

# Evaluation of urinary tract calculi in children

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Renal stone disease remains a significant health problem in the adult population, with the incidence of urolithiasis estimated to be as high as 12%.<sup>1</sup> The true incidence in childhood is not known, but a frequency of two children per million UK population per annum has been suggested.<sup>2</sup> Understanding the factors involved in urinary stone formation and the appropriate investigations for a child presenting with signs and symptoms of renal stone disease, will allow for earlier recognition of the problem and may assist in the prevention of recurrent stone formation.

The term "nephrocalcinosis" implies an increase in calcium content in the kidney, and is distinct from urolithiasis (stone in the urinary tract), although the two conditions may coexist. Nephrocalcinosis occurs less frequently than urolithiasis and may be focal, occurring in an area of previously damaged parenchyma, or generalised, usually as a result of an underlying metabolic disorder.

The incidence and composition of renal stones differs significantly with regard to geographic region.<sup>3</sup> In European children infection related stones predominate. These stones are often located in the upper urinary tract, are composed of struvite (magnesium ammonium calcium phosphate), and are frequently related to proteus urinary tract infection.<sup>2</sup> Hypercalciuria is the most common metabolic cause of stones in Western children. No diagnosis is determined in a quarter of cases. If more detailed investigations are undertaken it is possible that the number of "idiopathic" cases will decrease. The aim of this paper is to increase awareness of the importance of urolithiasis in children and to suggest an outline of investigations that will assist the physician in elucidating any underlying disorder.

## Pathophysiology of stone formation

The formation of renal calculi is a complex process and depends on the interaction of several factors, including:

- Urinary concentration of stone forming ions
- Urinary pH
- Urinary flow rate
- The balance between promoter and inhibitory factors of crystallisation, for example, citrate, magnesium, pyrophosphate
- Anatomic factors that encourage urinary stasis, for example, developmental anomalies, foreign bodies.

Attention given to the above factors forms the basis of therapy aimed at prevention of the recurrence of renal stones.

## Presentation

Abdominal or flank pain occurs in approximately half of the children presenting with urolithiasis, but the classical description of excruciating loin pain associated with the passage of the stone is uncommon. In infants stone symptoms may often be confused with colicky abdominal pain. Microscopic haematuria is present in over 90% of children with stones, and the possibility of urolithiasis should always be considered in children with non-glomerular haematuria. Urinary tract infections are often associated with renal calculi and pyuria may be seen. Table 1 shows the clinical disorders most frequently associated with paediatric renal stone formation.

## Investigations

The evaluation of a child presenting with a renal stone should proceed in an ordered manner. The initial consideration is whether urinary obstruction is present which must be relieved promptly. Further evaluation can usually be performed on an outpatient basis. Special dietary precautions should be avoided as these may obscure some diagnoses (for example, hypercalciuria).

### URINALYSIS

Urinalysis and microscopy will identify haematuria, pyuria, and bacteria which may be present. Urine microscopy of fresh urine may

Table 1 Classification of renal stones in childhood

<i>Struvite stones (radio-opaque)</i>
Associated with urinary tract infections (often proteus)
<i>Calcium stones (radio-opaque)</i>
See fig 1
<i>Oxalate stones (radio-opaque)</i>
Primary hyperoxaluria type I
Primary hyperoxaluria type II
Enteric hyperoxaluria
Idiopathic
<i>Uric acid stones (radiolucent)</i>
Familial
Over production
● Hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency
● Glucose-6-phosphatase (G-6-P) deficiency
● Phosphoribosyl pyrophosphate synthetase (PRPs) superactivity
● Adenine phosphoribosyl transferase (APRT) deficiency
Hyperuricosuria
● Related to high purine diet
● Tumourlysis
● Chronic volume contraction associated with bicarbonate losses, e.g. chronic diarrhoea, short gut syndrome
<i>Stones associated with hypocitraturia</i>
<i>Cystine stones (usually radio-opaque)</i>
Cystinuria
<i>Other metabolic disorders (radiolucent)</i>
Xanthinuria
Orotic aciduria

