

**Leading Article**

## **Renal stones in children: Evaluation and medical management**

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Renal stone disease, also known as nephrolithiasis, has become an important cause of childhood morbidity and healthcare expenditure worldwide<sup>1,2,3</sup>. Consequences of renal stones include pain, urinary tract infection (UTI), urinary obstruction and renal damage that can even lead to renal failure. The term ‘nephrocalcinosis’ refers to deposition of calcium within the renal parenchyma and is distinct from nephrolithiasis which refers to stones in the renal tract. Although nephrocalcinosis occurs less frequently than nephrolithiasis in children, the two can co-exist.

### **Epidemiology**

Although considered an adult disease in the past, nephrolithiasis has become increasingly prevalent in children. While the true incidence among the paediatric population is unknown, recent data show that during the last 25 years, incidence of renal stone disease in children has increased by approximately 6-10%<sup>4</sup>. The incidence among the adult population which was estimated to be about 12%<sup>5</sup> is also reported to be increasing worldwide<sup>6</sup>. The cause for these changes is not fully understood. Renal stones are usually caused by genetic and environmental factors. Since changes in the genetic pool occur at a slow rate, it is unlikely to be the driving force for the increase in stone incidence. Available data point to changes in two environmental factors, namely diet and climate, as the cause for these trends<sup>6</sup>.

Renal stones can occur in any paediatric age group. Reports regarding gender distribution have varied with more recent studies suggesting roughly an equal distribution or a slight female preponderance.

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Younger children more commonly have renal stones which are less likely to pass spontaneously, whereas older children more frequently have ureteral stones<sup>7,8</sup>. Bladder stones have disappeared from the developed world and have been confined to some pockets in the developing world due to lack of dietary phosphates, especially during infancy<sup>9</sup>.

### **Pathophysiology of stone formation**

The formation of a renal calculus is a complex process that is determined by the interaction of:

- urinary concentration of lithogenic solutes
- volume depletion
- urinary pH
- urinary flow rate
- anatomic factors encouraging urinary stasis e.g. obstructive developmental anomalies
- the balance between promoters and inhibitors of crystallization. Promoters include calcium, oxalates, uric acid, xanthines, cysteine, drugs and cell debris. Inhibitors include citrate, magnesium and phosphates.

The composition of renal stones varies geographically. Infectious stones (struvite stones - magnesium ammonium phosphate), previously accounted for a significant proportion of stones among European children<sup>10</sup>. However, as a result of improvements in the diagnosis and treatment of UTI in children over the past decades, the aetiology of renal stones in children has shifted from predominantly infectious to metabolic causes<sup>11</sup> with a predominance of calcium based stones<sup>12</sup>.

### **Presentation**

The presentation of renal stones in children is somewhat different from that in adults. While adults present with the classic, colicky loin pain, small children commonly present with macroscopic haematuria while older children and adolescents present with abdominal pain<sup>11,14</sup>. Dysuria, frequency, sterile pyuria, UTI and acute urine retention are other presenting features. Stones are sometimes identified as

an incidental finding on ultrasound scans done for unrelated reasons.

**Clinical evaluation**

The key to initial clinical evaluation of a child with renal stones is to get a detailed history. Particular attention should be paid to any consanguinity, family history of stone disease, renal dysfunction and metabolic disease. There is increased risk of recurrent stone formation among individuals having first-degree relatives with hypercalciuria or a previous history of renal stones<sup>14</sup>. In addition to familial factors, particular attention should be paid to the daily fluid intake, dietary intake of sodium, calcium and oxalates, medications (especially vitamins A and D, steroids, and diuretics) and any mineral supplementation. Children with neurological disorders (immobility, anti-convulsant drugs, low fluid intake), chronic bowel disease or abnormalities of the urinary tract that cause urine stasis and UTI are at special risk for stone formation. Presence of consanguinity and a family history of renal stones, young age at presentation and recurrent or bilateral stone disease are clues to an underlying metabolic disorder.

