Renal stone disease is an ancient and common affliction, whose clinical occurrence and presentation is described in the Aphorisms of Hippocrates. Renal stones occur once in a lifetime in 15% of white men and 6% of all women, and recur in about half these people. Despite urbanisation of black South Africans, renal stones have been reported in less than 1% of this population. Up to 75% of stones are calcium oxalate, the others are struvite (magnesium ammonium phosphate, 10–20%), uric acid (5%), 5% contain more than 50% brushite (calcium monohydrogen phosphate) or hydroxyapatite, and less than 1% are composed of cystine. Because the treatment for every stone type is different, stone composition should be analysed by polarisation microscopy. Although much progress has been made in understanding the pathophysiological mechanisms of stone disease, allowing for more effective diagnosis and treatment, stones still cause substantial morbidity from pain, urinary-tract obstruction, and infection.

Pathogenesis

The mechanisms of crystallisation need to be understood to outline the basis of stone formation. The states of saturation of ions in a solution are governed by their concentrations. For example, when concentrations of calcium and oxalate reach saturation (the saturation product), stone formation begins with association of small amounts of crystallloid to form nuclei (nucleation). These nuclei normally grow and aggregate on surfaces such as collecting ducts and renal papillary epithelium. Renal epithelial cells specifically bind and internalise calcium oxalate monohydrate crystals. Events that occur after crystal binding could be important in pathogenesis of stones—ie, cellular responses might be essential for initiation of stone formation.

Fortunately, stone formation is inhibited in urine of mammals by substances that prevent crystallisation, and will only take place once the formation product (the metastable limit) has been exceeded. Therefore, crystallisation in undiluted human urine will begin only in a supersaturated solution of calcium and oxalate. Estimates of urine saturation with stone-forming salts such as calcium, phosphate, urate, and oxalate are important in calculation of overall propensity to crystal formation. Urinary saturation with calcium oxalate is common in the general population so the role of other factors in stone formation must be crucial.

However, before discussion of inhibitory and promoting substances, other important factors need to be stressed. First, uric acid can precipitate in persistently acid urine, even in the absence of hyperuricaemia or hyperuricosuria. Second, uric acid can cause formation of calcium oxalate stones without being incorporated into the crystals. This catalyst-like ability is known as salting out, and is enhanced in acid urine. Finally, urinary pH has an essential role in many other inhibitor or promoter reactions. Lithogenic risk factors include stone promoters and inhibitors (panel 1). Effects of inhibitors on stone formation have been most studied in calcium oxalate stones. Most inhibitors are anionic and seem to exert their effects by binding to the calcium oxalate surface, although the specific structural mechanisms of this process are not known.

The many proteins found in stones could cause, be the result of, or have no role in their formation. Nephrocalcin is an acidic protein of renal tubular origin, and in some people who form stones this protein lacks the aminoacid, γ-carboxyglutamic acid, which reduces
healthy individuals. The peptide inhibits calcium excretion in healthy people but not from healthy individuals. They showed that a thiazide has an inhibitory role that prevents stone formation, but further research is required to show that any disorder that induces even mild hypercalcaemia. Such disorders include: (1) primary hyperparathyroidism, which results from an adenoma in 85% of cases, and is associated with mild to moderate hypercalcaemia. People who form stones and have hypercalcaemia are almost certain to have this parathyroid problem. Hypercalcaemia is a result of excess parathyroid hormone, which causes overproduction of 1,25-dihydroxyvitamin D in the kidney; both factors promote bone resorption, increasing the filtered load of calcium and hence calcruia. (2) Other disorders that induce hypercalcaemia can also result in hypercalciuria: malignancies, granulomatous diseases, sarcoidosis, thyrotoxicosis, and immobilisation. (3) Idiopathic hypercalciuria is a familial disorder affecting both sexes equally, in which urinary calcium concentration is raised despite normal concentrations of blood calcium. The primary mechanisms for such hypercalciuria can occur individually or in combination and include high intestinal calcium absorption (the commonest mechanism), with a normal or slightly raised serum calcium, suppressed parathyroid hormone, and increased renal filtered load; increased bone resorption; defective renal-tubular calcium reabsorption, with an inappropriately high phosphate excretion for any given calcium concentration, which might induce increased activation of 1,25-dihydroxyvitamin D; and raised phospholipid-arachidonic acid concentration in serum and erythrocytes, with raised urinary prostaglandin E2 concentrations. (4) Mutations in the CLCN5 chloride channel in Japanese patients resulted in low-molecular-weight proteinuria, hypercalciuria, and calcium stone formation. (5) Other causes of hypercalciuria are inherited syndromes of familial benign and autosomal dominant hypercalciuric hypocalcaemia. These disorders are the result of a mutation in the calcium receptor gene. The calcium receptor facilitates regulation of parathyroid hormone secretion and renal-tubular calcium reabsorption in response to changes in extracellular calcium concentrations. Another condition associated with renal stone formation is hyperoxaluria. Oxalate is an end-product of metabolism, is largely derived from endogenous sources, and is excreted unchanged in urine. Foods rich in oxalate—rhubarb, standard teas, nuts, beans, spinach, coffee, and chocolates—can increase concentrations in urine to 670 μmol/day (normal value 440 μmol/day). However, concentrations of more than 890 μmol/day indicate enteric oxaluria (associated with malabsorptive small-bowel diseases), mild metabolic hyperoxaluria, or primary hyperoxaluria.

