Medical management of renal stone disease

Nephrolithiasis can cause significant morbidity in affected individuals. Recurrent stone disease can be prevented through a multidisciplinary approach to management.

Nephrolithiasis is defined as formation of stones in the renal tubules or collecting system. Calcification of the renal parenchyma is defined as nephrocalcinosis. This article focuses on nephrolithiasis detailing the evolving knowledge of its aetiology, pathogenesis and clinical features and summarizing current evidence-based recommendations for the investigation and medical management of different types of renal stones.

Epidemiology

Nephrolithiasis is seen worldwide, but prevalence rates vary geographically. In the USA a prevalence of 5.2% is currently reported. Peak incidence occurs in middle age, with overall prevalence increasing with age (Stamatelou et al, 2003). Males are affected more often than females. In the USA prevalence of stone disease is higher in the south compared to the north, and east compared to west (Soucie et al, 1994). Increased temperature, longer exposure to sunlight and oral fluid intake may explain this geographical variation (Soucie et al, 1996). The reported prevalence of different stone types also varies in a geographical distribution. Uric acid stones are the most prevalent type of stones in the Middle East while calcium-containing stones are the most prevalent in western countries, accounting for almost 70% of presentations. Struvite stones account for 20–25%, calcium phosphate and uric acid stones account for less than 15% and cystine stones are rare in the UK. Other stones types occur such as drugs and chemicals precipitating as stones. The recurrence of nephrolithiasis after the first stone has passed is at least 27% at 7 years (Trinchieri et al, 1999).

Genetics

A positive family history is associated with an increased risk of developing nephrolithiasis. The formation of renal stones may be dependent on interaction between genetic and environmental factors (Gambaro et al, 2004). The presence of a genetic influence is shown by an increased prevalence of stone disease in relatives of stone formers as well as in twin studies which showed increased concordance rates for stones among mono-zygotic twins (Goldfarb et al, 2005). This genetic influence could be through monogenic inheritance which is rare or the more common polygenic inheritance. Examples of monogenic diseases causing nephrolithiasis are Dent's disease (CLCN5 mutation) and Bartter's syndrome (SLC12A1 or KCNJ1 mutations). Through linkage and genome-wide association studies there is evidence to suggest an association between claudin 14 (CLDN14), calcium sensing receptor (CASR), osteopontin (OPN), and vitamin D receptors (VDR) genes and an increased susceptibility to calcium stone formation in specific environmental conditions. This supports the hypothesis of a polygenic influence (Vezzoli et al, 2011).

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Pathophysiology

Crystallization is the basis of stone formation. This occurs when a substance reaches supersaturation levels in urine. Supersaturation depends on the activity of free ions in the urine rather than the concentration of the individual solute. Urine contains substances that act as inhibitors of crystallization such as citrate. The concentration of these inhibitors will influence the free ion activity of calcium and other ions. Therefore a high concentration of inhibitor will allow calcium concentration to reach a high level before supersaturation occurs. The supersaturation point of calcium oxalate, calcium phosphate and uric acid can be calculated from a 24-hour urine collection. It has been shown that patients with recurrent nephrolithiasis have abnormal supersaturation values, which may normalize after appropriate management (Parks et al, 1997).

Clinical presentation

Pain

Colicky pain is the most common symptom associated with nephrolithiasis. The severity of the pain does not relate to the size of the stone (Prina et al, 2002). Stones higher up in the collecting system can lead to the classical symptoms of acute colicky flank pain radiating to the loin (renal colic). The pain may become more localized as the stone approaches the ureterovesical junction, and can cause dysuria, urgency and genital pain (Teichman, 2004).

Incidental finding
Stones may be picked up in asymptomatic patients on incidental imaging.

Haematuria
Microscopic or gross haematuria is often present. However, stones may be present even in the absence of haematuria on urine dipstick (Argyropoulos et al, 2004).