**Investigations**

When a child presents with an acute episode, the first priority is to look for evidence of infection or obstruction by urinalysis and radiological assessment respectively. A complete urinalysis of a freshly voided random urine specimen is necessary for every acute stone episode. Microscopic examination of the urine is important not only for the identification of pyuria, haematuria and organisms but also to differentiate between glomerular and non-glomerular bleeding. Urinary leucocyte esterase and nitrites may be positive if there is associated UTI. Microscopy will also identify urinary crystals which can point to a possible diagnosis e.g. hexagonal cystine crystals in cystinuria, oxalate crystals in hyperoxaluria or hypercalciuria. The urine should be sent for culture and antibiotic sensitivity as infection is not an uncommon finding in a child presenting with a stone<sup>15</sup>.

Further evaluation to identify any predisposing causes should follow only after obstruction has been relieved and any infection adequately treated. The goals are to identify children at risk of recurrent stone formation and to diagnose specific treatable metabolic conditions. These laboratory investigations should preferably be done as an outpatient when the child is taking his or her normal diet as special dietary precautions could obscure some diagnoses such as absorptive hypercalciuria. When testing for oxalosis, patient should not be receiving vitamin C supplements as this can cause false elevation of oxalate levels.

Whenever an inherited metabolic disorder is suspected, family members need to be tested.

Since serum tests are required to interpret urinary results, serum and urine should be tested on the same day. Serum creatinine can identify renal impairment while bicarbonate and pH levels will help to identify renal tubular acidosis. Corrected serum calcium, phosphate and alkaline phosphatase levels are estimated to evaluate hypercalcaemic states and if found to be abnormal, serum parathyroid hormone level should be measured to identify hyperparathyroidism. Elevated serum urate levels are found in abnormalities of purine metabolism.

When it comes to urine testing, the best information is obtained by performing a 24-hour collection since many of the urine constituents are influenced by dietary intake. In addition, it provides an objective assessment of the child’s daily fluid intake. However, obtaining a 24-urine collection is challenging in infants and young children who are not continent. For such patients, measuring the ratio of the concentration of each solute to that of urine creatinine from a random sample is representative of results obtained from a 24-hour urine collection. When testing for calcium and oxalate levels, urine needs to be collected into an acidified bottle for both 24 hour and spot collections. Urine and blood investigations for children with renal calculi are shown in Table 1.

**Table 1: Urine and blood investigations for children with calculi**

<b>Urine</b>	Specific gravity, pH, glucose, protein, leucocyte esterase, nitrites, white cells, red cells, crystals Culture and sensitivity Spot urine: ratios of calcium, oxalate, uric acid and citrate to creatinine Cystine screening 24 hour collection: volume, calcium, oxalate, uric acid, citrate
<b>Blood</b>	Urea & electrolytes, creatinine, calcium, magnesium, phosphate, alkaline phosphatase, albumin Bicarbonate Uric acid Parathyroid hormone

*Radiological imaging*

Ultrasound scan is the initial imaging modality of choice for children suspected to have stones because it is readily available and has the advantage of detecting hydronephrosis, nephrocalcinosis and any anatomical abnormality of the urinary tract that might predispose to stone formation. However, it is less sensitive in

detecting small stones and ureteric stones<sup>16,17</sup>. If the suspicion of a stone is very high despite a normal ultrasound scan, a plain abdominal X-ray can be performed. However, radiolucent stones e.g. uric acid stones will not be visible in the plain radiograph.

The gold standard in diagnosing calculi in children is the non-contrast spiral computed tomography (CT) scan because of its high sensitivity in detecting both small stones and ureteric stones<sup>16,18,19</sup>. However, due to the potential risks of radiation exposure, availability and cost, it should be considered only if clinical suspicion of a stone persists despite a normal ultrasound scan. Intravenous urogram (IVU) which has been used before the availability of CT, has comparable specificity but significantly lower sensitivity than the latter<sup>17,20</sup> and has the disadvantage of having to administer intravenous contrast. However, as IVU can detect radiolucent stones, demonstrate anatomical details and obstruction, it remains a reasonable option.

