

# Medical management of pediatric stone disease

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Childhood urolithiasis remains endemic in certain parts of the world, namely, Turkey and the Far East. In these areas, bladder stones composed of ammonium acid urate and uric acid predominate, strongly implicating dietary factors, particularly the dependence on cereal and rice. In the United Kingdom and other European countries, 75% of calculi in children are composed of organic matrix and struvite, and many are found coincident with proteus infection and urinary tract anomalies. In contrast, in the United States and Scandinavia, infectious stones are rare.

The prevalence of nephrolithiasis in North American children varies widely among geographic regions and accounts for 1 per 1000 to 1 per 7600 pediatric hospital admissions, a rate one-tenth of that seen in adults [1]. Stones occur in children of all ages and do not disproportionately affect any age group. In general, there is no gender preference in children with urolithiasis [2,3] aside from a slight male preponderance, which is evident only in children with hypercalciuria and those with genitourinary anomalies [3]. Stones are uncommon in African-American children.

The rate of recurrent stones in childhood has been reported to be 6.5% to 54% with a mean interval to recurrence of 3 to 6 years [2–8]. Children with an identifiable metabolic disorder are nearly fivefold more likely to have recurrent stones than those with no identifiable metabolic disorder [2].

## Manifestations

Clinical manifestations of stone disease are often more subtle in children, particularly younger children, when compared with the dramatic adult

presentation with incapacitating pain. Abdominal, flank, or pelvic pain occurs as the initial clinical feature in approximately 50% of children with urolithiasis [3,9], whereas gross or microscopic hematuria leads to the diagnosis in 33%, incidental radiographic findings in 15%, and infection in 11% [3]. In infancy, pain from stones may mimic colic. Among children 5 years of age and younger, urinary tract infections and incidental radiographic findings lead to the diagnosis in 43% compared with 15% of the time in children 12 to 16 years of age [3]. Symptoms such as urgency, dysuria, frequency, and fever, as well as pyuria or documented urinary tract infection, are noted in approximately 20% to 50% of patients [1,10,11]. Thirty-seven percent of children with urolithiasis have a positive family history of such [3]. Microscopic or macroscopic hematuria has been reported in 33% to 90% of children with stones. In the United States, three fourths of pediatric stones are renal in location, with 10% being ureteral and 10% located in the bladder [3]. Younger patients are more likely to present with renal versus ureteral calculi. In addition, these stones tend to be larger in younger children; therefore, they have a lower rate of spontaneous passage [2]. The passage rate for ureteral calculi is surprisingly consistent in all age groups, with stones greater than 5 mm rarely passing spontaneously [2].

The popularity of urinary undiversion, bladder augmentation, and continent urinary diversion has contributed to an increased frequency of bladder calculi.

## Etiology

As is true in adults, greater than 75% of all urinary tract calculi reported in North American children are composed of calcium oxalate or

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calcium phosphate [3,12]. Infection stones, which represent 15% to 25% of the total, are the second most common form of calculosis [3,5–7]. The published etiology of renal stones in childhood varies depending on the source of the review, namely, a surgical or medical population, but in two large pediatric series that included both patient populations, metabolic conditions were found to account for greater than 50% of diagnoses [3,12]. In a purely surgical series of pediatric stone patients, urinary tract anomalies take on much more relevance [5]. A variety of genitourinary anomalies are found in 30% of children with urolithiasis [3].

### Pathophysiology

Urine is a complex solution containing ions that interact with other constituents. The generation of crystals is a process that is variably promoted or inhibited by several physicochemical or anatomic factors. These factors include the solute excretion rate, urinary supersaturation, urinary ionic strength, urinary flow rate, urine pH, and urinary tract developmental anomalies. In normal urine, the concentration of a component necessary to reach supersaturation is several times higher than would be expected from its solubility because of the presence of organic and inorganic inhibitors, that is, magnesium, glycosaminoglycans, glycoproteins, citrate, pyrophosphate, and nephrocalcin [13]. Urine pH affects the saturation of some potential stone-forming solutes by altering their solubility. Acidic urine decreases the solubility of uric acid and cystine, whereas an alkaline pH is conducive to the formation of struvite and calcium-containing stones.

Urinary supersaturation indexes that consider lithogenic and stone inhibitory substances in the urine have been shown in the adult stone-forming population to be useful in predicting the risk of stone recurrence [14]. In children, these indexes are more sensitive predictors of recurrent stone risk [15], although pediatric reference ranges have not yet been established.