Complications
Patients may present with symptoms of acute renal failure as a result of chronic hydronephrosis secondary to a renal stone if both kidneys are affected or the kidney affected is the only functioning kidney. Pain in patients with partial or slowly developing hydronephrosis may be minimal or absent (Rose and Black, 1988). The management of hydronephrosis is beyond the scope of this review. Patients with stone disease are at increased risk of developing chronic kidney disease (Rule et al, 2009).

Clinical evaluation
Clinical evaluation should include a comprehensive history, clinical examination and specific investigations. History will serve to establish risk factors and possible genetic defects. Drugs can increase the risk of stone formation or precipitate into stones (*Table 1*). Physical examination is often unremarkable but may demonstrate other evidence of hyperuricaemia for example in joints.

Investigations
There is controversy about investigating patients with an uncomplicated stone at the first presentation. The general consensus is to investigate all stone formers but reserve urinary metabolic screen for those who have single crystal stones, recurrent stones or complicated presentation with infection or obstruction. Investigations commonly used for patients presenting with stone disease are summarized in *Table 2*.

Stone analysis
When available analysis of a passed stone will enable targeting the management strategy to the stone composition.

Urine analysis
Basic urinalysis and urine culture should be performed in all stone formers. A urine pH of <5.5 is associated with uric acid stones, whereas alkaline urine pH is associated with calcium phosphate and struvite stones (Moe, 2006). Spot samples should be tested for cystine. Urine microscopy can reveal crystals of oxalate, uric acid, cystine and struvite.

Venous blood sampling
Calcium, phosphate, uric acid, bicarbonate, sodium, potassium, chloride, urea and creatinine should be measured and abnormalities investigated further.

Table 1. Clinical evaluation of the patient with renal stone disease

Assessing risk factors	Family history with details of affected patients where possible	
	History of stone disease (age at presentation, frequency, surgical history)	
	History of urinary tract infections	
	History of neoplastic disease, sarcoidosis, endocrine disease (risk factors for hypercalcaemia)	
Comorbidities	Diseases of the gastrointestinal tract	
	Gout	
	Obesity	
	Diabetes mellitus	
Environmental factors	Occupation	
	Fluid intake	
	Diet	
	Exercise intensity	
	Urine volume	
Drug history	Drugs that may precipitate into stones	Triamterene
		Aciclovir
		Indinavir
	Drugs that increase the risk of stone formation	Loop diuretics
		Calcium and vitamin D supplements
		Glucocorticoids
		Antacids
		Theophylline
		Acetozalamide
		Salicylates
		Probenecid
		Vitamin C

Table 2. Investigation of the patient with renal stone disease

Stone analysis	
Urinalysis	Urine culture
	Urine pH
	Urine microscopy for crystals
	Urine metabolic screen (24-hour urine collections)*
Venous blood chemistry	Calcium
	Sodium, potassium, creatinine, chloride, bicarbonate
	Uric acid
Imaging	Kidney, ureter bladder
	Computed tomography
	Ultrasound

* see text for indications

For the patient presenting with a non-calcium stone, a recurrent stone, a family history of stone disease or complicated stone a 24-hour urine collections should be performed. Hydrochloric acid in the collection bottles prevents the precipitation of calcium oxalate and calcium phosphate during storage. Urine analysis should include calcium, oxalate, creatinine (to ensure complete collection) and urate. Citrate values are helpful but most laboratories do not measure this without specific discussion. Despite the logistical challenges of 24-hour urine collections this remains the gold standard in evaluating urinary metabolic abnormalities in stone-formers (Hong et al, 2010).

Imaging

Imaging forms an essential part of the diagnostic process. Plain film abdominal X-ray of the kidney, ureter and bladder will demonstrate calcium-containing stones, as they are radio-opaque. Kidney, ureter and bladder films remain useful as a first-line and follow-up tool to confirm stone size and recurrence (Lamb et al, 2008).

