87 mmol/L (11.5 mg/dL); phosphorus, 0.39 mmol/L (1.2 mg/dL); urinalysis: pH, 5.5, 1+ blood.

   Which of the following is the most appropriate management for this patient’s kidney stones?
   A. Decrease dietary calcium to <1 g/d
   B. Refer for parathyroidectomy
   C. Refer for stone removal
   D. Initiate potassium citrate therapy
   E. Observe

Questions are largely from the ACP’s Medical Knowledge Self-Assessment Program (MKSAP). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.