### Evaluation

The evaluation of a child who presents with urolithiasis is not unlike that performed in an adult and should be directed toward identifying any physicochemical, anatomic, and genetic factors predisposing to urolithiasis. Because 78% of all stones analyzed in children are composed of

calcium oxalate or calcium phosphate [3], this finding is of limited assistance in the evaluation. Short of finding a uric acid, cystine, or struvite stone, the search for an etiology consists of blood and urine studies (Box 1), including a 24-hour urine collection (for calcium, oxalate, uric acid, sodium, citrate, creatinine, volume, pH, and a cystine screening) obtained on a routine diet. An abnormal value should be reconfirmed and examined in relationship to sodium excretion. For children who are not toilet trained, the evaluation may be performed by obtaining measurements of creatinine, calcium, uric acid, and oxalate on a random urine (Box 2), preferably 2 to 4 hours following a meal in which milk is ingested, if only one sample is obtainable.

The presence and appearance of crystals on a urinalysis provide clues to the type of stone, although only the finding of cystine crystals is pathognomonic. Measurement of intact PTH may be deferred until the results of serum and urinary calcium values are known. Reduced urinary citrate excretion may suggest the diagnosis of distal renal tubular acidosis. In patients with hypercalciuria, if a medullary sponge kidney is suspected in patients with a positive family history, an intravenous pyelogram (IVP) should be performed.

### Radiographic evaluation

Similar to the experience in adults, the search for urolithiasis in children with hypercalciuria is best accomplished by performing a nonenhanced

#### Box 1. Initial laboratory evaluation of a child with urolithiasis

##### *Serum*

Complete blood count; electrolytes, bicarbonate, blood urea nitrogen (BUN); creatinine; calcium; phosphorus; magnesium; alkaline phosphatase; uric acid; intact parathyroid hormone (PTH)

##### *Urine*

Urinalysis with pH (metered preferable); urine culture; 24-hour urine for calcium, phosphorus, magnesium, oxalate, sodium, uric acid, citrate, cystine, creatinine, volume

##### *Stone analysis*

**Box 2. Normal values for urinary solute excretion***Timed urine collections*

Calcium: &lt;4 mg/kg/24 hr

Oxalate: <30 mg/m<sup>2</sup>/24 hr (<50 mg/1.73 m<sup>2</sup>/24 hr)Uric acid: < 815 mg/1.73 m<sup>2</sup>/24 hrCystine: <75 mg/g creatinine (<60 mg/1.73 m<sup>2</sup>/24 hr)

Citrate: &gt;180 mg/g creatinine, &gt;128 (males) or &gt;300 (females) mg/g creatinine

Magnesium: 1.6 ± 0.8 mg/kg/24 hr

*Urinary solute: creatinine ratios<sup>a</sup>*

Calcium: children, &lt;0.21; neonates, &lt;0.6–0.81 (&lt;34 weeks gestational age) or &lt;0.15–0.42 (&gt;34 weeks gestational age)

Oxalate<sup>b</sup>: 0–6 months, ≤360 (values represent sample means); 7–24 months, ≤174; 2–4.9 years, ≤101; 5 years, ≤82; 9 years, ≤69; 12 years, ≤50; 14 years, ≤56; 16 years, ≤40Uric acid<sup>c</sup>: <0.56 mg/dL glomerular filtrate if >2 years<sup>a</sup> LAll ratios are expressed as mg/dL solute ÷ mg/dL creatinine.<sup>b</sup> Oxalate values are expressed as millimole of oxalate per mole of creatinine, where oxalate mg/88 = \_\_ millimoles oxalate, and creatinine mg/112,000 = \_\_ moles creatinine.<sup>c</sup> LCalculated as (U<sub>UA</sub> × S<sub>CR</sub> ÷ U<sub>CR</sub>), where U<sub>UA</sub> is urine uric acid, S<sub>CR</sub> is serum creatinine, and U<sub>CR</sub> is urine creatinine, all in mg/dL.*Modified from Polinsky MS, Kaiser KA, Baluarte HJ, et al. Renal stones and hypercalciuria. Adv Pediatr 1993;40:353–84; with permission.*