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Accepted 6 December 2000

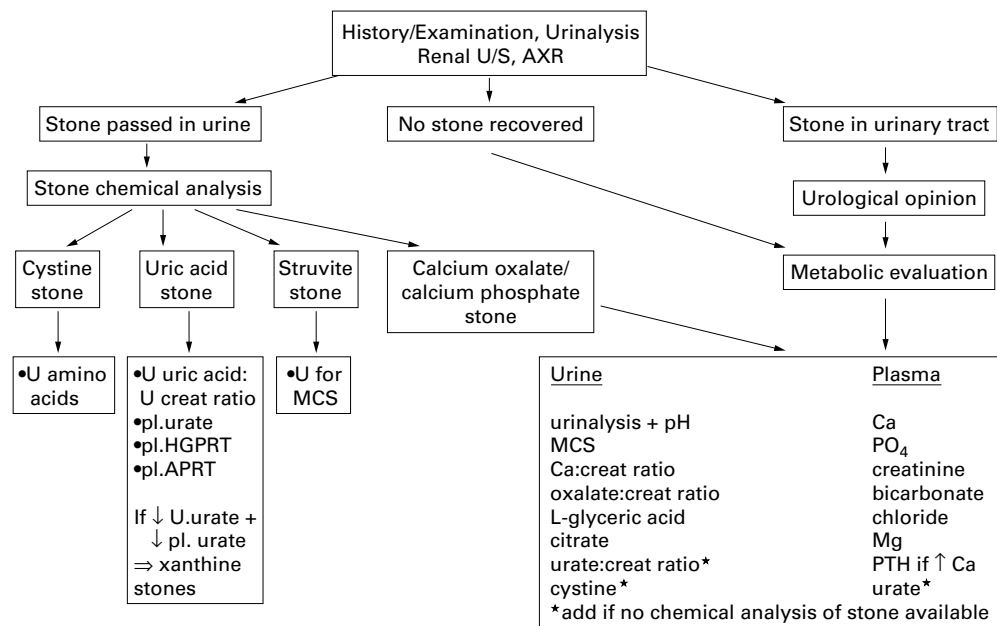


Figure 1 Diagnostic approach to childhood urolithiasis.

also identify crystalline elements that point to a diagnosis, for example, cystine crystals. The urine should be sent for culture and sensitivity to identify bacterial infection, which is not uncommonly noted at the presentation of children who are subsequently found to have an underlying metabolic cause for the renal stone.

RADIOLOGICAL IMAGING

All children presenting with a urinary tract infection or haematuria should undergo renal ultrasound examination to exclude urolithiasis. Small stones may not be detected by this method and plain abdominal radiography should be performed if the suspicion of stones is high. Ultrasound is more sensitive in detecting nephrocalcinosis and may detect radiolucent stones.

STONE ANALYSIS

Chemical analysis of a calculus passed in the urine or removed surgically is very helpful in elucidating the underlying cause and should not be overlooked. Parents should be encouraged to retain for analysis any granular material passed in their child's urine. One of the problems with lithotripsy is that renal stones are fragmented, and a whole stone is not available for analysis as is the case with surgically removed calculi.

There are no recent reports of the epidemiology of urinary tract stones in children in the UK, but North American data of analysed stones<sup>4</sup> identifies the frequency and composition of urinary tract stones as:

- Calcium oxalate: 70–80%
- Calcium phosphate: 5–10%
- Uric acid: 5–10%
- Struvite: 5–10%
- Cystine: 1–5%.

If infection related stones are not sent for analysis the frequency of struvite stones may be underestimated.

METABOLIC REVIEW

Inherited metabolic diseases are identified more frequently in children than in adults and therefore investigations to identify such disorders are indicated. The yield from a metabolic screen in a child with proteus urine infection and a stone is often small, but any child with recurrent stones, a family history, or sterile urine requires adequate assessment.

All children with urolithiasis must be screened for cystinuria as medical therapy improves long term outcome. Conditions such as hyperoxaluria, which have hitherto been considered very rare, may be identified more frequently if the appropriate tests are requested. Figure 1 presents a suggested protocol for investigations.

