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Nephrolithiasis

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SYNOPSIS

Kidney stones affect over 5% of adults in the United States, and the prevalence is rising. The fundamental cause for all stones is supersaturation of urine with respect to the stone components; factors affecting solubility include urine volume, pH, and total solute excretion. Calcium stones are the most common, in adults and children, and are associated with several metabolic disorders, the most common of which is idiopathic hypercalciuria. Therapy to prevent stones rests on lowering supersaturation, using both diet and medication. Effective treatment decreases stone recurrence and need for procedures for stone removal.

Keywords

kidney stones; calcium oxalate; kidney calculi

Nephrolithiasis is the most common chronic kidney condition, after hypertension, and also an ancient one: treatments for patients with stones have been described since the earliest medical texts. Stones are a preventable cause of morbidity, accounting for over 5 billion dollars in economic costs in the United States each year, both for hospitalization and procedures to remove symptomatic stones, as well as time lost from work[1].

EPIDEMIOLOGY

Stones are more common in men than in women, and stone types differ somewhat between the sexes (Table 1); in children, reported frequency of stone types differs modestly from those in adults, but the sexes are affected about equally[2]. Periodic studies of the United States population, called the National Health and Nutrition Examination Surveys, show that the prevalence of stones has been increasing over the past 30 years in both sexes[3]. The most recent survey found that by the seventh decade almost 12% of white men and 6% of white women reported having had a kidney stone; the prevalence in African Americans is less than half that in Caucasians, but has also been increasing. These surveys only include adults, so that prevalence rates in children are not as clear; however in the earliest cohort, ages 20–29,

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prevalence was 1.3% in males and 2% in females, giving an upper bound to prevalence prior to age 20.

The reasons for the increasing prevalence are not clear, but one factor may be increased rates of obesity, as risk of stones increases along with body mass index and waist circumference, especially in women[4]. Both inherited and environmental factors play a role in stone formation. The role of inheritance is clearest in monogenic diseases such as cystinuria, Dent's disease and primary hyperoxaluria[5], but there is a clear familial tendency in idiopathic stone formation as well[6], although the genes involved are currently unknown. Environmental factors, especially diet[6;7] play an important role in expression of the tendency to stone formation.

Calcium oxalate (CaOx) is the predominant component of most stones (Table 1), either as the monohydrate (whewellite) or dihydrate (weddelite), often admixed with some calcium phosphate (CaP) which may form the initial nidus of the stone. Stones composed predominantly of CaP (as apatite or brushite) are less common, and are seen more frequently in women. Rarely, insoluble drugs, such as indinavir, triamterene or ephedrine, may form stones[8].

Recurrence is the rule after a first stone, in the absence of preventive treatment. Probability of recurrence for idiopathic calcium stones after the initial event is 40–50% at 5 years and 50–60% by 10 years. The recurrence rate for stones associated with systemic diseases such as cystinuria or primary hyperparathyroidism is often higher.

Stone disease is associated with an increased risk of hypertension, especially in women; the mechanism is not known[9]. Some forms of nephrolithiasis, especially those associated with systemic disease, are associated with loss of renal function as well[10].

ACUTE PRESENTATION AND MANAGEMENT

The initial presentation of nephrolithiasis is often with renal colic - severe pain caused by stone passage - triggered by movement of a stone from the renal pelvis into the ureter, which leads to ureteral spasm and possibly obstruction. Pain starts in the flank area, and progresses downward and anteriorly into the genital region as the stone moves down the ureter. The pain is not usually aggravated or alleviated by change of position, and may be accompanied by nausea and vomiting. Hematuria is always present, but may be microscopic. If the stone is lodged at the uretero-vesical junction, it can cause a sensation of urinary frequency and urgency. All symptoms are relieved quite abruptly when the stone moves out of the ureter into the bladder, and passes. The differential diagnosis for flank pain and hematuria is not long: papillary necrosis with passage of a sloughed papilla, renal emboli, renal tumor, sometimes urinary tract infection. Symptoms in children can be similar, but may consist only of hematuria, generalized abdominal pain or urinary tract infection.

The initial evaluation of patients with suspected acute stone passage optimally includes non-contrast helical CT with 5 mm slices or less, which can accurately visualize the size and location of stones in the urinary tract. A KUB can often visualize calcium-containing stones in the kidney or ureter, including struvite stones, but uric acid or other purine stones may be radiolucent, and cystine stones often visualize poorly as well. Stones less than 5 mm in diameter will usually pass spontaneously, although it may require several weeks of conservative management, while about 50% of stones larger than 5 mm require urologic intervention for removal, and those above 10 mm are very unlikely to pass unaided[11]. Initial management of stones less than 5 mm in patients without anatomic abnormalities of the urinary tract is watchful waiting, to allow time for stone passage. Pain can be controlled with use of NSAIDS or narcotic agents[12]. Presence of any signs of urinary tract infection, inability to take oral fluids, or obstruction of a single functioning kidney requires hospitalization and active management. Some studies suggest that use of an α-(1)-adrenoreceptor antagonist such as tamsulosin may

hasten the time to stone passage in appropriately selected patients[13]. Patients should be instructed to strain their urine to recover passed stones for analysis.

Large stones in the renal pelvis may present with hematuria, infection or loss of renal function rather than colic. Stones with a branched configuration filling two or more calyces are called staghorn calculi. Struvite stones often present in this fashion, as may cystine stones.