In recent years non-contrast helical computed tomography scans have replaced intravenous pyelograms in diagnosis of renal stones, particularly those that are radiolucent (*Figure 1*) and in the acute presentation. Computed tomography renal colic has high specificity and sensitivity approaching 100% (Worster et al, 2002). Attempts have been made to develop imaging tools that do not expose patients to radiation. Doppler ultrasound can be used to assess for any obstruction in the pelviceal collecting system by measuring renal blood flow. Ultrasound has acceptable specificity but poor sensitivity. Computed tomography remains the first choice investigation in patients with nephrolithiasis (Granata et al, 2009). Magnetic resonance imaging is not particularly sensitive for nephrolithiasis, but can be used to assess for evidence of obstruction (Kalb et al, 2010).

General management of the patient with renal stones

The general principles of management for prevention of recurrent stones are detailed in *Table 3*. It has been considered appropriate to restrict sodium intake to less than 100 meq/day in all stone formers. Increased urinary sodium load inhibits passive proximal tubular reabsorption of calcium. However, there is evidence to suggest that the risk of calcium stones is not increased by increasing urinary sodium (Eisner et al, 2009). It may be more appropriate to advise a normal sodium diet.

Medical expulsive therapy is considered a useful adjunct in the management of renal stones. Alpha blockers like tamsulosin have been associated with increased expulsion of distal ureteric stones in randomized control trials (Parsons et al, 2007). Calcium channel antagonists like nifedipine have been shown to be effective expulsive agents for upper mid ureteric stones (Micali et al, 2007).

Role of surgery

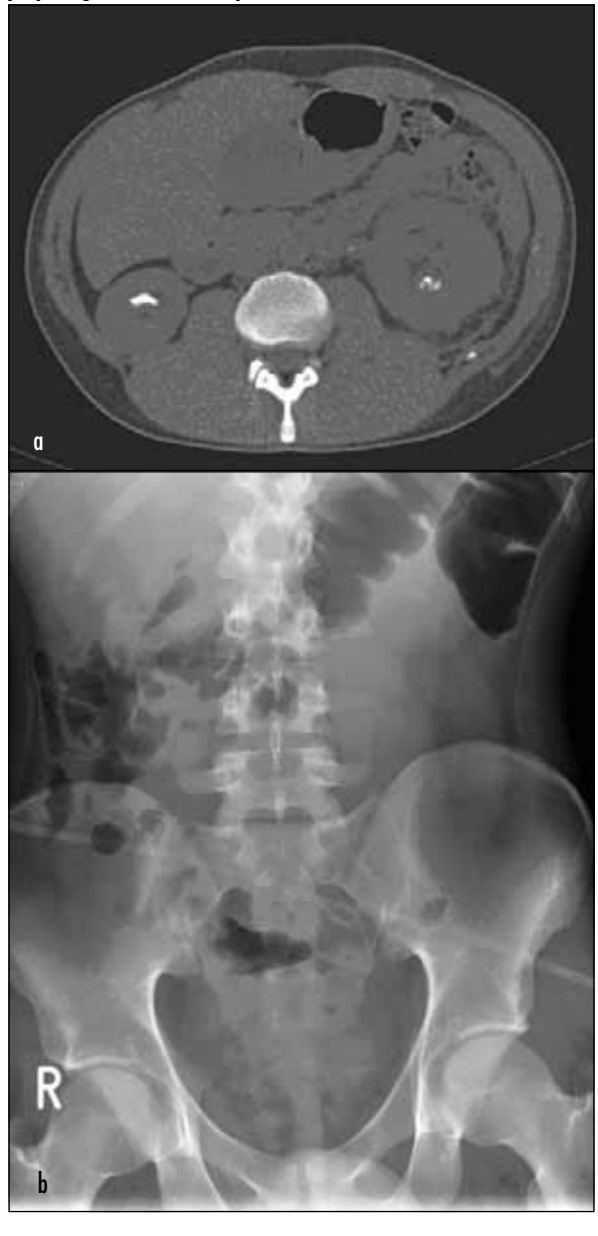
Multidisciplinary management of the patient with stone disease with surgical, nephrological and dietetics input is advisable. Struvite stones, stones greater than 7 mm in diameter and stones causing urinary obstruction often require surgical intervention.