#### *Stone analysis*

The qualitative analysis of a stone passed spontaneously or after intervention provides valuable diagnostic information. Therefore, parents should be told to retain any stone or gravel material passed in their child's urine and any recovered material should be sent for analysis. Calcium stones are often associated with underlying metabolic abnormalities especially if associated with nephrocalcinosis. Calcium oxalate is the predominant constituent of the majority of stones (75-80%) in the Western world in both adult and children followed by calcium phosphate (5-10%), magnesium ammonium phosphate (10-20%), uric acid (5%) and cystine (5%)<sup>13</sup>.

#### **Specific metabolic causes for stone formation**

##### ***Hypercalciuria***

Hypercalciuria, either alone or in combination with hypocitraturia is the most commonly identified metabolic abnormality<sup>21,22</sup>. Although urinary calcium excretion of more than 4 mg (0.1 mmol)/kg body weight per day is considered abnormal, it is the urinary concentration of calcium that determines the risk of stone formation. The normal values for urinary calcium to creatinine ratios are age dependent and can be as high as 2.2 mol/mol during infancy decreasing to <0.6 mol/mol by seven years of age<sup>23</sup>. As renal handling of sodium and calcium are closely linked, excessive consumption of dietary salt can result in hypercalciuria. The most common cause of hypercalciuria is idiopathic or primary, defined as hypercalciuria that occurs in the presence of normocalcaemia in which no other cause can be

identified. It can be sporadic or hereditary with a complex genetic background<sup>24</sup>. It is classified into two forms viz. renal hypercalciuria caused by a reduction in renal tubular calcium reabsorption and absorptive hypercalciuria caused by increased intestinal absorption of calcium. The two can be differentiated by demonstrating an elevated urinary calcium excretion in the fasting state in the renal form and a normal excretion in the absorptive form<sup>25</sup>. In addition to presenting with stones and nephrocalcinosis, idiopathic hypercalciuria is also known to be associated with dysuria, frequency, non-glomerular microscopic haematuria and urinary tract infections.

In distal renal tubular acidosis, the presence of alkaline urine, hypercalciuria and hypocitraturia almost invariably leads to medullary nephrocalcinosis and calcium phosphate stones. Hypercalciuria is observed in a number of other disorders with tubular dysfunction such as Bartter syndrome, Dent disease, Lowe syndrome and familial hypomagnesaemia hypercalciuria and nephrocalcinosis syndrome. Hypervitaminosis D caused by multivitamin supplements, excessive daily intake of vitamin A and mineral supplement can lead to hypercalcaemia and hypercalciuria. Primary hyperparathyroidism, the most frequent cause of hypercalcaemic hypercalciuria in adults is seen only rarely in the paediatric population. Long term administration of frusemide can also lead to hypercalciuria and nephrocalcinosis or stone formation.

##### ***Hyperoxaluria***

Primary hyperoxaluria (PH) types I and II are relatively rare, autosomal recessive disorders of hepatic oxalate production. PH type I, which is more common, is caused by mutations in the AGXT gene, which result in a functional defect of the hepatic peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT). Overproduction of oxalate by the liver causes excessive urinary oxalate excretion with resultant nephrocalcinosis and nephrolithiasis. However, the phenotype of PH type I shows great variability ranging from death during infancy due to end stage renal failure as a result of extensive nephrocalcinosis to milder forms with nephrolithiasis later in life<sup>27</sup>. The diagnosis of PH type I is strongly suggested by marked hyperoxaluria and can be confirmed by genetic testing for common mutations. PH type II is caused by mutations in the GRHPR gene which results in deficient glyoxylate reductase enzyme activity. It is characterized by excessive urinary excretion of oxalate and l-glyceric acid. PH type II has a less aggressive clinical course than PH type I and the main clinical picture is that of renal stone disease instead of nephrocalcinosis<sup>28</sup>. Diagnosis is suggested