**Panel 1: Urinary stone promoters and inhibitors**

<table>
<thead>
<tr>
<th>Promoters</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Citrate</td>
</tr>
<tr>
<td>Sodium</td>
<td>Pyrophosphate</td>
</tr>
<tr>
<td>Oxalate</td>
<td>Calcium</td>
</tr>
<tr>
<td>Urate</td>
<td>Citrate</td>
</tr>
<tr>
<td>Cystine</td>
<td>Citrate</td>
</tr>
<tr>
<td>Low urine pH</td>
<td>Pyrophosphate</td>
</tr>
<tr>
<td>Tamm-Horsfall protein</td>
<td>Citrate</td>
</tr>
<tr>
<td>Urinary prothrombin fragment 1</td>
<td>Citrate</td>
</tr>
<tr>
<td>Protease inhibitor: inter-α-inhibitor</td>
<td>Citrate</td>
</tr>
<tr>
<td>Glycosaminoglycans</td>
<td>Citrate</td>
</tr>
<tr>
<td>High urine flow</td>
<td>Citrate</td>
</tr>
</tbody>
</table>

its ability to inhibit nucleation. Additionally, nephrocalcin inhibits calcium oxalate aggregation, which some believe is a crucial step in initiation of stone formation. Nephrocalcin might also affect calcium phosphate crystallisation. Tamm-Horsfall protein (THP) is the most abundant protein in human urine, and is synthesised and secreted by epithelial cells of the thick ascending limb of the loop of Henle and early distal convoluted tubule. THP remains at crystal surfaces, and thus mainly affects aggregation of preformed crystals. Controversy still exists about whether this protein is a promoter or inhibitor of crystallisation. Glauser and colleagues measured THP in 24 h urine samples from people who formed stones and from healthy individuals. They showed that a rise in THP excretion correlated with increasing urinary calcium and oxalate excretion in healthy people but not in those who formed stones. This result could indicate that THP has an inhibitory role that prevents lithogenesis.

Of considerable interest is the role of proteins that are incorporated in substantial amounts in renal stones, and their effects on stone formation. One such protein, crystal matrix protein or prothrombin fragment 1, is a peptide generated from sequential cleavage of crystal matrix protein or prothrombin fragment 1, is a peptide that inhibits calcium oxalate crystallisation. The peptide inhibits calcium oxalate crystal aggregation and growth in rats, and might be excreted by the kidney to protect against stone formation, but further research is required to show that this process occurs in people. The peptide chain of inter-α-inhibitor has been isolated from urine, and has been reported to inhibit calcium oxalate crystallisation. Although research on this protein continues, Dean and colleagues concluded that inter-α-inhibitor does not have a substantial inhibitory role in crystallisation, which emphasises the point that some proteins associated with stones could have no active involvement in their formation. Lastly, glycosaminoglycans, or urinary polyanions, are potent inhibitors of growth of calcium oxalate in urine, and block adhesion of uric acid crystals.
Mild metabolic hyperoxaluria does not seem to represent a substantial fraction of hyperoxalurias, although in one study from South Africa, 20% of patients with recurrent renal stones had this disorder. Cytosolic enzyme perturbations are thought to result in mild hyperoxaluria and recurrent calcium oxalate stones, but the exact pathogenic mechanisms have not been identified. Pyridoxine, which is a cofactor in shunting glyoxalate to glycine and pyruvate (ie, away from oxalate), has been successfully used to treat these patients.

