Renal stones

causes, treatment and prevention

Increased fluid intake remains the cornerstone of therapy in the prevention of renal stones. Pharmacological agents may be required in patients with multiple recurrences.

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Renal stones cause significant pain and morbidity. They affect between 8 and 15% of people in Europe and North America, with a similar prevalence across most western countries. They are more frequent in warmer climates, and about 50% of patients with an initial stone will have recurrences within five to 10 years.[1]

Although management of acute attacks has improved dramatically in recent years, prevention of recurrent episodes remains important to reduce the associated morbidity and the requirement for hospitalisation and stone removal.

Predisposing factors

Kidney stones result from crystallisation of urinary solutes. Three main factors contribute to stone formation:

- increased concentration of urinary crystalloids – due to either inadequate fluid intake or increased solute excretion
- reduced urine flow – as occurs with obstruction, diverticulum or dehydration
- altered solubility of urinary crystalloids – due to changes in pH or changes in stone inhibitors or promoters.

Types of renal stones

The different types of renal stones are listed in Table 1.[2-5]

Calcium stones

Calcium containing stones are by far the most common type of renal stone. Most consist of calcium oxalate or a mixture of calcium oxalate

Table 1. Types of renal stones[2,3]

Stone types	Percentage of cases
Calcium containing stones	80%
– calcium oxalate	75%
– calcium phosphate	5%
Uric acid stones	5–15%
Infection/struvite stones	5–10%
Cystine stones	1%
Others – drug-related (e.g. triamterene, indinavir,[4] ephedrine[5]), xanthine, silica, factitious	Rare

IN SUMMARY

- **Increased oral fluids remains the cornerstone of stone prevention and is all that is required in most patients.**
- **The majority of stones are calcium containing, and up to 80% of patients with calcium stones have an underlying biochemical abnormality.**
- **Patients with a single stone should be investigated to detect significant associated medical problems or complications that require treatment, such as hyperparathyroidism, urinary tract infection and renal impairment.**
- **Patients with multiple recurrences usually warrant more extensive biochemical evaluation and consideration of specific prophylactic therapy.**

Figure 1. Small, smooth 'hempseed' calcium stone.

Figure 2. Calcium stones with ragged external spicules.

Table 2. Risk factors for calcium containing stones[2,3]

Risk factors	Percentage of cases
• Hypercalciuria	40-60%
– hypercalcaemic (e.g. hyperparathyroidism, sarcoidosis, excess vitamin D supplements, lithium, malignancy, thyrotoxicosis)	
– normocalcaemic (idiopathic hypercalciuria)	
• Hyperuricosuria	10-30%
• Hypocitraturia	15-30%
• Hyperoxaluria	10-30%
– mild (dietary)	
– severe (e.g. 'enteric hyperoxaluria' due to fat malabsorption, primary hyperoxaluria)	
• Low urine volume (<1000 mL per day)	10-30%
• Others (e.g. type 1 renal tubular acidosis [calcium phosphate stones], medullary sponge kidney)	

and calcium phosphate, and the proportion of calcium oxalate stones is increasing.

Calcium stones are hard and densely radio-opaque. Small, smooth 'hempseed' stones are most common, but larger stones, often with an irregular 'mulberry-like' surface or ragged spicules, also occur (Figures 1 and 2). Calcium stones are more common in men than in women (the reason why is as yet unknown although there are some experimental data suggesting sex hormones affect lithogenic risk factors[3]). They can be associated with various biochemical and anatomical risk factors or abnormalities (Table 2).[2,3]

The most common associated abnormality is hypercalciuria (above about 6.2 to 7.5 mmol/day). This is most frequently idiopathic hypercalciuria, usually due to increased gastrointestinal calcium absorption. Hyperparathyroidism is also a relatively frequent cause of hypercalciuria, usually with only mildly elevated or borderline serum calcium levels.

Citrate normally binds urinary calcium and inhibits stone formation. Low urinary citrate levels are, thus, also associated with an increased risk of calcium stones. Hypocitraturia is found in conditions causing chronic acidosis such as chronic diarrhoea and type 1 renal tubular acidosis but has also been found in up to 30% of otherwise unremarkable calcium stone formers.

Hyperuricosuria (above about 4.0 to 4.5 mmol/day) is a risk factor for calcium oxalate stones as calcium oxalate crystals can develop on the surface of uric acid crystals ('heterogenous nucleation'), leading to the formation of mixed uric acid and calcium stones or seemingly pure calcium oxalate stones.