Twenty four hour urine collections are extremely difficult to arrange in young children and are not necessary in the evaluation of a child presenting with renal stones. A spot urine collection can be used to determine the excretion of a substance in the urine by comparing it to the concentration of creatinine in the urine. Traditionally the second morning urine sample is used to determine the calcium and magnesium excretion and is fairly representative of a 24 hour calcium/creatinine concentration.<sup>5</sup>

Particular attention must be paid to the method of urine collection for oxalate analysis. The patient must not be receiving vitamin C supplements, as the latter falsely elevate oxalate values. A fresh sample must be collected and sent immediately to the laboratory for analysis unless the urine is collected in a container acidified with hydrochloric acid. Delays will cause false elevation of oxalate concentration by oxidation. Urinary L-glyceric acid estimation is required to diagnose primary hyperoxaluria type II, but special handling of the urine collection is not necessary as this forms part of a urinary organic acid screen.

Table 2 Conditions associated with calcium stones

<i>Hypercalciuria with normocalcaemia</i>	
Idiopathic	
Distal renal tubular acidosis	
Frusemide treatment	
Generalised renal tubulopathies	
Hyperalimantation	
Hypophosphataemia	
Juvenile rheumatoid arthritis	
Medullary sponge kidney	
<i>Hypercalcaemia</i>	
Endocrine disorders	
Hyperparathyroidism	
Hypothyroidism	
Adrenocorticoid excess	
Vitamin D excess	
<i>Hypercalciuria and low molecular weight proteinuria</i>	
Dent's disease	
Hypercalciuria	
Tubular proteinuria	
Nephrocalcinosis	
Rickets	
Renal impairment	
Chloride channel defect X linked Xp 11.22-3	

### *Struvite stones*

Infective stones are frequently diagnosed in male children under 5 years of age, over 90% of whom have infected urine at the time of diagnosis.<sup>2</sup> Stone fragments are soft and easily passed in the urine, and are sometimes described by parents as a paste. The urine infection may be resistant to antibiotic treatment and a proteus infection should always alert the physician to the possibility of renal calculi. The stone is frequently located in the upper tract, usually renal pelvis, and is termed "staghorn" as a result of its shape.

### *Calcium stones*

Calcium containing stones are often associated with underlying metabolic abnormalities, particularly if nephrocalcinosis is also present (see table 2). In childhood, the three most common causes of nephrocalcinosis are hypercalciuric states, distal renal tubular acidosis, and the hyperoxalurias. Idiopathic hypercalciuria is not well understood, but two forms are described:

- Absorptive hypercalciuria, in which there is increased intestinal absorption of calcium
- Renal hypercalciuria, in which there is reduced renal tubular calcium reabsorption as a primary abnormality.

These two forms can be differentiated by the response to a low calcium diet as well as to calcium loading.<sup>6-7</sup> The distinction between these two forms may be considered relevant as the absorptive hypercalciuria can be controlled by moderate dietary calcium restriction, whereas the renal hypercalciuria is managed by a thiazide diuretic. The introduction of a high potassium but low sodium diet is of benefit to hypercalciuric children as the urinary calcium excretion can be reduced, as long as the diet can be maintained.<sup>8-9</sup> Hyperparathyroidism is very rare in children and occasionally may cause renal calculi.

Frusemide use in low birth weight infants and cardiac patients is more frequently recognised nowadays as a cause of diffuse nephrocalcinosis. Frusemide inhibits the Na/K/2Cl channel in the thick ascending limb of the loop

of Henle, which induces notable calciuria associated with the natriuresis.<sup>10</sup> Nephrocalcinosis as a complication of the treatment of hypophosphataemic rickets, is much less frequently seen now, as a result of the use of 1,25-dihydroxycholecalciferol. It is suggested that this form of nephrocalcinosis is compounded by the hypercalciuria complicating oral phosphate supplementation.<sup>11</sup>

In distal renal tubular acidosis the finding of an alkaline urine and hypercalciuria with a low urinary citrate excretion, favours the precipitation of calcium salts with resultant stone formation. Therapy consists of sufficient alkali to neutralise endogenous acid production, but unfortunately stone formation sometimes continues despite adequate alkali supplementation.