Primary hyperoxaluria type 1 disease is caused by lack of the liver enzyme alanine:glyoxylate aminotransferase, and type 2 disease by lack of D-glycerate dehydrogenase. The defective genes that cause these diseases and their abnormal liver enzyme products cause excessive oxalate metabolism, which results in systemic calcium-oxalate deposition from a young age.

Finally, hypocitraturia is also associated with renal lithogenesis. Citrate forms a highly soluble complex with calcium, and thus acts as an inorganic inhibitor of stone formation and interferes with surface-controlled crystallisation. Hypocitraturia could result from causes of intracellular acidosis such as renal failure, potassium deficiency, distal renal tubular acidosis, chronic diarrhoeal states, and drugs such as acetazolamide. Many patients with stones have unexplained low urinary citrate, dysfunction of the renal sodium-citrate cotransporter has been proposed as a possible mechanism.

Uric acid stones
Uric acid stones are smooth, round, yellow-orange and nearly radiographically transparent—unless mixed with calcium crystals or struvite. They are typically seen as filling defects on intravenous pyelograms, and computed tomography scanning can distinguish them from kidney tissue or blood clots. Diets high in purines, especially those containing organ meats and fish, result in hyperuricosuria, and, in combination with low urine volume and low urinary pH (as a result of impaired renal ammonia production), can exacerbate uric-acid stone formation. Uric acid salts out calcium oxalate, and can precipitate out in acid urine even in the absence of raised serum or urinary uric-acid concentrations. Furthermore, hyperuricaemic disorders including gout (about 20% of patients with gout are hyperuricosuric), myeloproliferative disorders, tumour lysis syndrome, and inborn errors of metabolism (such as Lesch-Nyhan syndrome and glucose-6-phosphatase deficiency) result in an increased filtered load of uric acid and thus, hyperuricosuria.

As with all stones, certain drugs may enhance stone formation, and in the case of uric acid stones, hyperuricosuric agents include low dose salicylates, probenecid, and thiazides.

Struvite or triple phosphate stones
Radiographs show struvite stones as large, gnarled, and laminated. They are associated with substantial morbidity including bleeding, obstruction, and urinary-tract infection. Signs of struvite stones include urinary pH greater than 7, staghorn calculi, and urease that grows bacteria on culture (proteus, klebsiella, pseudomonas). Stones develop if urine is alkaline, contains trivalent phosphate, and contains urease produced by bacteria.

Cystine stones
Cystine stones should be suspected in patients with a history of childhood stones or a strong family history. They are greenish-yellow, flecked with shiny crystallites, and are moderately radio-opaque with a rounded appearance. Calcium stones are denser than vertebral bodies, whereas cystine stones are less dense. People who are homozygous for cystinuria (an autosomal recessive disorder) excrete more than 600 mg per day of insoluble cystine. More than half the stones in cystinuria are of mixed composition, and many patients have associated physiological problems such as hypercalciuria (19% of patients), hyperuricosuria (22%), and hypocitraturia (44%).

Clinical presentation of acute stone episode
When a urinary stone moves into the renal collecting system, the resulting increase in intraluminal pressure stretches nerve endings in the mucosa, and produces a severe and often colicky pain. This pain radiates downward on the anterior from the flank toward the groin, and is often accompanied by frequent urination, dysuria, oliguria, haematuria, acute nausea, and hypotension. In the acute setting, stones can obstruct the urinary tract producing serious symptoms, or obstruction can be a relatively slow and painless process resulting from slow stone growth and presenting with advanced renal parenchymal damage. Precipitants of acute stone episodes include dehydration and reduced urine output, increased protein intake, heavy physical exercise, and various drugs (panel 2).