Specific stone types

Calcium stones

Specific risk factors for calcium stone formation include hypercalciuria, hyperoxaluria, hypocitraturia, distal renal tubular acidosis and hyperuricosuria. In some patients no risk factors can be identified.

Figure 1. a. Spiral computed tomography image showing bilateral renal stones involving the calyceal system in a patient with cystinuria. b. Plain kidney, ureter and bladder film of the same patient showing a much smaller burden of faintly calcified stones projecting over both kidneys.



Excess excretion of urinary calcium

Idiopathic hypercalciuria is commonly familial and presents in the third decade of life. The mechanism is unclear but is likely to be a combination of increased intestinal absorption and abnormal handling of calcium by the kidney. Hypercalcaemia of any cause can lead to hypercalciuria. Management follows the general guidance above and correcting the cause of hypercalcaemia if present. Pharmacological treatment consists of a long-acting thiazide (e.g. chlorthalidone 25–50 mg/day) to reduce urinary calcium excretion. This should be in combination with potassium supplements or potassium citrate to maintain serum potassium levels and increase urinary citrate (potassium citrate liquid or urocit-K wax tablet 20–40 mmol/day) (Preminger et al, 1985; Escribano et al, 2009). Monitoring of urine pH is advisable as pH >7 will increase the risk of calcium phosphate precipitation into stones.

Distal renal tubular acidosis

Distal renal tubular acidosis (type 1) leads to high urine pH in the context of normal-anion gap metabolic acidosis. Urinary calcium excretion is increased and citrate excretion reduced because of the effect of acidosis. This in combination with alkali urine pH increases urinary calcium phosphate supersaturation and the risk of calcium phosphate stone formation (Unwin and Capasso, 2001). Management strategy is to alkalize serum and treat underlying cause of renal tubular acidosis if present. Avoid urine pH above 6.5 as this encourages calcium phosphate precipitation. Patients can be trained to check urine pH at home regularly using bedside urine testing kits.

Hyperoxaluria

Presence of hyperoxaluria is not necessary for formation of calcium oxalate stones. Hyperoxaluria may occur for several reasons:

- Dietary hyperoxaluria can be managed by restricting dietary oxalate while maintaining the balance between calcium and oxalate. Some foods high in oxalate are listed in *Table 4*. Excessive intake of ascorbic acid can contribute to hyperoxaluria as it is oxidized to form oxalate. Referral to a dietician with experience in stone disease is recommended.
- Enteric oxaluria is caused by excessive colonic absorption of oxalate in disorders leading to fat malabsorption such as Crohn's disease, chronic pancreatitis and short bowel syndrome. Fatty acids increase oxalate absorption from the colon and malabsorption also leads to reduced urine volume, hypokalaemia and hypocitraturia – all factors that promote stone formation. Management is by treating the underlying cause, increasing dietary calcium (as part of diet not with additional supplements) to enhance oxalate binding in the gut and reduce its absorption, increasing urine volumes and correcting hypokalaemia and hypomagnesaemia (Su et al, 1991). Pharmacological agents such as cholestyramine can be used to bind fatty acids.
- Increased systemic production of oxalate occurs in inherited liver enzyme deficiency (primary hyperoxaluria I and II). Treatment is with pyridoxine and liver transplantation if multiorgan involvement occurs. Alkalinization of urine and use of orthophospate (in patients with well preserved glomerular filtration rate) may reduce stone formation.
- Ethylene glycol intoxication as ethylene glycol is metabolized to oxalate. Management as in ethylene glycol poisoning with alkalinization of the urine.