Gastrointestinal absorption of oxalate is limited by its binding to calcium within the gut lumen. Increased absorption and mild hyperoxaluria (just over the normal range of 500 to

600 mmol/day) can occur with increased dietary oxalate or reduced dietary calcium. More marked hyperoxaluria (above approximately 800 mmol/day) can occur with fat malabsorption, as fatty acids in the colon bind calcium ions, which leaves free oxalate to be absorbed. Primary hyperoxaluria is a rare genetic condition causing excessive metabolic oxalate production with calcium oxalate deposition and recurrent stones. This usually presents in childhood but may not become symptomatic until the fourth decade of life.

No metabolic or anatomical abnormality is detected in up to 20% of people who form calcium stones.

Uric acid stones

About 10% of stones are composed of uric acid. They are radiolucent on plain radiographs and can only be seen as filling defects on intravenous pyelograms (IVP), but are clearly visualised by computed tomography (CT) scanning (Figures 3a, b and c).

The two main predisposing factors for this type of stone are low urinary pH and high urinary urate concentration. About 90% of uric acid stone formers have constantly acid urine and this is a major predisposing factor since the solubility of uric acid increases sixfold between pH 5 and 6; even normal urinary concentrations of uric acid can become supersaturated at pH 5. Although a high protein diet presumably plays a role, the metabolic basis of persistently acid urine is not understood.

A little over half of uric acid stone formers have hyperuricosuria. This is usually hereditary but can be worsened by ingestion of a high purine diet (e.g. organ meats and yeast in beer). Rapid cell turnover, as seen in myeloproliferative disorders or genetic defects of purine metabolism (e.g. Lesch–Nyhan syndrome), is rarely responsible.

Infection stones

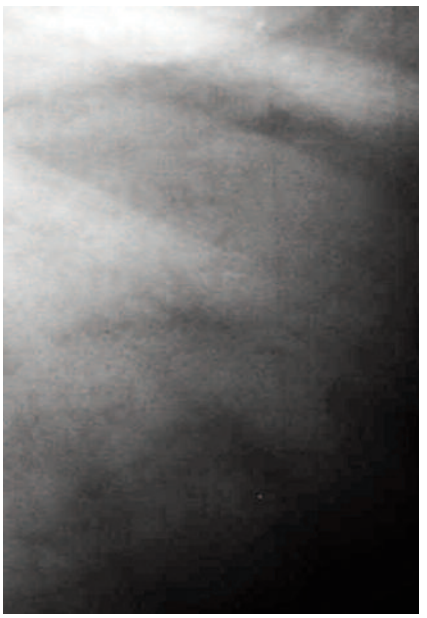
Infection, struvite or triple-phosphate (so-called because they are composed of calcium–magnesium–ammonium phosphate) stones are becoming less frequent in developed countries. They form when the urine is infected by urea splitting organisms (such as *Proteus*, *Pseudomonas* and *Klebsiella*). These bacteria convert urea to ammonium and bicarbonate, causing alkalinisation of the urine and consequent precipitation of calcium, magnesium, ammonium and phosphate. The urine of patients with infection stones typically has a pH above 7.5. Urinary infection and infection stones are more common in women.

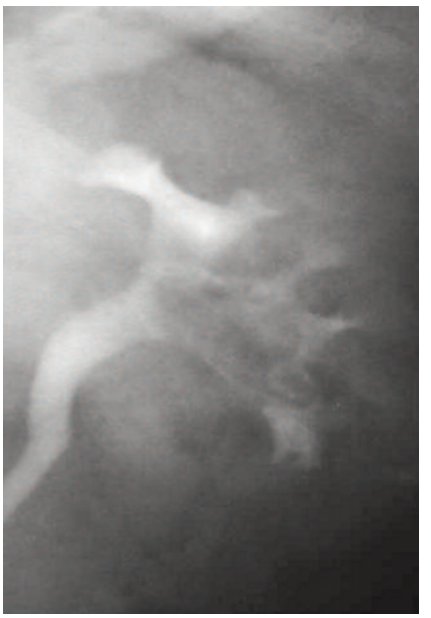
Infection stones grow rapidly and can fill the renal pelvis, forming moderately radio-opaque staghorn calculi (Figures 4a and b). They are commonly associated with pyuria and can cause renal failure if bilateral staghorn calculi are present.