Investigations

Acute setting
Documentation of stone characteristics is extremely important (type, size, and location). Although there is a risk of allergy and contrast nephropathy, intravenous pyelography remains the gold standard for such identification. Ultrasonography can indicate whether a stone is in the kidney or ureter, the degree of any obstruction, and quality of renal parenchyma. Plain abdominal radiography is useful for stones above the pelvic brim, and, with ultrasonography, is the investigation of choice in patients unable to tolerate an intravenous pyelogram (for reasons such as allergy to iodine or renal insufficiency).

Medical management of a stone depends on the type of stone, and includes correction of dietary aberrations, metabolic defects, or both. Panel 3 shows recommended investigations.
Panel 3: Investigations for a renal stone

Blood
- Full blood count
- Urea and electrolytes
- Calcium
- Phosphate
- Bicarbonate or carbon dioxide
- Uric acid
- Parathyroid hormone
- Alkaline phosphatase
- Cholesterol

Urine
- Spot pH (include an acid load test if pH >5-4)
- Specific gravity
- Culture
- 24-h analysis of urinary: volume, calcium, sodium, urate, creatinine, phosphate, citrate, and oxalate
- Polarisation microscopy (after fracture of calculi)
- Urinary calcium: creatinine ratios
- Infrared spectrometry

Classification of hypercalciurias is of limited use in management patients with calcium stones, and the calcium-loading test has become obsolete.24

Chronic setting
All kidney stones should be investigated25 and assessment needs to include a thorough medical history, drugs taken, family history, lifestyle and diet, fluid intake, and a clinical examination. Investigations outlined in panel 3 should be done. Saturation with stone-forming salts can be calculated from these measurements with commercially available computer software. More than one 24 h urine sample might be needed, especially to be able to define a stone as idiopatic if all results are negative. Optimum values of 24 h urine sample constituents are shown in panel 4.

Management of acute stones

Pain relief
Renal colic is one of the most intense forms of pain and requires prompt symptomatic treatment. Non-steroidal anti-inflammatory drugs given orally or intravenously have good analgesic properties,26 although they also have serious gastrointestinal and renal side-effects. Renal side-effects are especially important in dehydrated patients and those at risk of allergy to these drugs. Cyclo-oxygenase-II inhibitors have been developed to reduce gastrointestinal effects, but they also inhibit renal vasoactive substances and are contraindicated in patients with renal insufficiency.27 Paracetamol given every 4 h is well tolerated, but pain relief is often inadequate with this agent alone. Narcotic analgesics including morphine (given intramuscularly or intravenously) and pethidine offer excellent pain relief and are the drugs of choice for acute renal colic. However, they are sedative and have the risk of dependence if used for a long time. Their emetogenic side-effects can be counteracted with antihistamines such as hydroxyzine, which has additive analgesic properties in combination with narcotic agents. Codeine is physiologically related to morphine, and, when combined with paracetamol or aspirin, is effective for moderate pain. Dextropropoxyphene combined with paracetamol has been used in the acute setting, and offers fair pain relief if other opiates are contraindicated.

Fluids
An increase in diuresis will help patients to pass stones, and stone and urinary supersaturation can be reduced by judicious fluid management. Patients should drink 2–3 L of water daily, or be given water by intravenous infusion if nauseous. However, an increase in diuresis can worsen pain, hydrenephrosis, and ureteral function, in which case ureteral stenting might be necessary.

General therapies
A regular catharsis should be encouraged, and although uncommon in the acute setting, urinary-tract infection should be investigated and treated if found. Education of patients about maintenance of adequate hydration, and avoidance of precipitating drugs and foods should begin as soon as possible after an acute event.

Management of chronic stones

General measures
Non-pharmacological interventions reduce 5 year rate of stone recurrence by up to 60%28 in people who adhere to a sensible diet. Patients should be encouraged to increase their basic intake of water to at least 2 L daily, and especially so during heavy exercise, pyrexial episodes, and when travelling long distances. Maximum urine output should be encouraged in patients with renal insufficiency, with careful monitoring of volume status and weight gain.

