The patient with a urinary calculus

What to do next

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.

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Urinary stones are a common problem. They are frequently symptomatic and costly in terms of hospital presentations, investigations and treatment. In the USA, the yearly cost of urinary stones has been estimated at US$1.23 billion per year.[1] Furthermore, medical stone prevention has been shown to save approximately US$2000 per patient.[2]

The purpose of investigating the patient with urinary stones is primarily to prevent recurrence. In the case of asymptomatic stones, the aim is to prevent these stones from becoming symptomatic.

Why do patients form stones?

The propensity to form urinary stones relates to the physicochemical derangement of urine composition whereby solutes are deposited in crystalline form rather than remaining in solution.[3] There are a number of basic steps in stone formation, which are outlined in the box on page 15.

A number of opportunities exist for clinical intervention in the process of urinary stone formation. Crystal growth and supersaturation can be altered by changing the urine volume and the amount of filtered solute. Nucleation can be prevented by introducing inhibitors or reducing the concentration of promoters in the urine and existing stones can be dissolved.

Urinary stone formation is the final common pathway of a very complex physicochemical system. Intervention focusing on one single variable is unlikely to be effective because stone formation is multifactorial. A more holistic approach is therefore needed.

Initial general investigations

All patients with suspected and proven urinary stones should have radiological imaging of their urinary tracts. In addition to making the diagnosis, imaging may demonstrate other asymptomatic

IN SUMMARY

- **Urinary stones are a common problem. They are frequently symptomatic and costly in terms of hospital presentations, investigations and treatment.**
- **Approximately 80% of urinary stones are calcium stones.**
- **Noncontrast CT scanning in the best imaging modality for urinary stones.**
- **Stones should be retrieved for composition analysis.**
- **Extensive metabolic assessment is only required for patients who are recurrent stone formers.**
- **All patients should be encouraged to drink more than 3 litres of water daily. Most patients who form stones are also likely to benefit from dietary changes.**

Basic steps in urinary stone formation

Supersaturation

Supersaturation of a solution exists when the amount of dissolved material exceeds the maximum that can usually be dissolved in a given solvent. There is a net drive toward crystallisation in a solution in this state.

Crystal formation

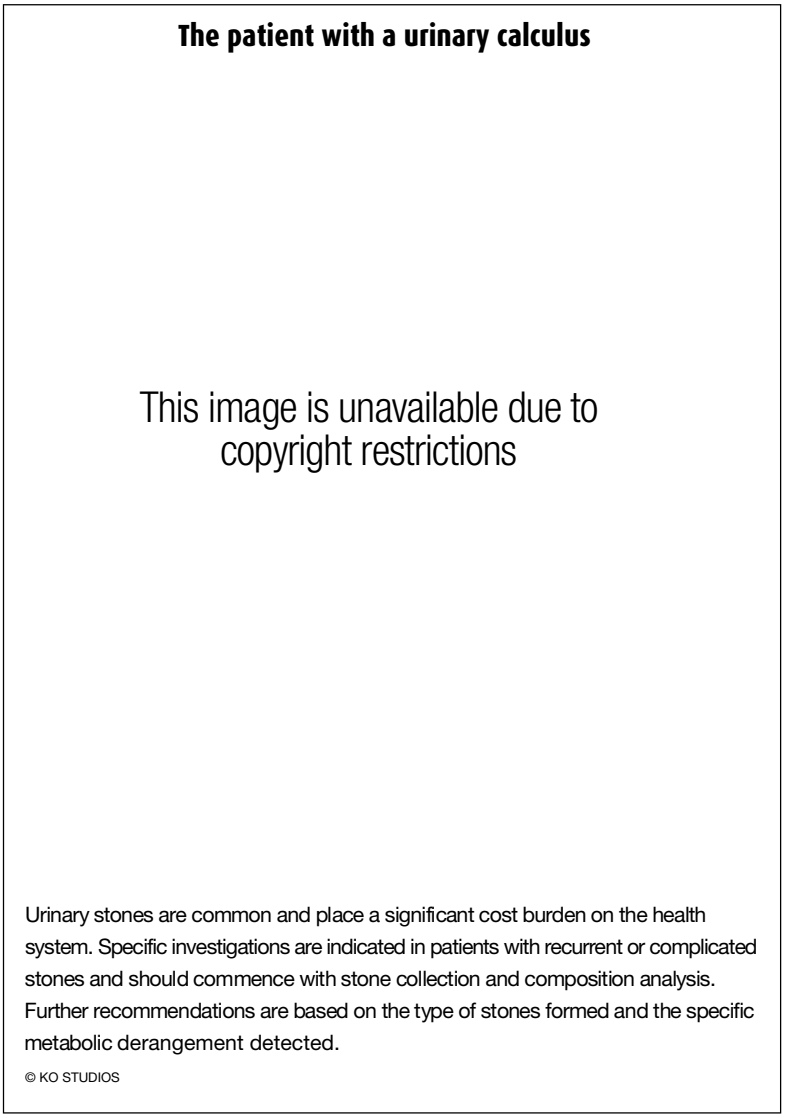
Crystal formation occurs when solutes come together to form a nucleus in a process known as nucleation. Although the supersaturated state favours crystal formation, it still requires the presence of promoters of nucleation.