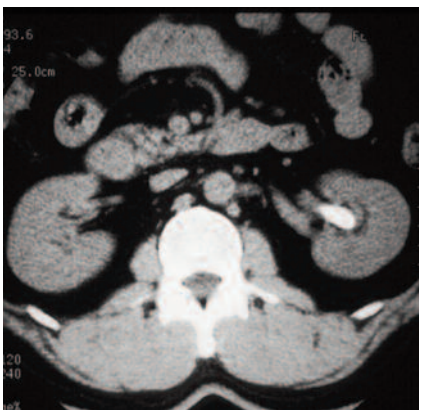
Cystine stones

Cystinuria is an autosomal recessive condition resulting in impaired renal tubular transport and increased urinary excretion of dibasic amino acids (cystine, ornithine, lysine and arginine). Cystine is an insoluble amino acid, forming flat hexagonal crystals in neutral or acid urine (Figure 5). Cystine stones are faintly radio-opaque due to the sulfur content of the cystine molecule. Like urate stones, they are easily detected by CT scanning.

People who are heterozygous for the mutation have mildly increased urinary cystine levels and are usually asymptomatic, although they may develop calcium stones. (Patients with cystinuria

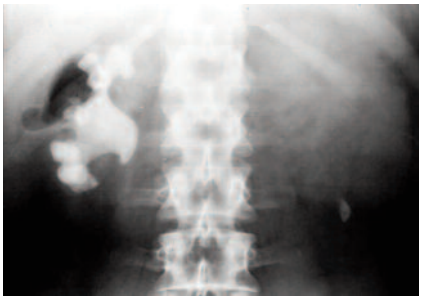


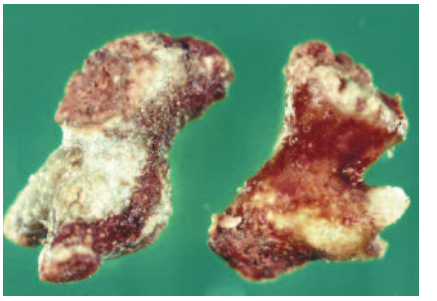




Figures 3a to c. Uric acid stones. a (far left). Plain radiograph of radiolucent uric acid stone. b (centre). IVP of same uric acid stone showing filling defect. c (above). CT clearly demonstrates the uric acid stone in the renal pelvis.

who develop other stones – calcium or mixed – often have concomitant abnormalities such as hypercalciuria, hyperuricosuria or hypocitraturia.) Those who are homozygous have greatly increased urinary cystine levels (two to 10 times normal) and develop multiple stones or staghorn calculi. These people often present in childhood or early adulthood with bilateral stone disease. Repeated episodes of obstruction and infection may cause renal impairment.





Figures 4a and b. Infection stones. a (above left). Plain radiograph of staghorn calculus in right kidney. b (above right). Renal infection stones showing characteristic staghorn shape.

Management of acute stone episodes

Patients with renal stones usually present with acute ureteric colic. This is severe pain radiating from the flank to the groin and is often associated with nausea and vomiting. Paroxysms of severe pain usually last 20 to 60 minutes and are due to muscular contraction of the ureter or stretching of the ureter due to obstruction. The pain is fully relieved when the stone passes from the ureter into the bladder. Stones can also present as a result of complications such as obstruction, infection or bleeding, or can be found incidentally on imaging studies.

Initial investigations

Renal tract imaging will demonstrate the presence of a stone and characterise its size and position. Plain radiograph or renal ultrasound are appropriate initial investigations, followed if necessary by an IVP. Ultrasound and IVP are also able to detect renal tract dilatation due to obstruction. More recently the role of noncontrast helical CT scanning has been studied in the evaluation of patients with suspected renal colic. It has a very high sensitivity and specificity (greater than 90%) for the detection of stones and renal tract obstruction, and is also able to demonstrate other intra-abdominal pathology that might be the source of pain.[6,7] Unlike IVP, helical CT does not require intravenous contrast administration and has replaced IVP in many centres.

Serum creatinine measurement and urine microscopy should be performed in people with suspected renal stones. The presence of haematuria supports the diagnosis of renal colic but is absent in at least 10% of patients with confirmed stones.[8] Importantly, pyuria may indicate the alternative diagnoses of pyelonephritis or an infected obstructed kidney (which is a medical emergency).

Pain relief

Initial management of renal colic is directed towards pain relief. NSAIDs given orally, intravenously or by rectal suppository have similar efficacy as narcotic analgesia but must be used cautiously in patients with renal impairment. Some patients will still require opiates.

Relief of obstruction

Urinary tract obstruction requires urgent relief when there is either infection or acute renal failure. This is usually achieved by percutaneous nephrostomy performed under ultrasound guidance or, less commonly, by endoscopic placement of a double J-stent.