helical CT scan, as demonstrated by Nimkin et al [16] in a study of 25 children with documented urolithiasis. CT had by far the highest sensitivity for detecting calculi when compared with renal ultrasound, IVP, or abdominal flat plate imaging. Advantages of noncontrast, thin-section, helical CT over excretory urography include shorter examination times, higher sensitivity and specificity for calculi, no need for intravenous contrast, and a greater potential for making alternative diagnoses [17,18]. Disadvantages include a higher radiation dose using current protocols and a higher cost. Despite the demonstrated advantages of CT scans, in practice, many pediatric nephrologists, because of concerns relating to radiation exposure, will use an abdominal flat plate and ultrasound for routine surveillance in the asymptomatic child (monitoring every 12–18 months), reserving the nonenhanced, thin-cut helical CT for patients who are symptomatic.

A comparison of renal ultrasound/abdominal flat plate (RUS/KUB) with CT has not been performed in pediatrics, and further work is needed to optimize CT imaging parameters while maintaining diagnostic accuracy and minimizing the radiation dose. In a small study of children with suspected renal colic and atypical abdominal

pain, nonenhanced helical CT was diagnostic in seven children, although this study was not directly compared with ultrasound and KUB [19].

When a stone is seen on ultrasound or CT but is nonopaque on a plain film, the differential diagnosis includes uric acid, cystine, and xanthine stones.

**Hypercalciuria**

Hypercalciuria is the most common cause of urolithiasis in children, accounting for up to 34% of all pediatric stones [3]. Normal calcium excretion during childhood has been defined as less than 4 mg/kg per day measured in a 24-hour urine collection with the patient consuming a routine diet [20–22], preferably confirmed with a second sample. In children with documented idiopathic hypercalciuria, it is reasonable to institute a sodium-restricted diet (2–3 g/day) for 2 to 4 weeks and recollect a third 24-hour urine sample [23] owing to the known calciuric effect of dietary sodium. A simple screening test for hypercalciuria can be performed by determining the ratio of urinary calcium to creatinine concentrations in a random specimen. Values greater than 0.2 in a 24-hour urine sample [24,25] are considered elevated. Use of

random urinary collections must be interpreted with caution [25], because the urine calcium to creatinine ratio may increase by 40% to 0.28 following a meal [25]. Neonates and infants have higher calcium excretion and lower creatinine excretion than older children. Sargent et al [26] have reported that the urinary calcium-to-creatinine ratio declines during childhood and may generally be higher than previously reported. Urinary calcium-to-creatinine ratios during the first 6 months of life are up to 0.8 mg/mg and, from age 7 months to 1 year, up to 0.6 mg/mg [26–28]. In infants, normal calcium excretion is markedly influenced by diet. Children receiving breast milk have the highest calcium excretion, whereas children given soy-based formulas produce the lowest calcium excretion [27]. No racial or gender differences in calcium excretion have been found in childhood.

The differential diagnosis of hypercalciuria despite normocalcemia is limited in children, with the majority having idiopathic hypercalciuria. Initial studies of idiopathic hypercalciuria suggested two relatively easily defined and genetically distinct subtypes: renal and absorptive. In patients with renal hypercalciuria, urinary calcium excretion was not primarily influenced by dietary calcium intake, did not normalize with dietary calcium restriction, and was associated with increased serum PTH concentrations. Absorptive hypercalciuria was characterized by an exaggerated calciuresis in response to dietary calcium. When patients with absorptive hypercalciuria restrict dietary calcium, urinary calcium excretion returns to normal. In such patients, serum PTH levels are normal. In children and adults, initial studies suggested that the majority of patients with hypercalciuria and urolithiasis had renal hypercalciuria [25,29]. Subsequently, absorptive hypercalciuria has been found to be the most common metabolic cause of urolithiasis in adults. Although considerable effort was expended initially to differentiate renal versus absorptive hypercalciuria in childhood, use of the oral calcium challenge following a week of dietary calcium restriction is no longer recommended. The results have not been reproducible or diagnostic and offer little additional information beyond that obtained from analyzing calcium excretion before and after dietary calcium restriction in children with documented hypercalciuria, with the exception being children with elevated PTH levels. Aladjem et al [30] convincingly demonstrated the lack of reproducibility of the oral calcium challenge when they retested 30 children aged 3 to 7

years after their original classification. Less than half of the children retained their original classification. The pattern of distribution of the patients during restudy was found to be unpredictable by any parameter studied. A highly significant correlation between urinary calcium and sodium excretion was observed during both studies.