Dent's disease is a renal tubular disorder characterised by low molecular weight proteinuria and hypercalciuria with nephrolithiasis, and is associated with inactivating mutations of the X linked chloride channel, CLC-5.<sup>12-13</sup> The renal impairment is slowly progressive and rarely seen in childhood, although the other clinical features may be overlooked. An increase in the urinary excretion of low molecular weight proteins, beta 2-microglobulin, or retinol binding protein, is highly specific for renal tubular disease.<sup>14</sup>

Familial renal magnesium wasting, hypercalciuria with nephrocalcinosis, and partial distal renal tubular acidosis has been identified as a course of renal failure in children.<sup>15-17</sup>

### *Oxalate stones*

The primary hyperoxalurias (PH) are rare autosomal recessive defects of oxalate metabolism that cause excessive endogenous oxalate production. The toxicity of oxalate in humans results from the extreme insolubility of its calcium salt, calcium oxalate, which may precipitate in the renal parenchyma or renal tract, causing either nephrocalcinosis or stones. There are two recognised forms of PH. Type I (PH I) is more common and is caused by a functional deficiency of the peroxisomal enzyme, alanine glyoxylate aminotransferase. Phenotypically PH I shows great heterogeneity, ranging from severe infantile oxalosis and death, to milder forms with renal stone disease in later life. Primary hyperoxaluria type II (PH II) is characterised by hyperoxaluria and L-glyceric aciduria, the underlying defects being the result of decreased glyoxylate reductase activity. Patients with PH II have a less severe clinical course than PH I and their predominant clinical feature is nephrolithiasis rather than nephrocalcinosis. With increased awareness of the appropriate tests indicated in patients presenting with hyperoxaluria, more patients with these disorders are currently being diagnosed.<sup>18-19</sup>

Children with small bowel disorders, particularly those affecting the terminal ileum, may present with enteric hyperoxaluria related to increased dietary oxalate absorption. This results from the loss of the normal inhibitory

effect of calcium ions, as they are precipitated by the unabsorbed free fatty acids as calcium soaps.

The finding of calcium oxalate stones in older children and adults is often not associated with hyperoxaluria.<sup>20</sup>

#### Cystine stones

Cystinuria is an inherited error of defective transport of cystine, lysine, ornithine, and arginine across intestinal and renal tubular cell membranes. Cystine stones occur in children of all ages and have been identified in the newborn period.<sup>21</sup> Twenty five per cent of patients pass their first stone during childhood.<sup>22</sup> In very young children bladder calculi may occur, but in later childhood renal calculi are more frequent. All cystine calculi are radio-opaque, although at times are not as dense as calcium containing stones, and may sometimes be missed on the plain abdominal film.

#### Uric acid stones

Uric acid is derived from endogenous sources, as well as from dietary ingestion of purines. Reduced urine volume with dehydration, hyperuricaemia, and a urinary pH that is consistently less than 6 are important factors that influence uric acid stone formation. Uric acid gravel in both kidneys may lead to acute renal failure in the absence of radiological evidence of calculi. This latter complication is less common with the adequate preparation of leukaemia patients undergoing therapy. The inborn errors of purine metabolism are rare, for example, Lesch-Nyhan syndrome (a disorder characterised by self mutilation, hyperuricaemia with uric acid calculi, and choreoathetosis). Uric acid stones have been reported in patients with type I glycogen storage disease, but the mechanism is unclear. Some children, particularly males of Mediterranean background, may present with uric acid stones without hyperuricaemia or uricosuria. It is possible that these children have dihydroxyadenine stones which are not routinely distinguished from uric acid stones, unless specifically requested of the laboratory staff. Dihydroxyadenine stones occur as a result of a deficiency of the enzyme adenine phosphoribosyl transferase. The diagnosis of these cases is important because allopurinol has a satisfactory therapeutic effect and alkalinisation of the urine decreases solubility of the dihydroxyadenine.<sup>23</sup>

Xanthinuria is a rare condition caused by a deficiency of xanthine oxidase with a resultant failure to convert xanthine to uric acid. The plasma uric acid concentration is therefore very low, but because xanthine is insoluble in acid

urine, radiolucent calculi develop. Xanthine calculi should be considered if the parents report an orange/brown sediment in the urine or similar coloured staining of the nappy.<sup>24 25</sup>

I thank Dr C Mark Taylor for his support and advice.

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