Stone removal

Most ureteric stones less than 5 mm in diameter will pass spontaneously, encouraged by a high urine output, and are therefore generally treated conservatively. Stones larger than 5 mm are much less likely to pass spontaneously, with only 6% of those larger than 6 mm passing.[9]

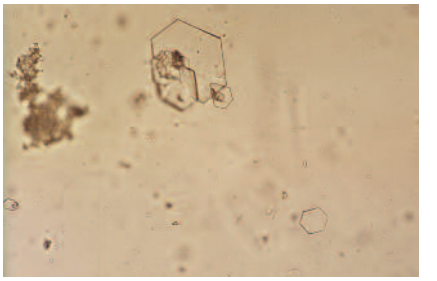


Figure 5. Cystine crystals are visible in the urine in about half of cystinuric patients. They form flat hexagonal 'benzene ring' shapes.

Stones larger than 5 mm and smaller stones that do not pass within two to four weeks require intervention. This can be via ureteroscopic removal, extracorporeal shock wave lithotripsy, percutaneous nephrolithotomy or a combination of these, depending on the stone position, size and type. Surgical nephrolithotomy is rarely required.

Dissolution of stones with large volumes of oral fluids (5 to 10 L) combined with allopurinol and bicarbonate (for uric acid stones) or penicillamine (D-Penamine) and bicarbonate (for cystine stones) can be successful in very compliant patients. Dissolution is not effective for calcium stones.

Underlying abnormalities

Personal history might reveal previous gout in patients with uric acid or calcium stones, urinary tract infection in those with infection stones, or chronic

diarrhoea or bowel disease in those with calcium oxalate stones. Onset of stones in childhood can indicate cystinuria or an anatomical abnormality. A family history of stones might be found in patients with calcium stones due to idiopathic hypercalciuria and in those with uric acid or cystine stones.

Investigating patients with renal stones is important for detecting underlying medical conditions (such as hyperparathyroidism and urinary tract infection) and complications of stones (such as renal impairment). It is also useful for detecting other predisposing metabolic or anatomical abnormalities that may help guide preventative therapy.

The extent to which patients are investigated depends on the number and frequency of stones. Patients with a first stone should have the investigations listed in Table 3.

Analysis of stones or fragments is vital and should always be undertaken if possible. Patients should be instructed to collect any stones or fragments by straining their urine after passing it into a container.

More extensive metabolic evaluation is undertaken in patients with recurrent renal stones and for all children with stones. Twenty-four hour urine collections should be obtained on two occasions and analysed according to Table 3. The diagnostic yield can be improved by doing these collections at least three months after a stone has passed, and while the patient is on his or her normal diet.

Table 3. Investigations in patients with stones

Patients with first stone

Imaging
X-ray and/or ultrasound
IVP or helical CT if needed

Blood
Electrolytes, urea, creatinine
Calcium
Uric acid

Spot urine
pH, blood, leucocytes

Midstream urine
Microscopy
Culture

Stone or fragments
Analysis for composition

Patients with recurrent stones and all children

All the tests above

24-hour urine collection
Volume
Creatinine
Calcium
Uric acid
Oxalate
Citrate
Cystine

Preventing stone recurrence

Interventions for reducing stone frequency include increased fluid intake, dietary modification and medications. Since stone recurrences can be infrequent and therapy is long term, issues such as medication compliance, cost and potential side effects must be carefully weighed against the benefit of reduced stone frequency. Patients with single or infrequent stones usually only require advice regarding fluid intake and diet. Medications are generally reserved for patients with frequent or multiple recurrences but may be considered for those with multiple stones at presentation.

Increased fluid intake, resulting in increased urine volume, is probably the most important factor in preventing recurrence of all stone types. Patients should be encouraged to drink sufficient fluids to raise their urine volume to 2 to 3 L per day. Epidemiological evidence links low fluid intake and low urine volume with an increased incidence of stones, and it has been shown that increased fluid intake reduces the rate of stone recurrence.[10-12]

Interestingly, the type of fluid consumed might be important. Several large observational studies have reported reduced stone risk with consumption of tea, coffee, beer and wine but increased risk with grapefruit juice.[10,11]

Calcium stones

Patients with secondary causes of calcium stones, such as hyperparathyroidism or sarcoidosis, require treatment directed at the underlying disease.

The remaining patients, those with idiopathic calcium stone disease (normal serum calcium and without urine infection or marked hyperoxaluria), form the largest group with recurrent stones. Although dietary advice has often included reducing dietary calcium, oxalate, sodium and protein, there is little evidence that these measures reduce stone recurrence. Indeed, low dietary calcium increases intestinal oxalate absorption, and has been found to increase the incidence of calcium oxalate stones in observational studies and in a randomised trial.[10,13] In fact, high calcium intake might be protective but it would need to be taken at times when the gut contains food and therefore oxalate.[11] (A low calcium diet might also be associated with a loss of bone mineral density.) Similarly, one trial of low protein diet demonstrated an increased risk of stones.[14] On current evidence, therefore, no specific dietary recommendations can be made other than a normal calcium intake and an increased fluid intake.