by marked hyperoxaluria and elevated urine L-glyceric acid. Confirmation can be obtained by genetic testing. Among children with oxalate stones, hyperoxaluria is often secondary to increased intake of foods rich in oxalates such as nuts, beet, rhubarb, turnips, sweet potatoes, strawberries, tea, cocoa and chocolate<sup>26</sup>. This is associated with only a mild elevation of urinary oxalate levels. Less commonly, secondary hyperoxaluria is the result of an underlying disorder that leads to the presence of free fatty acids that bind calcium in the intestinal lumen. This results in more unbound oxalates being available for absorption. This form of enteric hyperoxaluria is seen in inflammatory bowel disease, cystic fibrosis, after gastric bypass surgery and intestinal resection.

### ***Hyperuricosuria***

Uric acid stones are uncommon in children. Uric acid is an end product of purine metabolism and has to be excreted via the kidneys. As the solubility of uric acid is pH dependant, a urine pH of less than 6 is the main risk factor for stone formation. Other contributory factors include dehydration resulting in a low urine volume as well as hyperuricaemia resulting from inborn errors of purine metabolism and lymphoproliferative disorders. Lesch-Nyhan syndrome is a rare inborn error of purine metabolism characterized by self-mutilation, mental retardation, hyperuricaemia with uric acid calculi and choreoathetosis.

### ***Cystinuria***

Cystine stones accounts for about 5% of the renal stones in children. Cystinuria is an autosomal recessive disorder of amino acid transportation in the proximal tubule resulting in urinary hyper secretion of cystine, lysine, arginine and ornithine. Cystine stones may develop at any age, starting from the neonatal period, but usually occur during childhood<sup>29</sup>. In very young children cystine calculi may occur in the bladder but in older children renal calculi are more frequent<sup>30</sup>. Large staghorn calculi are also seen. Cystine stones are of intermediate density on plain X-ray films so that smaller stones may be missed. Ultrasonography and CT imaging provide better visualization.

### ***Hypocitraturia***

Approximately 10-30% of the citrate filtered in the glomerulus is excreted in the urine. Citrate forms soluble complexes with urinary calcium so that less calcium remains available in the urine for binding to oxalates. A low urinary citrate excretion has been commonly associated either alone or in combination with hypercalciuria in children with stones<sup>21,31</sup>. Hypocitraturia is observed in patients with metabolic

acidosis, complete distal renal tubular acidosis, hypokalaemia and malabsorptive syndromes.

The causes of nephrolithiasis in childhood are shown in Table 2.

**Table 2: Causes of nephrolithiasis in childhood**

#### *Normocalcaemic hypercalciuria*

Idiopathic hypercalciuria  
Distal renal tubular acidosis  
Bartter syndrome  
Frusemide induced  
Dent disease  
Familial hypomagnesemia and hypercalciuria syndrome

#### *Hypercalcaemic hypercalciuria*

Primary hyperparathyroidism  
Immobilization  
Cushing syndrome  
Adrenal insufficiency  
Metastatic bone disease

#### *Increased intestinal absorption of calcium*

Hypervitaminosis D or A  
Sarcoidosis

#### *Hyperoxaluria*

Primary hyperoxaluria  
Cystic fibrosis  
Inflammatory bowel disease  
Short bowel syndrome

#### *Hyperuricosuria*

Inborn errors of purine metabolism  
Lesch-Nyhan syndrome  
Gout  
Glycogen storage disease type I, III, V and VII  
Tumor lysis syndrome  
Protein-rich diet

#### *Hypocitruria*

Distal renal tubular acidosis  
Idiopathic or treatment induced

#### *Cystinuria*

#### *Xanthinuria*

### **Medical management**

#### *Acute management*

The first step in the management of a child presenting with a renal stone is to treat any acute complications. Any possible UTI should be treated with an

appropriate antibiotic. Attacks of colicky pain associated with the passage of a renal stone are often very severe and should be treated with a parenteral narcotic analgesic such as morphine sulphate and / or a non-steroidal anti-inflammatory drug. If obstruction is demonstrated on ultrasonography, prompt urology referral should be made with the aim of relieving the obstruction by urine drainage (by placing a percutaneous nephrostomy tube) or by removing the stone ureteroscopically or by extracorporeal lithotripsy. In the absence of any obstruction or oliguric renal failure, adequate hydration should be given to maintain a good urine output.