Urologic management

There are several options available for surgical treatment of the 10–20% of symptomatic stones that fail to pass spontaneously[14]. The appropriate modality for a given case depends on the size, location and type of stone; the presence of anatomical abnormalities or infection also may influence the choice. Extra-corporeal shock wave lithotripsy (ESWL), which uses sound waves to fragment stones into small pieces that can be easily passed, is effective for most stones less than 2 cm in size, although cystine stones and phosphate stones may be resistant to fragmentation. Larger stones, particularly those composed of cystine or struvite, can be approached via percutaneous access through a small flank incision, allowing direct visualization and intracorporeal lithotripsy for stone disruption, and removal of fragments. Ureteroscopy is becoming increasingly useful for stones in the ureter and renal pelvis, and may be used with laser lithotripsy as well. The American Urological Association (www.auanet.org) has developed evidence-based recommendations to guide the choice of modality.

PHYSICOCHEMICAL FACTORS IN STONE FORMATION

Supersaturation

Initiation and growth of stones requires that crystals must form and be retained within the kidney. In order for crystals to form, urine must be supersaturated with respect to the stone material, meaning that concentrations are higher than the thermodynamic solubility for that substance. Supersaturation for stone salts is often expressed as the ratio of the concentration in urine to the known solubility; a level greater than one indicates that urine is supersaturated with a given substance. Levels of urinary supersaturation correlate with the type of stone formed[15], and lowering supersaturation is effective for preventing stone recurrence.

For CaOx, the most important determinants of urinary supersaturation are total daily calcium excretion and urine volume, in other words, urine calcium concentration[16]. In a large cohort study of both men and women, relative risk for stone formation was strongly correlated with urine calcium concentration in a continuous manner[17]. Oxalate excretion has a somewhat less marked effect on supersaturation until levels are frankly elevated. However, urine in both normal subjects and stone formers is almost always supersaturated with respect to CaOx, although more markedly in stone formers, so that for CaOx, at least, supersaturation is necessary but not sufficient for stone formation.

In addition to solute concentration, urine pH is a critically important determinant of solubility for CaP, uric acid and cystine[16]. CaP solubility drops as urine pH rises above 6, while uric acid solubility increases. Disorders affecting urine pH regulation are often found in patients with these types of stones. Solubility of cystine is also affected by pH, increasing as pH rises.

Inhibitors of crystallization

As noted, urinary supersaturation with respect to CaOx is frequently found in normal subjects. One reason stone formation is not more widespread may be the presence of crystallization inhibitors in urine, which can impede the nucleation, growth and aggregation of crystals in vitro, and have been experimentally shown to interfere with their attachment to renal epithelial

cells[18;19]. Small molecules such as citrate and pyrophosphate, as well as at least a dozen proteins and glycosaminoglycans have been isolated from urine and found to have inhibitory activity with respect to one or more of these aspects of crystallization. Whether abnormalities of these inhibitors play a role in stone formation is not clear; some of these macromolecules are found in the matrix of stones, and might promote crystal retention or organization under some circumstances. Differences have been found in the types of inhibitor molecules excreted by stone formers compared to normal subjects[20].

Renal pathology in stone formers

Retention of crystals within the kidney is necessary for stone formation. Recent studies of endoscopic renal papillary biopsies, carried out during percutaneous nephrolithotomy for treatment of stones, have provided information on sites of crystal attachment. There are several patterns of crystal deposition in kidneys of stone formers, associated with specific stone types.

Patients with idiopathic CaOx stones have white deposits on their papillae, called Randall's plaques[21]. Plaque deposits are found in non-stone formers also, but their abundance is much less. Biopsy of these areas reveals interstitial deposits of CaP in the form of biological apatite, which start in the basement membrane of the thin loops of Henle; the deposits also contain layers of protein matrix. Deposits can extend down to the tip of the papilla, and if the overlying urothelium is denuded, the exposed plaque can become an attachment site for stones[22]. Stones appear to start as deposits of amorphous calcium phosphate overlying the exposed plaque, interspersed with urinary proteins. With time, more layers of protein and mineral deposit, and the mineral phase becomes predominantly CaOx. Most idiopathic CaOx stones appear to form on plaque; the amount of plaque covering the papilla correlates with urine calcium and volume[23].

By contrast, patients with stones that contain mainly CaP (apatite or brushite) have a different picture on papillary biopsy[24]. Although a modest amount of Randall's plaque may be found on their papillae, stones are not attached to plaque. Instead, many collecting ducts are filled with crystal deposits made of apatite that fill the tubule lumen, and may protrude from the mouths of the ducts of Bellini. Stones may be attached to these crystal plugs, or are sometimes suburothelial. The papillary morphology is often abnormal, with retraction and scarring. A similar picture, thought with more generalized papillary damage, is seen in patients with renal tubular acidosis, who form apatite stones[25]. Cystine stone formers have a closely related pathology, although the crystal deposits contain mainly cystine, with some admixed CaP[26].

Overall, most stone formers studied so far have crystal deposits in their medullary collecting ducts, with the exception of those with idiopathic CaOx stones, who have not been found to have intra-tubular deposits, but instead abundant deposits of apatite in the papillary interstitium. Collecting duct deposits are presumably driven by supersaturation, but the etiology of interstitial plaque is not yet known. Whether treatments for stone affect papillary histology is also unknown. The appearance of papillae in stone forming children has not been studied as yet.