Urine contains both promoters and inhibitors of nucleation. Membrane fragments, pre-existing calcium phosphate, sodium urate and uric acid stones are all examples of nucleation promoters, whereas urinary citrate, magnesium and some macromolecules are examples of nucleation inhibitors.

Crystal growth

Crystalluria is very common but stone formation is much less frequent. Both supersaturation and crystallisation must be followed by retention and growth of the crystal for a stone to form. This is akin to dropping a salt crystal into different solutions. If the solution is a concentrated salt solution, the original crystal will grow; however, if the solution is water only, the crystal will itself dissolve.

The patient with a urinary calculus



Urinary stones are common and place a significant cost burden on the health system. Specific investigations are indicated in patients with recurrent or complicated stones and should commence with stone collection and composition analysis. Further recommendations are based on the type of stones formed and the specific metabolic derangement detected.

stones and complications of urinary stone disease such as ureteric obstruction (see the flowchart on page 16). Patients with multiple stones are by definition 'recurrent stone formers'.

The imaging test of choice for urinary stones is a noncontrast helical CT scan. An ultrasound is an alternative for patients in whom it is necessary to avoid radiation (i.e. in women who are pregnant). However, an ultrasound is less sensitive than a CT scan, especially for ureteric stones.

An evidence-based concise set of guidelines with suggestions for the clinical care of patients with urinary stones is available on the Caring for Australasians with Renal Impairment (CARI) website.[4]

Simple metabolic tests on urine and blood should be undertaken in all patients who present with stones. These tests include:

- measurement of serum calcium levels
- measurement of serum urea and creatinine levels
- measurement of serum bicarbonate and potassium levels as a screen for renal tubular acidosis
- measurement of urine pH
- urine culture.

Complete metabolic investigation is not necessarily required after a patient presents with their