#### *Preventive measures*

Prevention of recurrent stone formation is an important part of the management of children with renal stone disease. Treatment that is specifically directed to the causes identified in each child provides the most effective method. Most of the steps in the process of stone formation can be exploited to reduce stone forming activity. The mainstay of therapy of all forms of calculi is to maintain a good urine output by a high daily fluid intake in order to reduce the concentration of lithogenic solutes in the urine and to prevent any crystals from getting adherent to the urinary tract epithelium. However, the exact volume to achieve this is unknown. Most clinicians recommend an intake of at least the calculated daily maintenance volume. Increased intake may be required during periods of increased insensible losses.

Urine pH can also be modified to advantage by alkalinisation of the urine in patients with cystinuria or uric acid stones. Alkalinisation will enhance the solubility of cystine and uric acid crystals. Enhancing the activity of naturally occurring inhibitors of crystal formation in the urine such as citrate, magnesium and pyrophosphate can also be incorporated into the treatment programme. Foods rich in potassium such as fruits and vegetables contain a large quantity of citrates. Adult studies have shown that diets rich in potassium are protective against formation of calcium oxalates stones by increased urinary citrate levels as well as dietary potassium content<sup>32</sup>. Other studies involving men have shown that diets rich in magnesium are associated with a lower risk of stone formation and hence magnesium supplementation may be helpful in the treatment of children with secondary hyperoxaluria<sup>33</sup>.

As increased sodium intake is associated with increased calcium excretion, a low-sodium diet is recommended for children with hypercalciuria or calcium based stones. Although calcium excretion in the urine is influenced by the amount of calcium in the

diet, dietary calcium restriction does more harm than good. As calcium in the food binds to intestinal oxalates preventing their absorption, restriction of calcium intake would leave more unbound oxalates for absorption. This in turn would lead to increased excretion of oxalates and formation of stones. Therefore, the current recommendation is not to completely restrict but to curtail excess calcium intake, particularly in absorptive hypercalciuria.

A high animal protein intake has been shown to enhance urinary calcium excretion and reduce urinary pH and citrate excretion as a result of metabolic acidosis caused by increased metabolism of sulphur containing amino acids<sup>34</sup>. Vegetable proteins and dairy products have not shown the same association. Therefore, children with renal calculi are advised not to eat animal proteins in excess but to take 100% of the daily recommended allowance to promote growth.

Pharmacotherapy is indicated when fluid and dietary management fail to control stone recurrence or when an underlying metabolic disorder is identified. A thiazide diuretic which reduces renal calcium excretion by enhancing the distal tubular reabsorption is often required for children with hypercalciuria who do not respond to salt restriction and fluid therapy. The general recommendation is hydrochlorothiazide 1-2 mg/kg/day. Hypokalaemia is a troublesome side effect which can be counteracted by treatment with amiloride or administration of potassium citrate. Potassium citrate (2-4 mmol/kg/day) reduces calcium oxalate stone formation in the presence of reduced urinary citrate levels and is used for the treatment of idiopathic and secondary hypercalciuria. In addition, potassium citrate is given to patients with distal renal tubular acidosis to correct the metabolic acidosis and to patients with cystinuria to alkalinize the urine. Thiol containing agents such as D-penicillamine are exclusively used for the treatment of cystinuria. Allopurinol is the main therapeutic agent for children with uric acid calculi used along with fluid therapy and urine alkalinisation. Pyridoxine which is an important cofactor of alanine glyoxylate aminotransferase has been shown to be effective in 10 - 30% of patients with PH type I. It has not been shown to be effective in other forms of hyperoxaluria at present.

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