EVALUATION OF STONE FORMERS

Recurrent stone formation is associated with the potential for renal injury from obstruction, interventions to remove stones, or associated infection, as well as from the tissue changes noted above[27], particularly in patients with systemic diseases, such as cystinuria or renal tubular acidosis. In addition, stone passage or surgical treatment is costly in time lost from work, and use of medical resources[1]. Preventive therapy significantly reduces recurrence rates, so it is worthwhile to evaluate patients for underlying causes of stone formation, to guide appropriate

treatment. Table 2 is an outline of our evaluation strategy, which should be done as an outpatient, after the acute episode resolves. The same strategy applies to children with stones.

Any stone material passed should be analyzed. X-rays, especially non-contrast CT scans, can define the location, size and number of stones remaining in the kidneys; coronal sections are particularly helpful. A patient with several stones present on X-ray is already defined as a recurrent stone former. They also allow one to judge the success of treatment by the yardstick of new stone formation or growth of old stones. For patients with a single episode of calcium stone, or if stone type is unknown, initial evaluation should rule out systemic disorders such as hyperparathyroidism, distal renal tubular acidosis or hyperoxaluria; conservative therapy with increased fluids is indicated for patients with a single probable calcium stone and without systemic illness (Table 2).

Preventive treatment, indicated for patients with non-calcium stones and in patients with recurrent calcium stones, relies on measures that decrease supersaturation, so 24-hour urines should be collected once or optimally twice prior to starting therapy to assess for factors leading to supersaturation. Several commercial labs, including Dianon, Litholink, Urocor, and Mission, offer urine testing for stone formers which is cost effective and includes the analytes shown in Table 2 and Table 3 as well as calculated supersaturations for CaOx, CaP and uric acid. Although increased solute concentrations correlate with supersaturation, it is difficult to accurately estimate supersaturation without a computer algorithm, particularly for solutes whose solubilities are pH dependent. Normal ranges for urine solute excretion are suggested in Table 3, however there is a great deal of overlap between stone formers and non-stone formers, and these values should be thought of as continuous risk factors. After treatment has been prescribed, another 24- hour urine should be collected in 4–8 weeks to evaluate the results. Successful therapy should decrease supersaturation into the normal or low-normal range; in practice, lower is better.

Normal excretions of calcium, oxalate, citrate and uric acid are higher in children than in adults, when factored by urine creatinine, and urine pH is higher as well[28;29]; the excretion rates fall during puberty, reaching adult levels in the late teens. Supersaturation with respect to CaOx is similar in both normal adults and children, but supersaturation with respect to CaP is higher and uric acid is lower in children because of their higher urine pH. Although spot urine samples are sometimes used for diagnosis in very young children, they cannot give the same accuracy as 24-hour collections due to variation in excretion of many solutes over the feeding cycle.

CALCIUM STONES

By far the most common stones in clinical practice, calcium stones are associated with a number of metabolic derangements (Table 4), the most common of which is hypercalciuria. Many rare monogenic diseases are associated with hypercalciuria[5;30], but the majority of cases in stone formers are due to either idiopathic hypercalciuria or primary hyperparathyroidism.

Primary hyperparathyroidism

About 10–20% of patients with primary hyperparathyroidism (PHPT) make stones[31], and patients with PHPT account for about 5% of calcium stone formers[32]. They are diagnosed by detection of an elevated serum calcium level, which is often only modestly increased, usually between 10–11.5 mg/dl, usually accompanied by a low serum phosphorus level, and a serum parathyroid hormone (PTH) level that is elevated or not suppressed. Repeated measurements may be needed to confirm the diagnosis. At surgery, 85% will be found to have a single adenoma, the rest having hyperplasia of multiple glands. Parathyroid cancer occurs in less than 1% of patients, and is rarely a cause of stones. Surgery results in normalization of serum calcium

if all affected glands have been removed, and urine calcium falls markedly, although it may remain above normal in a minority of patients.

Hypercalcemia is the result of the effects of PTH to increase bone turnover and renal reabsorption of calcium directly, and intestinal absorption of calcium indirectly through activation of vitamin D. All these actions lead to increased entry of calcium into extracellular fluid, with a resulting increase in filtered load of calcium in the kidney. PTH stimulates increased calcium reabsorption in the distal tubule, but at other sites in the nephron, notably thick ascending limb, calcium reabsorption is depressed because of activation of the calcium sensing receptor by hypercalcemia. Hypercalciuria causes the urine in PHPT patients to be supersaturated with respect to both CaOx and CaP, and although most stones are predominantly CaOx, there is an increased incidence of CaP stones. Surgery leads to a marked drop in stone recurrence and need for stone procedures.

Hypercalcemia from other causes leads to suppressed PTH levels, so high serum and urine calcium in a patient with non-suppressed PTH confirms the diagnosis of PHPT. If urine calcium is not elevated, familial hypocalciuric hypercalcemia should be considered. Use of thiazide or lithium should be excluded.

Idiopathic hypercalciuria

Elevated urine calcium excretion is the most common abnormality found in both adults and children with kidney stones; 30–60% of adult stone formers have hypercalciuria, as do a similar or greater percentage of pediatric stone formers[33]. In children it may also manifest as isolated hematuria[34]. The term idiopathic hypercalciuria (IH) is applied to cases in which serum calcium is normal, and other causes of increased calcium excretion, such as vitamin D excess, renal tubular acidosis, granulomatous diseases such as sarcoid, steroid use, hyperthyroidism and so forth have been excluded. The syndrome is familial, illustrated by a study of 9 patients with IH and stones; hypercalciuria was found in 19 of 44 first-degree relatives[35], in multiple generations. The trait is likely polygenic, and the genes contributing to the phenotype may vary from individual to individual[30].