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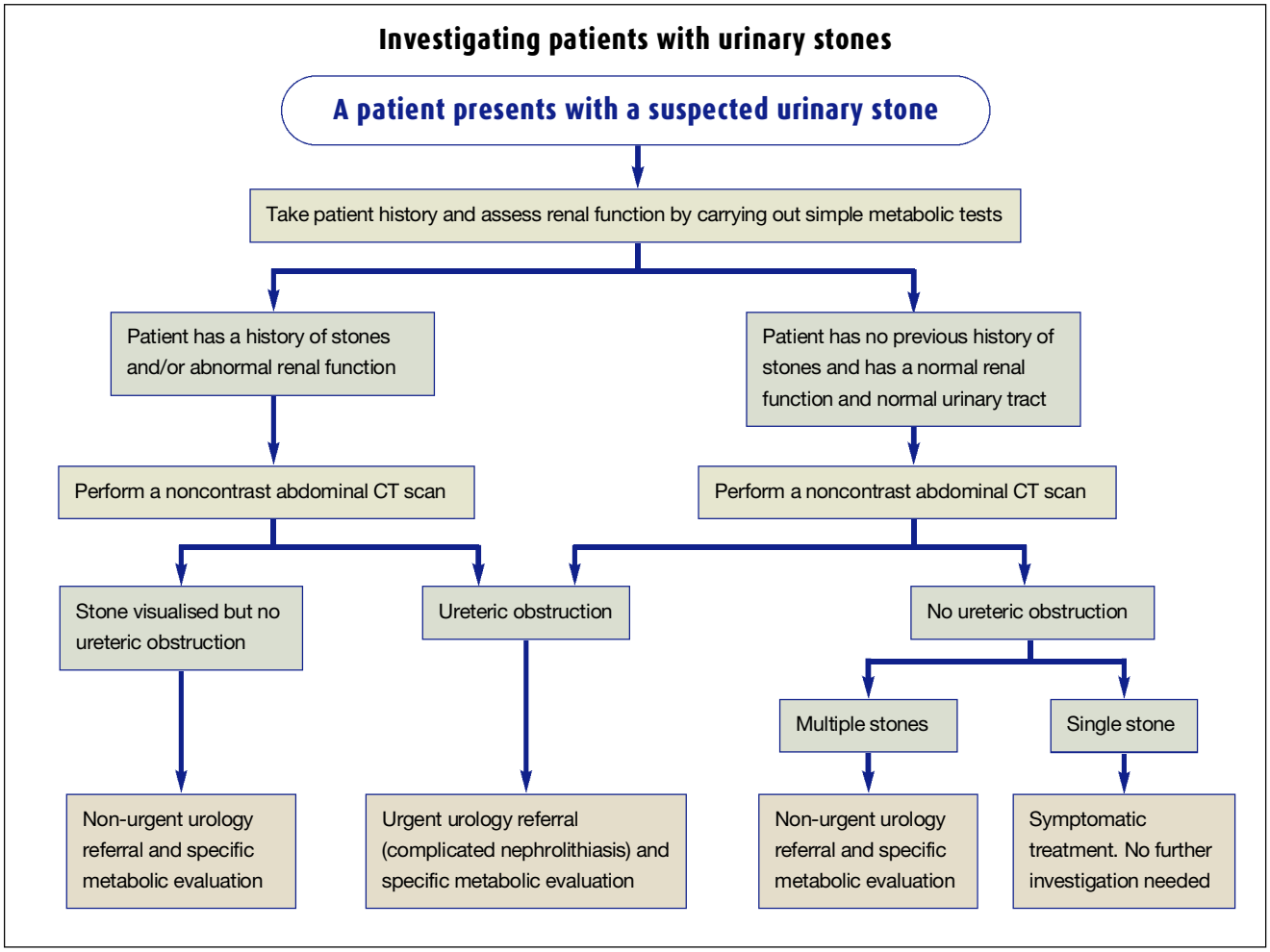


first stone. However, complete investigation should be undertaken if there are recurrent episodes. Investigations for the most common types of stones (i.e. calcium and uric acid stones) should be included in this group of patients. Details of these investigations are described in the relevant sections below and in Table 1.

If passed or extracted, all stones should be sent for composition analysis unless this has been established with previous calculi. Knowledge of the composition of stones formed in a particular patient is the best guide to effective prophylaxis. In the setting of an acute episode of nephrolithiasis, straining of the urine for 48 hours after the onset of pain should be routinely undertaken.

General treatment measures

In many cases, the stone composition will not be known. These patients should be treated with general treatment measures, as described below, to prevent stone recurrence and limit growth of existing calculi.

Fluid intake

All patients who form stones benefit from increased fluid intake.[5,6] Assuming the same excretion of solute, increased fluid intake will reduce the supersaturation of urine. In addition to dilution, increased urine flow will reduce the contact time available for crystal growth.

The aim of treatment should be to increase urine output to at least 2 litres per day. Fluid intake should be spaced evenly during the day. Increasing fluid intake just before going to bed can be especially helpful but will result in some degree of nocturia. Some patients find this an unacceptable imposition on lifestyle.

Dietetic intervention

Urinary stone disease appears to be largely a disease of wealthy developed countries. It has been linked to a diet containing excessive amounts of refined carbohydrates, animal proteins and salt in association with a low intake of fruit and vegetables. This diet can lead to hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia. All of these have been

Figure. Multiple calcium oxalate urinary stones (scales in centimetres).

shown to be powerfully predictive of urinary stone disease. Most patients who form stones are therefore likely to benefit from dietary changes to remedy these problems.