Randomised trials have shown that several medications reduce the recurrence rate of calcium stones. Some trials have tailored therapy to the metabolic abnormality (e.g. thiazides for hypercalciuria) but, with a few exceptions, this has not been found to be necessary. Available drug treatments for idiopathic calcium oxalate stones, their effectiveness and evidence supporting their use is

summarised in the box on this page.[15-29]

A simplified approach to the prevention of idiopathic calcium stones is to use thiazides or indapamide (a thiazide-like diuretic) as first line treatment as they are usually well tolerated and effective in patients with or without hypercalciuria. Thiazides and indapamide act by reducing renal calcium excretion and therefore reduce net calcium loss, a problem common in people with idiopathic hypercalciuria. For those patients who are compliant and continue to form stones, allopurinol may be added if hyperuricosuria is present and potassium citrate (Urocit-K) used in the remainder. (Allopurinol will reduce uric acid excretion and, therefore, the formation of mixed uric acid and calcium stones; potassium citrate will increase citrate levels and, therefore, the binding of urinary calcium.) It is important to note that the passage of a stone does not necessarily represent treatment failure if the stone was present radiologically at the initiation of therapy.

Uric acid stones

Raising the urinary pH is the most effective way of increasing the solubility of uric acid. This can be achieved with potassium citrate, titrated to increase the urinary pH to 6 to 7. However, compliance is often a problem because three to six tablets (30 to 60 mEq) daily are usually required. Allopurinol can also be used in patients with hyperuricosuria, titrated to reduce the uric acid excretion into the normal range.

Infection stones

Urine culture is important for identification of the responsible organism and its sensitivities in order to guide appropriate long term antibiotics. Stone removal, including removal of infected fragments, is also critical for clearance of infection and often requires lithotripsy and percutaneous nephrolithotomy. Appropriate antibiotics should be continued for at least three months after removal of all stone fragments.

Cystine stones

Patients with cystinuria require a lifetime of effort to prevent recurrent stones. Adequate fluid intake to provide a urine volume of 3 to 4 L per day is vital. As urine is more concentrated overnight, fluid before retiring and throughout the night is particularly important. Urinary alkalinisation to a pH above 7.4, preferably with oral potassium citrate, is also useful, but compliance can be a problem.

Penicillamine forms soluble complexes with cystine and is used in patients with persistent stone formation despite increased urine volume and alkalinisation. Commencing with 250 mg daily, the dose is gradually increased up to a maximum of 2 g daily. Unfortunately, the significant incidence of side effects, including taste disturbance, nausea, skin rashes, pancytopenia and membranous glomerulonephritis, often limit treatment. Other options include tiopronin in doses from 100 to 400 mg daily (available through the Therapeutic Goods Administration's Special Access Scheme and possibly captopril (although it is not indicated for such use).

Conclusion

Medical prevention of renal stones is worthwhile to reduce the morbidity associated with renal colic, the requirement for stone removal and the potential complications of stones. The extent of investigation and complexity of treatment is dictated by the number and frequency of recurrences. There is increasing evidence for various pharmacological agents in the prevention of stones but increased fluid intake remains the cornerstone of therapy. MT

A list of references is available on request to the editorial office.

Evidence for drug treatment in recurrent idiopathic calcium oxalate stone disease[15,16]

Thiazides

Five randomised controlled trials (RCTs; n = 343) show reduction in stone formation in both unselected and hypercalciuric patients.[17-21] No benefit seen in two RCTs (n = 113), both with inadequate duration of follow up.[22,23]

Approximate relative risk (RR) of recurrence compared with no treatment, 0.45.

Indapamide

Reduced stone formation rate in one RCT (n = 40) with hypercalciuric patients.[24]

Approximate RR of recurrence compared with no treatment, 0.37.

Alkali citrate

Reduced stone formation rate in two RCTs (n = 79) – one trial with potassium citrate (hypocitraturic patients) [25] and one with potassium magnesium citrate (unselected patients).[26] No benefit in one RCT (n = 38) using sodium potassium citrate (possibly due to sodium).[27]

Approximate RR of recurrence compared with no treatment, 0.19 to 0.35.

Allopurinol

Benefit in one RCT (n = 60) in patients with hyperuricosuria.[28] No benefit in three RCTs (n = 74) in unselected patients.[20,21,29]

Approximate RR of recurrence compared with no treatment, 0.55.

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