IH involves abnormal calcium handling by gut, kidney and bone. Patients with IH often have elevated serum 1,25-dihydroxy vitamin D levels, and an increase in intestinal calcium absorption[36]. Their kidneys exhibit a decreased ability to reabsorb filtered calcium[37], and if placed on a calcium-restricted diet they may excrete calcium in excess of absorption, thereby losing calcium from bone stores[38]. It is therefore not surprising that studies have frequently shown decreased bone density in IH patients, and an increased risk for fractures, especially vertebral[39]. A decreased renal reabsorption of phosphate may also occur, and serum phosphate levels are often somewhat low in patients with IH.

High dietary sodium and sugar intake increase urine calcium excretion. High protein intake does the same, probably because of the effect of the acid load created by protein intake. On the other hand, higher dietary calcium intake (800–1200 mg/day) has been associated with decreased stone formation compared with lower calcium intake[7], while calcium supplements may raise the risk of stones, especially if taken away from meals[40]. A recent randomized controlled trial compared a diet low in calcium with one low in sodium and animal protein but containing 1200 mg/day of calcium for prevention of recurrent stones in male calcium stone formers[41] (Table 5). Patients on the low protein, low sodium, normal calcium diet had significant decreases in urine calcium and oxalate excretion, and in CaOx supersaturation; no changes were seen in those on the low calcium diet. After 5 years on the diets, stone recurrence was significantly lower among patients on the low salt, low protein, normal calcium diet compared to those on low calcium diet. Adherence with such a diet may be difficult, however.

Treatment of stones in patients with IH should include advice to increase fluids, in order to keep urine volume over 2 liters/day (Table 5). A randomized trial has shown that this treatment is effective at preventing recurrence in patients with a single episode of calcium stone formation[42]. Epidemiologic studies looking at specific fluids found that only apple and grapefruit juices were associated with increased risk of stones[43]. Sodium intake should be restricted to 100 mmol/day, or lower if possible, and high protein intake (> 1gm/kg/day) should be avoided, as should excessive consumption of carbohydrates. For those with recurrent stones, thiazide diuretics, which can lower urine calcium, are the treatment of choice. Three randomized prospective trials of thiazide have shown significant protection from recurrent calcium stone compared with placebo[44–46]. The mechanism appears to be, at least in part, an increase in calcium absorption in the proximal tubule, induced by volume contraction. Balance studies have shown that thiazide treatment results in a positive calcium balance in stone patients[47]. Similar measures can be used to treat calcium stones in children, including the use of thiazide, which can lower urine calcium and lead to resolution of hematuria in many hypercalciuric subjects[34;48].

Hypocitraturia

Low urinary citrate excretion may occur in a large fraction of stone formers, as a consequence of acidosis or potassium depletion, or as an idiopathic disorder; it frequently co-exists with other metabolic disorders that increase stone risk. Citrate can inhibit stone formation because of its ability to chelate calcium, forming a soluble complex which prevents calcium binding with oxalate or phosphate. In addition, citrate can act on the surface of preformed CaOx or CaP crystals as a growth inhibitor.

Citrate has been used as a treatment for idiopathic calcium stones (Table 5), especially in those with low urine citrate. It is usually given in the form of potassium alkali (potassium citrate or bicarbonate) to avoid the calciuric effect of sodium. Citrate treatment resulted in a significant decrease in stone formation in the two trials that used the potassium salt[49;50], but not in the trial in which the sodium form was used[51]. Citrate treatment can raise the urine pH, and this will increase the risk for CaP stones if urine calcium remains high; we usually avoid treatment with citrate when the urine pH is above 6.5 or if CaP supersaturation remains elevated.

Hyperoxaluria

Mild hyperoxaluria is rather common among stone formers, and may be due to increased oxalate absorption fostered by low calcium diet[52]. Dietary precursors of oxalate, including large amounts of ascorbic acid or protein, may also increase oxalate excretion. However, to date, epidemiologic studies have not implicated oxalate intake per se with risk for stone formation[53], and no randomized trials have been done to test the effect of low oxalate diet on stone recurrence. In part, the absence of epidemiologic and trial data is due to methodological problems with accurate determination of oxalate in foods. Restriction of high oxalate foods such as spinach is sensible in those with elevated oxalate excretion, and these patients should be cautioned against low calcium diet and high doses of vitamin C. The role of oxalate degrading bacteria in stool is a subject of current research; lack of such bacteria in the gut flora may permit increased oxalate absorption and eventual renal excretion[54].

Primary hyperoxaluria (PH)—Type 1 (PH1) and type 2 (PH2) primary hyperoxaluria are caused by rare autosomal recessive genetic disorders of oxalate synthesis[52]. PH1 (OMIM 259900), the most common, is caused by deficiency of a liver-specific enzyme, alanine:glyoxylate aminotransferase (AGT) which leads to impaired glyoxylate metabolism in the peroxisomes of hepatocytes. The end result is an increase in synthesis of oxalate, a metabolic end-product; urine oxalate excretion is 100–300 mg/day, and urine glycolate may also be elevated. The clinical manifestations include kidney stones, nephrocalcinosis and renal

failure, and symptoms often begin in childhood. High doses of pyridoxine lower oxalate production and excretion in some patients; in those with persistent hyperoxaluria definitive treatment is liver transplantation which supplies a functional enzyme. The diagnosis should be suspected in patients with early onset of CaOx stones, or those with renal failure and a history of stones, although onset of symptoms in adulthood may occur. PH2 (OMIM 260000), which accounts for about 20% of cases of primary hyperoxaluria, results from deficiency of the enzymes glyoxylate reductase and hydroxypyruvate reductase, caused by the lack of a single cytosolic protein with multiple enzyme activities. The clinical manifestations are similar to PH1, but the course seems to be milder, with less renal failure. Diagnosis depends on metabolic workup and genetic testing when appropriate[55]. An international registry exists for patients with primary hyperoxaluria, to improve the diagnosis and treatment of patients with these rare disorders[56].