Specific investigation and treatment of different stone types

Patients who require more specific investigations and treatment include:

- those who are 'recurrent stone formers' (including those found to have multiple stones at presentation)
- those with complications of their stone disease
- those who are 'first stone formers' with:
  - pre-existing renal impairment
  - a single functioning kidney
  - abnormal urinary tracts
  - a strong family history of recurrent urinary stones.

Table 1 lists the specific metabolic investigations, depending on stone type, recommended in patients with recurrent or complicated stones.

Of patients presenting with their first stone, 5 to 15% will develop another symptomatic stone within one year, suggesting that some form of prophylaxis should be considered.[7] There are a number of interventions that have proven benefit in all patients who form stones. More specific intervention depends on the underlying cause and the type of stone being formed.

Patients who form stones can be broadly divided into four groups: calcium stone formers, uric acid stone formers, cystine stone formers and struvite stones formers. Clearly, knowledge of the biochemical composition is extremely helpful. Major risk factors for forming the different types of stones are outlined in Table 2.

Calcium stones

About 80% of urinary stones are calcium-containing, with most consisting of calcium oxalate (Figure).

Investigation

Patients with normal urinary tracts presenting with their first calcium stone do not need extensive investigation. Measurement of serum creatinine, urea, calcium, bicarbonate and urate levels, in addition to renal imaging preferably with noncontrast CT, are sufficient investigations in these patients. The identification of significant abnormalities suggests underlying pathology, an extensive discussion of which is outside the scope of this article.

Patients with calcium phosphate stones are specific cases because their stones are critically dependant on urine pH. Given the role of the kidney in excreting endogenous and exogenous acid, the urine pH is usually acidic. Calcium phosphate stones therefore suggest either impaired urinary acidification, such as distal renal tubular acidosis, or high oral intake of alkali. Morning urine pH greater than 6 or recurrent pH never less than 5.8 is highly suggestive. Measurement of serum bicarbonate levels will distinguish renal tubular acidosis from a high intake of alkali.

If the calcium stone is recurrent or there are other high-risk features as described previously, more extensive investigation is indicated. This includes the following:

- measurements of 24-hour urinary calcium, oxalate, citrate and urate excretions
- measurement of parathyroid hormone levels.

Treatment

Dietetic intervention should be seen as an extension of the usual advice given for healthy eating. The aspects relevant to urinary stones are a reduction in animal protein (reduced purine metabolism and oxalate excretion) and reduced salt intake. Foods such as spinach, rhubarb and black tea are particularly high in oxalate and should be limited in patients who form calcium stones.

Table 1. Metabolic evaluation in patients with recurrent or complicated stones

Calcium stones
- Serum calcium levels
- 24-hour calcium excretion
- Serum creatinine levels
- Serum bicarbonate levels
- 24-hour citrate excretion
- Urine pH
- 24-hour urinary urate excretion

Uric acid stones
- 24-hour urinary urate excretion
- Serum urate levels
- Urine pH

Cystine stones
- 24-hour urinary cystine excretion

Struvite stones
- Urine pH
- Urine culture

Stones of unknown composition

All the above investigations should be carried out; however, 24-hour urinary cystine excretion should only be measured if the patient has a strong family history of cystine stones.

Table 2. Major risk factors for urinary stone formation

Calcium stones

Urinary

- Low urinary volume
- High urinary calcium levels
- High oxalate levels (specific for calcium oxalate stones)
- Low urinary citrate levels
- High urine pH (specific for calcium phosphate stones)

Anatomical

- Medullary sponge kidney
- Horseshoe kidney

Diet

- Low fluid intake
- Low calcium intake
- High oxalate intake
- Low potassium intake
- High animal protein intake
- High sodium intake

Other medical conditions

- Primary hyperparathyroidism
- Gout
- Obesity
- Diabetes mellitus

Uric acid stones

- High urinary urate excretion
- High serum urate levels

Cystine stones

- Cystinuria

Struvite stones

- Urinary infection

Counterintuitively, strategies involving restriction of dietary calcium to treat patients with calcium stones are not effective, even in those with hypercalciuria, and may cause a number of adverse effects.[8-10] Both primary and secondary prevention studies have shown that calcium restriction is ineffective in the prevention of calcium stones.