Colonic colonization with *Oxalobacter formigenes* appears to be associated with reduced risk of recurrent oxalate stone (Kaufman et al, 2008). Investigators have used oral formulation of the bacteria in patients with primary hyperoxaluria but found no effect on urine oxalate excretion (Hoppe et al, 2011).

Decreased citrate excretion

Citrate binds urinary calcium inhibiting crystallization. Metabolic acidosis results in an increase in citrate reab-

Table 3. General advice for prevention of recurrent stone formation

Intervention	Reason
Sodium intake less than 100 meq/day (5 g)	Increased reabsorption of calcium in the proximal tubule
Urine output >2 litres/day with drinking at bedtime to induce nocturia	Reduce supersaturation and precipitation of crystals. Urine concentration physiologically increased at night
Reduce animal protein intake	Acidosis increases calcium resorption from bone and renal tubules and leads to hypocitraturia. Sulphate and uric acid generated reduce calcium solubility and can result in uric acid stones
Encourage potassium intake	Hypokalaemia causes intracellular acidosis and hypocitraturia
Review medication use and where possible avoid drugs that increase risk of stone formation	
Normal calcium diet without additional calcium supplementation	Low calcium diet associated with bone demineralization and hyperoxaluria. No evidence that restricting calcium reduces risk of stone formation (Borghi et al, 2002)

Table 4. Foods rich in oxalate

Spinach
Rhubarb
Peanuts
Instant tea
Almonds
Chocolate
Pecans

sorbtion and therefore hypocitraturia. Other causes include hypokalaemia, hypomagnesaemia, infection and acetozalamide therapy. Most laboratories will not measure urinary citrate so diagnosis is based on clinical suspicion in the patient with recurrent stone disease in the presence of low urine pH. Management is to reduce dietary animal protein and supplement with potassium citrate or bicarbonate.

Uric acid stones

Pure uric acid stones are radiolucent and therefore not detectable on a plain kidney, ureter and bladder film. A computed tomography scan, ultrasound or intravenous pyelogram is indicated to confirm the presence of a radiolucent stone. Sodium urate or uric acid stones can form a nidus for calcium stone formation. Screening for risk factors for uric acid stone formation is indicated in patients with recurrent calcium stones. Uric acid excretion can be monitored with repeated 24-hour urine collections. Risk factors for stone formation are:

- Low urine volume which can be a feature of gastrointestinal disease such as small bowel pathology or result from living in temperate climates (Romero et al, 2010). Increasing urine volumes to over 2 litres per day can help reduce stone formation.
- Low urine pH promotes uric acid stone formation as uric acid solubility increases with rising pH (Moe, 2006). Alkalinization of urine with bicarbonate or citrate is recommended aiming for a pH between 6 and 7 avoiding the sodium salts. Patients are encouraged to use bedside urine pH testing at home.
- High levels of urinary uric acid can be a feature of several metabolic disorders such as gout, tumour lysis syndrome and inherited disorders of metabolism such as Lesch–Nyhan syndrome. Allopurinol or febuxostat may be of benefit in this group of patients.
- High dietary purine intake from animal protein increases urinary uric acid secretion. Restricting animal protein is indicated and also serves to increase urinary citrate (see above section on hypocitraturia).
- Drugs such as salicylates increase uric acid urinary excretion and should be avoided.
- There is evidence linking obesity with uric acid stone formation (Cameron et al, 2006).

Struvite stones (magnesium ammonium phosphate)

Struvite stones occur in patients whose urine is infected with a urea-splitting organism such as *Proteus*, *Haemophilus*, *Pseudomonas* or *Klebsiella*. Stones can increase to a large size forming a staghorn calculus (*Figure 2*). Risk factors include female gender, indwelling catheters, neurogenic bladder and alkali urine (generated by ammonium formed by urinary bacteria). Occasionally special culture medium is required to isolate urea-splitting organisms such as *Mycoplasma* and the laboratory will need to be alerted if this is suspected in a patient with sterile urine on routine culture. Struvite stones are difficult to eradicate and surgical management is often required. Residual fragments form a nidus for new stone formation. Indications for antimicrobial therapy are still a matter of controversy. In symptomatic infection and following surgery treatment with antimicrobials is indicated. In the asymptomatic patient with a struvite stone the urine can be colonized. Cyclical therapy has been used but emergence of multi-resistant organisms is a concern and the mainstay of management is early surgical intervention (Gettman and Segura, 1999). Urease inhibitors such as acetohydroxamic acid are not commonly used as they are poorly tolerated.