Enteric hyperoxaluria—Augmented absorption of dietary oxalate occurs in all forms of small bowel and pancreatico-biliary disease that result in fat malabsorption, particularly ileal resection or bypass, provided that the colon is present and is receiving small bowel effluent[57]. Stone formation is increased in these patients, both because of the increased oxalate excretion and because of the low urine volume and decreased citrate excretion that occurs in patients with diarrheal states. Modern bariatric surgery also leads to an increase in urine oxalate excretion[58], and stone formation may be a complication of this procedure. Treatment measures include a diet reduced in fat and oxalate, increased calcium intake with meals to bind oxalate and prevent absorption, and additional fluid intake. Potassium alkali may be helpful, and other oxalate binders, such as cholestyramine, may also be used.

Hyperuricosuria

Elevated urine uric acid excretion may be seen in patients with CaOx stones, often as a result of excessive protein intake. Myeloproliferative states and uricosuric drugs may be contributing factors in some patients. Hyperuricosuria decreases the solubility of CaOx and promotes stones. Patients with hyperuricosuric calcium stones differ from patients with gout and uric acid stones in having a higher urine pH, as well as (paradoxically) a generally higher urine uric acid level[59]. Allopurinol was shown to decrease calcium stone recurrence in such patients in a randomized controlled trial (Table 5)[60]; decreased protein intake is also helpful.

Calcium phosphate stones and renal tubular acidosis

Most calcium stones are predominantly composed of CaOx, with small amounts of admixed CaP. Stones that contain over 50% CaP are uncommon (Table 1), and form when urinary supersaturation with respect to CaP is persistently elevated. The major determinants of CaP supersaturation are alkaline urine pH (>6.3) combined with hypercalciuria[61]. This is seen in patients with distal renal tubular acidosis, whether genetic or acquired, but most patients with CaP stones do not have metabolic acidosis and the cause of their persistently alkaline urine pH is unclear. CaP stones are associated with a more destructive renal pathology[25;62], and also with an increased need for procedures to remove them, particularly ESWL. For unclear reasons, the numbers of CaP stones have been increasing over the past 3 decades. Treatments that lower urine supersaturation with respect to brushite, such as fluid or thiazide, are effective in preventing CaP stones. Use of alkaline citrate should be monitored carefully to avoid raising urine pH further. Unfortunately, there is no safe method of lowering urine pH therapeutically.

URIC ACID AND OTHER PURINE STONES

Uric acid stones

The majority of uric acid stones in adults are not associated with hyperuricosuria, but rather with decreased uric acid solubility because of low urine pH (Table 6). Uric acid stones are

increased in patients with diarrheal illness[63], diabetes[64;65], obesity[66;67], gout, and the metabolic syndrome[68]. The common factor is persistently acid urine. The solubility of undissociated uric acid is only 90 mg/L, and at a pH below the pKa of 5.35 over half the uric acid present will be in the undissociated form; thus a normal daily uric acid excretion of 500 mg could not be kept in solution with a urine volume under 3 liters. Diarrhea lowers urine pH because of loss of alkali in the stool. In the other groups of uric acid stone formers, persistently acid urine has been linked to impaired ammonia synthesis secondary to insulin resistance. Insulin stimulates ammonia synthesis in normal subjects. Patients with recurrent uric acid stones who were not diabetic have been found to be insulin resistant, and the tendency to excrete an acid urine correlated with the degree of insulin resistance[68]. Uric acid stone formers have a defect in ammonia excretion both at baseline and in response to acid load[69]. Thus, uric acid stone formation may be a manifestation of the metabolic syndrome.

Prevention of recurrent uric acid stones requires alkalinization of the urine. Potassium salts are preferred, in doses of 10–20 meq 2–3 times daily; increased fluid is usually advisable as well, to aid in solubilizing uric acid. Urine pH should be raised to 6–6.5, which will markedly decrease urinary supersaturation with respect to uric acid, and decrease stone recurrence. Serum potassium should be monitored, particularly in diabetics, to avoid hyperkalemia. If urine uric acid excretion is elevated, dietary protein restriction is advised.

Children with uric acid stones may have low urine pH and insulin resistance, as in adults. However, in patients with uric acid stones, hyperuricemia and hyperuricosuria, consideration should be given to inherited syndromes of uric acid overproduction, such as deficiency of hypoxanthine-guanine phosphoribosyltansferase (HGPRT) (OMIM 308000), which is X-linked. Complete deficiency of this enzyme, Lesch-Nyhan syndrome, also results in mental retardation and self-mutilation, but incomplete deficiency may present with uric acid stones and gout in adolescence or adult life. Phosphoribosyl pyrophosphate synthetase superactivity (OMIM 300661) is a second X-linked disorder resulting in hyperuricemia, gout, and uric acid stones.