A number of agents have been shown to reduce urinary calcium excretion, including thiazide diuretics, indapamide, sodium or potassium phosphate and bisphosphonates. Of these drugs, only thiazide diuretics and indapamide have been shown to reduce the occurrence of stones. Patients treated with these agents need to be monitored for adverse effects, including hypotension, hypokalaemia, hyperglycaemia and hypercholesterolaemia. Addition of potassium citrate may be useful to supplement potassium and replenish citrate when using these agents for stone prevention. (Citrate supplementation will be discussed in more detail below.)

Increased oxalate excretion usually occurs as a result of dietary intake and is best treated with dietary modification. Two additional conditions, described below, can also cause hyperoxaluria.

- **Primary hyperoxaluria.** This rare autosomal recessive disorder results from one of a number of mutations in genes involved in the metabolism of glycoxalate. The excess glycoxalate is metabolised to oxalate instead of the more soluble glycine or glycolate. Affected individuals present with urinary stones or nephrocalcinosis, usually during childhood. Very high 24-hour urinary oxalate excretion confirms the diagnosis. However, the disease spectrum is wide and some patients present with urinary stones during adulthood. The definitive treatment is liver transplantation, which replaces the deficient enzymes. Liver transplantation is most often required for patients who present during childhood. Adult patients with milder forms of the disease may be managed medically.
- **Enteric hyperoxaluria.** This occurs following surgery such as small bowel resection and intestinal diversion, which can cause fat malabsorption. The excess fatty acids in the gut form complexes with intestinal calcium, freeing oxalate for absorption. The result is excessive oxalate absorption.[11]

Pharmacological treatment of patients with hyperoxaluria has a limited effect, regardless of the cause. Cholestyramine has been shown to decrease oxalate absorption but no controlled trials have been undertaken to demonstrate an effect on stone formation. Pyridoxine (vitamin B_6) induces enzymes involved in oxalate metabolism, thereby lowering oxalate levels. Observational studies have shown an inverse relationship between stone formation and high pyridoxine intake. Given the lack of toxicity associated with pyridoxine, its use is not unreasonable in patients with hyperoxaluria.

Decreased concentrations of urinary citrate are a major risk factor for stone formation. Citrate has an important physiological role in keeping solutes in solution. It effectively forms soluble complexes with urinary calcium preventing crystallisation. Plasma citrate is derived from dietary intake and metabolism of oxaloacetate in the citric acid cycle and is freely filtered at the glomerulus. The urinary concentration of citrate depends both on the filtered load and the amount reabsorbed.

The western diet, which is high in animal protein, causes a reduction in urinary citrate probably via the acid load. Increased acid excretion in the urine increases the proportion of the divalent form of citrate, which is preferentially taken up by tubular cells. Although all urinary alkalinisers will, therefore, increase citrate levels, potassium citrate is the preferred urinary alkaliniser for use in patients with calcium stones. Sodium-containing alkalinisers such as sodium bicarbonate and sodium citrate are not recommended as the sodium load tends to increase urinary calcium excretion.[12]

Finally, although low urinary magnesium levels are a risk factor for calcium stones, there is no evidence that magnesium supplementation prevents stones. However, if low serum magnesium levels are detected then it may be reasonable to consider supplements.

Uric acid stones

Investigation

Patients with uric acid stones require only measurement of serum urate levels and 24-hour urinary urate excretion. These tests are useful to monitor treatment, but are not relevant to the diagnosis if the presence of uric acid stones has been established by stone analysis.

Treatment

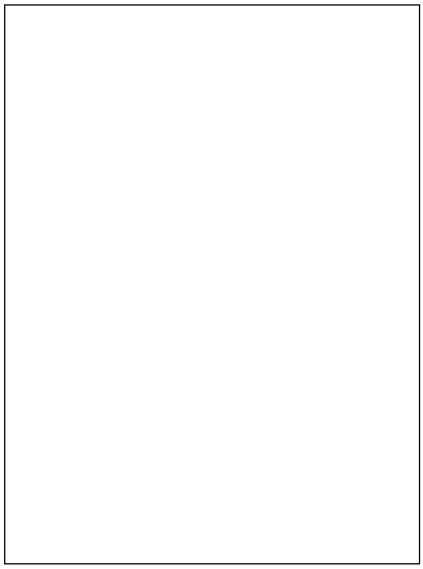
Treatment of uric acid stones includes the use of allopurinol to reduce uric acid formation and uricosuria. Some patients with calcium oxalate stones also have hyperuricosuria in the absence of any other metabolic abnormality. They may or may not have hyperuricaemia. Hyperuricosuria is associated with the formation of calcium oxalate stones; however, it has been difficult to show a reduction in stone formation with allopurinol. Nonetheless, it is reasonable to treat patients who have hyperuricosuria and recurrent calcium stones with allopurinol, providing it is well tolerated.