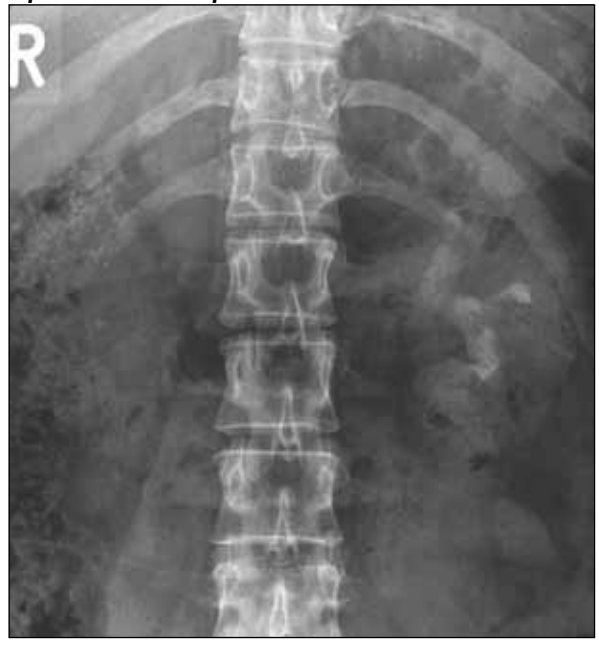
Cystine stones

Cystine stone disease presents as multiple or staghorn calculi in the fourth decade. Patients have a rare hereditary disorder, cystinuria, in which dibasic amino acid transport is impaired. Diagnosis is by measuring urine cystine initially on a spot urine sample then quantifying it in a 24-hour collection. Solubility of cystine is higher in alkaline urine. Management is based around encouraging very large urine volumes of greater than 3 litres/day and alkalinization of the urine. Penicillamine 250 mg to 2 g/day or tiopronin 800 mg/day reduce urinary supersaturation of cystine. Captopril has also been used to bind cystine and increase its solubility (Printza et al, 2007).

Melamine exposure

Melamine, an organic base, was implicated in an outbreak of renal stones in about 300 000 Chinese infants

Figure 2. Plain kidney, ureter and bladder film showing a radiopaque left staghorn calculus in a patient with recurrent proteus urinary tract infection. Note speckled calcification of bilateral nephrocalcinosis in this patient.



and children in 2008. This followed the contamination of milk products. Stones were a mixture of uric acid and melamine. Along with cyanuric acid, it has been shown to cause renal stones in adults (Liu et al, 2011).

Conclusions

Nephrolithiasis is a relatively common condition and is associated with significant morbidity and potential mortality. Emergency admissions for pain relief and the recurrent nature of nephrolithiasis lead to a significant cost to the health service. Recurrent stone formation is preventable through a multidisciplinary approach to management. Although medical management has meant less frequent surgical intervention recent advances have mainly been in the surgical field with the development of extracorporeal shock wave lithotripsy, percutaneous nephrolithotomy lithotripsy and endoscopic stone removal techniques. Further knowledge of pathophysiology of stone formation will be instrumental in developing new medical therapies for prevention and treatment. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Renal stone disease is common. Careful clinical evaluation may identify relevant risk factors.
- Crystallisation, which occurs when a urinary substance reaches supersaturation levels, is the basis of stone formation.
- Patient with recurrent renal stones warrant careful investigation so that appropriate treatment can be instigated.
- Patients may require both medical management and surgical intervention for their renal stone disease.