Rare purine stones

Pure uric acid stones are radiolucent on plain abdominal X-rays, but are easily seen on non-contrast CT. Other radiolucent stones include xanthine or 2,8-dihydroxyadenine stones, and stones due to drugs. Xanthine stones form in patients with severe hyperuricemia taking allopurinol, or in those with the rare inherited forms of xanthinuria, while 2,8-dihydroxyadenine urolithiasis occurs in patients with a deficiency of adenine phosphoribosyl transferase (APRT) (OMIM 102600). These stones do not respond to the usual treatment for uric acid stones. Patients with APRT deficiency can be treated with allopurinol, however.

Ammonium acid urate stones

Ammonium acid urate stones are rare in developed countries, though they are more common in developing countries, often seen as bladder stones in children. They are associated with diarrheal illness, including laxative abuse and bowel resection, and with hypokalemia. They are radiolucent if pure, but are often admixed with other minerals. Correction of hypokalemia and increased fluid intake, with control of diarrhea if possible, are therapeutic.

CYSTINE STONES

Cystine stones are found in patients with inherited defects of dibasic amino acid transport in the kidney and intestine, leading to increased urinary excretion of lysine, ornithine, cystine and arginine because of defective reabsorption in the nephron (Table 6). The limited solubility of cystine can result in stone formation. Cystinuria is an autosomal recessive disorder, due to

defects in either SLC3A1 (OMIM 220100) (Type I or type A) or SLC7A9 (OMIM 604144) (Type non-I or type B). The proteins encoded by these genes form a hetero-dimer, which is responsible for cystine transport at the apical membrane. The two types are clinically indistinguishable with respect to age of stone onset (mean age of first stone is 12), metabolic presentation, or clinical course and treatment is the same for both.

Cystine stones may become very large, are often recurrent, and are difficult to fragment with ESWL, so that preventive therapy is essential, and should be started as soon as the diagnosis is made. Renal function in patients with cystinuria is often reduced from a young age[70], and the renal pathology shows diffuse interstitial fibrosis and plugging of collecting ducts[26].

Cystinuria is diagnosed by family history, stone analysis, or by measurement of urine cystine excretion. When stone type is unknown, patients should have one urine screened with a qualitative test for cystine, using the cyanide-nitroprusside test, which if positive indicates a cystine concentration >75 mg/L. Normal cystine excretion is about 30 mg/day, while patients with cystine stones often excrete 400 mg/day or more. Heterozygotes may excrete as much as 250 mg (1 mmol) daily, but rarely form stones. Diagnosis in infancy can be difficult, as excretion is elevated in this age group.

Cystine solubility is higher in alkaline urine, but may still vary from 175–360 mg/L at urine pH over 7[71]. A reasonable goal is to attempt to keep the cystine concentration under about 240 mg/L and urine pH about 7, in order to maintain solubility. High fluid intake is prescribed based on the known daily cystine excretion, in order to achieve average concentrations below 240 mg/L, with intake distributed throughout the day and at bedtime. If the urine pH is below 7, potassium alkali in doses of 10–20 meq tid can be used to raise it. Cystine excretion may fall modestly on a sodium (<100 mmol/day) and protein (0.8 gm/kg/day) restricted diet.

If stones recur despite adequate hydration and alkaline urine pH, a cysteine-binding drug should be added to fluids and alkali. Cystine is a dimer of cysteine, and cystine-binding drugs have sulfhydryl groups that allow them to form mixed disulfides with cysteine, which are more soluble than the homodimer. D-penicillamine in a daily dose of 1–2 gm/day in 3–4 divided doses has been used for this purpose. More recently tiopronin, in a daily dose of 400–1200 mg/day in 3–4 divided doses has been found to be effective as well[72]. Both drugs have side effects including fever, arthralgias, rash, dysgeusia, leucopenia and proteinuria, but tiopronin is better tolerated, with a lesser incidence and severity of adverse reactions. Recurrent stones should be analyzed, as patients may begin to form stones containing CaP because of the alkaline urine pH, and therapy may need to be adjusted to prevent this. Patients should have follow-up every 6 months with urine chemistry to assess the efficacy to treatment. Direct measurement of cystine supersaturation is helpful, but only available from a specialized lab.[73]

STRUVITE STONES

Struvite stones, a mixture of magnesium ammonium phosphate and carbonate apatite, form when the urinary tract is infected with microorganisms that possess the enzyme urease, such as Proteus, Providencia, and sometimes Klebsiella, Pseudomonas and enterococci. Urease hydrolyzes urea to ammonia and CO_2, raising the urine pH and leading to formation of carbonate. Calcium carbonate precipitates with struvite, forming large branched stones in the collecting system, to which bacteria adhere. Antibiotics are ineffective at eradicating the infection when stone material is present, and as long as infection is present the stone will continue to grow. Therefore treatment requires both removal of all stone material and effective antibiotic therapy.

Struvite stones are seen in patients with urinary tract infections, particularly when complicated by chronic bladder instrumentation, neurogenic bladders or urinary diversion, or in the presence

of foreign material such as staples in the urinary tract. Other types of stones may become secondarily infected with urea-splitting organisms, leading to secondary struvite stone formation; these stones may contain a mixture of struvite and other stone material. They may grow rapidly and lead to chronic renal failure. Because of their size, passage is rare, and they present with vague flank pain, or with persistent urinary tract infection and urine pH > 7, and characteristic “coffin-lid” struvite crystals in the urine.