The only word of caution is in patients with significant overproduction of uric acid (i.e. those with myeloproliferative disorders and haemolytic anaemia). Blockade of xanthine oxidase with allopurinol can cause build up of the urate precursor xanthine, which itself can form stones when excreted in the urine. These stones, similar to pure uric acid stones, are radiolucent and difficult to detect radiographically.

Cystine stones

Cystinuria is a genetic disorder and patients with this condition can present with recurrent urinary stones, mostly during childhood. Cystinuria results from mutations in genes producing amino acid transporters in the proximal nephron. In the 'normal' individual, a number of amino acids are filtered into the urine and then reabsorbed in the proximal nephron. In patients with cystinuria, the reabsorption does not occur, resulting in aminoaciduria (including cystine).

Cystine is less soluble than the other amino acids and at high concentrations forms crystals and stones in the urine. Patients with cystinuria frequently form mixed stones of cystine and calcium oxalate.



Investigation

Diagnosis of cystinuria is made by measuring 24-hour urinary cystine excretion and should be considered under the following circumstances:

- presence of urinary stones containing cystine
- urinary stones presenting during childhood
- frequent recurrences and formation of staghorn calculi
- a strong family history of urinary stones.

Treatment

Treatment of patients with cystine stones includes increased fluid intake, dietary modification, urinary alkalinisation and pharmacological chelation of cystine.

Increasing fluid intake is effective in reducing recurrent cystine stones; however, urine output needs to be increased to over 3 litres per day. Night-time fluid needs to be increased to limit the high concentration of cystine in the urinary system overnight.

The urinary excretion of cystine in these patients is related to endogenous production or conversion, as their intestinal cystine transporters are also defective. Limiting cystine intake is not an effective treatment for cystine stones. However, avoiding excessive protein intake is effective. Sodium intake increases cystine excretion; therefore, these patients should be commenced on a low sodium diet. Urinary alkalinisation increases cystine solubility and, again, potassium citrate is the agent of choice.

Cystine chelation therapy is available for patients not responding to the measures described above. D-penicillamine is the only drug licensed in Australia and available on the PBS for patients with cystinuria. Unfortunately, its use is associated with many side effects and it should not be commenced without consultation with a specialist.

Struvite stones

Discussion of struvite stones is included in this article for completeness. They form as a result of infection with urease-producing bacteria. This produces alkaline urine, causing formation of crystals containing magnesium, ammonium and phosphate mixed with carbonate. The most common organism involved is *Proteus mirabilis*. Stagnation of urine is also a major risk factor, occurring in patients with spinal cord injuries and neurogenic bladder. Treatment is eradication of the infection, which may also involve removal of foreign bodies such as catheters and stents, or correction of anatomic abnormalities or improvement of drainage of the urinary tract.[13]

When to repeat investigations

If the stone composition is unknown and no specific predisposing factors are identified, continued attempts to retrieve stones for analysis is the only ongoing investigation required. These patients

should be treated with all the general measures described above.

If a specific predisposing factor is identified and treatment instituted, repeat testing to assess the efficacy of treatment should be undertaken. For example, if a patient is commenced on a thiazide diuretic to treat increased urine calcium excretion, repeat urine calcium measurements should be performed after stablisation on the drug.

Conclusion

Urinary stones are common and place a significant cost burden on the health system. Specific investigations are indicated in patients with recurrent or complicated stones and should commence with stone collection and composition analysis.

All stone formers should be advised to increase fluid intake to greater than 3 litres per day. Dietary calcium restriction is not recommended regardless of stone type and metabolic abnormality. Treatment recommendations are based on the type of stones formed and the specific metabolic derangement detected. MT

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