A non-animal low protein diet (0·8–1·0 g/kg per day) prevents the mild acidosis induced by animal protein breakdown, and improves calcium homeostasis. Severe protein restriction results in malnutrition and muscle breakdown and should be discouraged.29 Measurement of urea and, if possible, inorganic sulphate excretion are easy ways to assess total and animal protein intakes. Calcium binds oxalate in the gut, thus people who form stones and are on a high calcium diet paradoxically have a lower occurrence of stone formation than those not on such a diet. Dietary calcium should be limited to about 1 g/day in patients who remain hypercalciuric despite pharmacological treatment. An increased tubular sodium load results in reduced tubular reabsorption of calcium, therefore a low sodium diet (2–3 g/day) is recommended for hypercalciuric patients.

Specific therapies
These therapies are designed for patients with metabolically active stone disease. After general
measures have been instituted, further treatment is based on stone composition and abnormalities noted from the 24 h urine sample analyses.

**Calcium stones—hypercalciuria**

Thiazide diuretics such as hydrochlorothiazide (at doses of 25–50 mg/day) increase distal tubular reabsorption and reduce intestinal calcium reabsorption. Indapamide (2.5–5.0 mg/day) has been shown to be best for treatment of recurrent stones associated with idiopathic hypercalciuria. This agent has fewer untoward metabolic effects than other thiazides if used in high doses. Addition of potassium citrate maintains potassium concentration at the ideal of 3.5–4.0 mmol/L and this, together with citrate, improves citrate excretion in the tubules thereby reducing crystal agglomeration. Persistent hypercalciuria can respond to potassium-sparing diuretics, calcium restriction (800–1000 mg/day), and reassessment of compliance. Phosphate rarely needs to be replaced even in patients on thiazides. Calcium carbonate (500–650 mg tablets, two or three times per day) in combination with magnesium carbonate (0.5–1.0 g/day) is a useful adjunct. Mild metabolic acidosis that accompanies hypercalciuria can be treated with sodium bicarbonate, because citrate is an effective treatment for most calciumstones, although occasionally side-effects (agranulocytosis and thrombocytopenia) limit its clinical use.

**Calcium stones—hyperphosphaturia**

Because urinary phosphate losses exceed intake, it is essential to ensure adequate dietary phosphate intake. Phosphate levels should be maintained above 400–1000 mg/day. As phosphate intake is normal or increased, dietary calcium restriction is critical.Patients with hypercalciuria and idiopathic hypercalciuria are at increased risk of kidney stones. To prevent stone formation, dietary calcium should be reduced to less than 200 mg/day and urinary calcium excretion should be reduced to less than 200 mg/day. Calcium supplements should be avoided and dietary calcium intake should be less than 600 mg/day. Patients with hypercalciuria should be carefully monitored for signs of bone demineralization. Dietary calcium restriction is also important in the prevention of recurrent calcium stones in patients with hypercalciuria.

**Calcium stones—hyperuricosuria**

Recommended therapies are increased fluid intake, treatment of the underlying cause of disease, and a low purine diet with the addition of allopurinol if other measures fail.

**Uric acid stones**

Recommended therapies include adequate fluid intake, a low purine diet, and urinary alkalinisation (pH 6.5) with potassium citrate. Such measures should pre-empt use of allopurinol and acetazolamide for urinary uric acid secretion and alkaline pH maintenance. Antacids are not recommended. Because urate stones form at a lower pH than calcium stones, urinary alkalisation is necessary to dissolve uric acid stones. Allopurinol is used to reduce uric acid production, and potassium citrate is used to increase urinary urate solubility.

**Struvite stones**

Because urease-producing bacteria are often embedded in these stones, antibiotics can be ineffective in eradication of the offending pathogen. Early urological intervention is warranted in patients with these stones, as is use of culture-specific antibiotics around the time of operation. Furthermore, once the patient is stone free, Wong and colleagues recommend continuation of antibiotics until cultures remain negative for at least 3 months. As an adjunct, oral phosphate binders reduce phosphate content of these stones.

**Calcium stones—renal tubular acidosis**

These patients have a mild metabolic acidosis that results in increased renal tubular reabsorption, metabolic citraturia, and hypercalciuria. In patients with type 1 renal tubular acidosis (distal), raised urinary pH promotes calcium phosphate precipitation, and high doses of potassium might be necessary to prevent stone formation.