Removal of stone material may require several treatment modalities, such as a combination of percutaneous nephrolithotomy and ESWL, and requires a urologist skilled in endourologic techniques. This should be combined with specific antibiotic therapy. In cases where removal of all stone material is not possible, acetohydroxamic acid, a urease inhibitor, has been used to slow or prevent stone growth[74]. Use is limited by occurrence of side effects such as headache, thrombophlebitis, tremor, nausea, vomiting and rash in up to 60% of patients.

SUMMARY

Stone disease is an increasingly common form of renal disease which is associated with crystal deposition in the renal medulla in all cases studied so far. The majority of stones are composed of calcium oxalate, often mixed with calcium phosphate, in both adults and children. The acute presentation is usually unmistakable, and evaluation with non-contrast CT is advisable for diagnosis. Stones smaller than 5 mm will generally pass, but larger stones often require urologic procedures for removal; any stone passed or removed should be analyzed. The basic pathophysiology of all stones is urinary supersaturation with respect to the stone material, and treatment is based on decreasing or eliminating supersaturation. Recurrence is the rule after a first stone, therefore preventive treatment is justified to avoid the risks and costs of repeated episodes. After a first calcium stone, if systemic disease is ruled out, treatment with fluids is reasonable; after further recurrence medical therapy is advised. Other stone types require active treatment after a first stone to prevent recurrence.

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Table 1

Kidney Stone Types and Frequencies

Stone type	Adults			Children
	Males	Females	Both	
Calcium oxalate	82%	66%	76%	45–65%
Calcium phosphate	8%	19%	12%	14–30%
Uric acid	8%	6%	7%	4%
Cystine	1%	4%	2%	5%
Struvite	1%	5%	2%	13%

Adults, data from University of Chicago Kidney Stone Evaluation Program.
Major stone component for each patient with at least one analysis.
(N=2011, 1402 male, 675 female).

Children, data from ref. [2].

Table 2

Evaluation of Stone Formers

Evaluation should be done after recovery from stone passage and treatment of any infection, while patients are eating their usual diet as outpatients, and off medications that affect mineral metabolism.

First presentation

Rule out systemic diseases and stone types associated with frequent recurrence and damage to the kidney (cystine, struvite, uric acid).

1. Determine stone type:
   - a. Analyze passed stone or stone fragments by X-ray crystallography or infrared spectroscopy
   - b. Urinalysis (may identify crystal type, or infection with urea-splitting organism)
   - c. Qualitative cyanide-nitroprusside test for cystine × 1 if stone type unknown.
2. Determine whether first stone or recurrent:
   - a. History of prior episodes
   - b. X-ray – other stones seen, or nephrocalcinosis noted
3. Rule out systemic diseases or co-morbidities:
   - a. History (including family history and dietary history) and physical exam
     - Known anatomic renal abnormalities (single kidney, UPJ obstruction).
     - History of bowel disease or resection.
     - Urinary tract infection with organisms possessing urease.
   - b. Blood and urine tests
     - Normal serum calcium
       - – Primary hyperparathyroidism, other hypercalcemic diseases unlikely
     - Normal serum bicarbonate
       - – Renal tubular acidosis unlikely
     - Normal urine oxalate
       - – Primary or secondary causes of hyperoxaluria unlikely

If **first** episode of idiopathic calcium oxalate stone –

Conservative treatment (fluids and dietary modification).

Recurrent idiopathic calcium stone **or** stone type is uric acid, cystine, or struvite –

Workup to determine proper preventive therapy, with analysis of 2 24-hour urines. The following analytes are the minimum needed for diagnosis. Several commercial labs offer kidney stone testing which is cost effective, includes all needed analytes, and calculates supersaturation.

Calcium stone (or if stone type unknown): creatinine, calcium, oxalate, sodium, urea, uric acid, citrate, volume, pH (sulfate, ammonia, potassium, and supersaturation helpful).

Uric acid stone: creatinine, pH, uric acid, volume.

Cystine stone: creatinine, pH, volume, cystine, calcium, sodium, urea.

Struvite stone: Urine culture for identification of organism and antibiotic sensitivity. Surgical treatment needed. Some struvite stone formers have risk factors for other stone types, may have become secondarily infected.

Follow-up after treatment

Repeat 24-hour urine in 4–8 weeks to assess effect of treatment. Thereafter, if urinary supersaturation has fallen, repeat urine every year to monitor.

Table 3

24-Hr Urine stone chemistries used for kidney stone evaluation

ANALYTE	UNITS	NORMAL VALUES (non-stone formers)	
		ADULTS	CHILDREN (< age 18)
VOLUME		> 1.5 L/day	25 ± 7 ml/kg/day*
pH		5.8–6.2	5.85–7.05*
CALCIUM	mg/day	<250 (F), <300 (M), < 4 mg/kg or <140mg/g creat (both sexes)	<4 mg/kg or < 0.21 gm/gm creat (>2 yr)
OXALATE	mg/day	30–50	<45 mg/1.73 m^2/day or < 0.56 mg/kg/day (> 2 yr) (spot urine values vary with age)
CITRATE	mg/day	>550 (F), >450 (M)	> 400 mg/g creat
URIC ACID	mg/day	<750 (F), < 800 (M)	< 815 mg/1.73 m^2/day or < 0.56 mg/100 ml GFR
PHOSPHATE	mg/day	500–1500	
MAGNESIUM	mg/day	50–150	< 88 mg/1.73 m^2/day
SULFATE	mmol/day	20–80	
AMMONIA	mmol/day	15–60	
SODIUM	mmol/day	50–150	
POTASSIUM	mmol/day	20–100	
CREATININE	mg/day	15–19 mg/kg (F), 20–24 mg/kg (M)	
SS CAOX		6–10	8.2 ± 4*
SS CAP		0.5–2	2.5 ± 1*
SS URIC ACID		0–1	0.58 ± 0.4*

F, female; M, male; creat, creatinine; GFR, glomerular filtration rate.

Adult values from University of Chicago Stone Clinic. Children's values from: Milliner DS. Urolithiasis. In: Pediatric nephrology. Philadelphia: Lippincott Williams & Wilkins; 2004, except *, from ref. [28]; values are mean ± SD.

Table 4

Major Causes of Calcium Stone Formation

May Cause Either Calcium Oxalate or Calcium Phosphate Stones		
Hypercalciuria with normocalcemia		
	Idiopathic hypercalciuria	
	Granulomatous diseases (sarcoid)	
Hypercalciuria with hypercalcemia		
	Primary hyperparathyroidism	
	Granulomatous diseases (sarcoid)	
	Vitamin D excess	
	Malignancy (rare)	
	Hyperthyroidism	
Hypocitraturia		
	Secondary to hypokalemia	
	Secondary to metabolic acidosis	
	Idiopathic	
Causes primarily Calcium oxalate stones		
Hyperoxaluria		
	Primary hyperoxaluria – Type 1, Type 2	
	Enteric hyperoxaluria	
		Small bowel resection
		Bariatric surgery
		Fat malabsorption from any cause
	Dietary hyperoxaluria	
		Low calcium diet
		Excess vitamin C
Hyperuricosuria		
		High purine diet
		Myeloproliferative disorder
Persistent low urine volume		
		Diarrheal states
Causes primarily Calcium phosphate stones		
Hypercalciuria with normocalcemia and metabolic acidosis		
	Distal renal tubular acidosis	

Table 5

Randomized Trials of Preventive Treatment for Calcium Stones in Adults

Treatment	Dose	Controlled trial	Recurrence (%)	
			Treated	Control
First Calcium Stone (+/− Hypercalciuria, mild hyperoxaluria, hypocitraturia, hyperuricosuria)				
Fluid[a]	Told to increase fluid intake to keep urine volume > 2 liters/day	5 years, High fluid intake vs. usual intake n=199	12	27*
Recurrent Calcium Stones (+/− Hypercalciuria, mild hyperoxaluria, hypocitraturia, hyperuricosuria)				
Diet[b]	Calcium 1200 mg/d Na 50 mmol/d, Protein 52 gm/d	5 years, Study diet vs. 400 mg Ca diet n=120	20	38*
Chlorthalidone[c]	25 or 50 mg/day	3 years, drug vs. placebo; n=73	14	46*
Hydrochlorothiazide[d]	25 mg bid	3 years, drug vs. placebo; n=50	20	48*
Indapamide[e]	2.5 mg/day	3 years, drug vs. placebo; n=75	15	43*
Potassium citrate[f]	30–60 meq/day	3 years, drug vs. placebo; n=57	28	80*
Potassium Mg citrate[g]	60 meq/day	3 years, drug vs. placebo; n=64	13	64*
Sodium potassium citrate[h]	Variable dose to keep urine pH 7–7.2	3 years, drug vs. no Rx; n=50	69	73**
Recurrent Calcium Oxalate Stones with hyperuricosuria				
Allopurinol[i]	100 mg tid	3 years, drug vs. placebo, n=60	31	58*

Patients are idiopathic calcium stone formers. Patients with systemic disease, such as hyperparathyroidism, bowel disease, renal tubular acidosis, were excluded.

* $p < 0.05$ vs treated

** p=NS vs treated.

[a] ref. 42

[b] ref. 41

[c] ref. 45

[d] ref. 46

[e] ref. 44

[f] ref. 49

[g] ref. 50

[h] ref. 51

[i] ref. 60.

Table 6

Causes of organic and infection stones

Purine Stones

Uric acid stones

- Low urine pH
  - Gouty diathesis
  - Idiopathic (metabolic syndrome)
  - Diabetes
  - Obesity
  - Bowel disease (especially colon resection)
- Low urine volume
- Hyperuricosuria
  - High protein diet
  - Overproduction
    - Myeloproliferative disorders
    - Hypoxanthine–guanine phosphoribosyl transferase deficiency
    - Phosphoribosyl pyrophosphate synthetase superactivity
  - Uricosuric drugs

Rare monogenic causes of purine stones:

- 5-dihyroxyadenine stones **(**Adenine phosphoribosyl transferase deficiency**)**
- Xanthine stones (Xanthine oxidase deficiency)

Ammonium acid urate stones

- Volume depletion with hypokalemia
  - Bowel disease, laxative abuse

Cystine Stones

Inherited gene defects in cystine transport

- SLC3A1 (Type I or type A cystinuria)
  - Encodes rBAT, the heavy chain of the dibasic amino acid transporter
- SLC7A9 (Type non-I or type B cystinuria)
  - Encodes b^{o+}AT, the amino acid transporting subunit of the transporter

Struvite Stones

Urinary tract infection with urea-splitting organisms

- Usually Proteus mirabilis
- Other urease producing bacteria include: Proteus sp., Providencia, Enterobacter, Bordetella, Bacteroides, Staph aureus, Corynebacterium, Ureaplasma
- Occasionally urease producing: Serratia, Pseudomonas, Klebsiella, Aeromonas, Pasteurella
- May also have metabolic or anatomic abnormality predisposing to stone formation