Forty-six percent of children with hypercalciuria have a positive family history of urolithiasis, supporting the impression that idiopathic hypercalciuria is a hereditary trait [31]. Although the genetic basis of hypercalciuria is unknown, idiopathic hypercalciuria seems to follow an autosomal dominant pattern of inheritance and can be diagnosed in approximately 4% of an unselected pediatric population [20,31–34]. The pathogenesis of idiopathic hypercalciuria is a continuum of increased renal calcium excretion, increased gastrointestinal absorption, and, occasionally, increased bone resorption [23]. The latter effect has important clinical implications, because lowering calcium intake may lead to negative calcium balance and osteopenia. Recent studies have suggested significant osteopenia in children with familial hypercalciuria [35], leading to a hypothesis that a defect in bone mineralization may be the proximal cause of hypercalciuria, at least in some children.

In three families with severe absorptive hypercalciuria, a gene defect localized to chromosomal area 1g23-q24 has been identified [36]. The factors responsible for the elevation in calcitriol levels in patients with idiopathic hypercalciuria are poorly understood but may include a urinary phosphate leak as a primary defect. Among children who can be classified as having renal hypercalciuria, 1,25-dihydroxy vitamin D<sub>3</sub> levels are found to be incompletely suppressed following a high-calcium diet. A subset of these children may also experience renal glycosuria, hyperuricosuria, or hypocitrat-uria. Initial efforts to link familial idiopathic hypercalciuria with the vitamin D receptor gene have been unsuccessful. In children and adults, absorptive and renal forms of hypercalciuria most likely represent a continuum of a single disease.

Dent disease is an X-linked recessive disorder of urolithiasis secondary to a form of Fanconi syndrome with hypercalciuria, low molecular weight proteinuria ( $\alpha$ -microglobulin and retinol-binding protein), nephrolithiasis, and nephrocalcinosis [37]. Glycosuria, aminoaciduria, phosphaturia, microscopic hematuria, and renal failure may also occur. Urinary acidification is normal in 80% of cases. Two other conditions, X-linked

recessive hypercalciuric hypophosphatemic rickets and low molecular weight proteinuria with nephrocalcinosis, have been described with similar phenotypes [38]. These diverse syndromes are all caused by mutations affecting a chloride channel [39–41] linked to the short arm of the X chromosome encoding for the *CLC-5* gene. *CLC-5* mutations have not been identified in individuals with idiopathic familial hypercalciuria. It is not clear how loss of *CLC-5* function leads to hypercalciuria; however, abnormal regulation of PTH and 1,25-dihydroxyvitamin D<sub>3</sub> synthesis seems important.

Children with Bartter's syndrome, a condition sometimes inherited as an autosomal recessive trait in which the primary defect is a failure to reabsorb sodium adequately in the thick ascending limb of Henle's loop, have hypokalemia, hypochloremic metabolic alkalosis, and hypercalciuria. Bartter's syndrome is also believed to be related to abnormalities in the family of genes that encode voltage-gated chloride channels.

Table 1 lists possible inheritance patterns for conditions associated with hypercalciuria. A single genetic abnormality responsible for idiopathic hypercalciuria is unlikely, because there seems to be a continuum in the rates of calcium excretion between normal and hypercalciuric humans [42]. Distal renal tubular acidosis (RTA) is an uncommon cause of normocalcemic hypercalciuria and is encountered in 2% to 3% of children with urolithiasis.

Hematuria without overt urolithiasis may be associated with hypercalciuria, hyperoxaluria, and

hyperuricosuria [9,43–46]. The clinical presentation of hypercalciuria without urolithiasis may be painless microhematuria, dysuria, urinary frequency, and painless or painful macroscopic hematuria. In the absence of infection, proteinuria, or calculi, hypercalciuria is found as the cause of macroscopic hematuria in 27% of children [9], although the frequency in African-American children is considerably less, and hypercalciuria is only occasionally reported as a cause of hematuria in Asian children. The risk of urolithiasis in a child with hypercalciuria who has had no previous stones has been variably reported but seems to be approximately 13% to 17% within 3 to 5 years [34,47], with a mean interval of 13.1 months (range, 1 to 41 months).

Because the single greatest risk factor for stone formation is a low urinary flow rate, the cornerstone of preventative management is maintenance of adequate daily fluid intake with the resultant production of at least 1400 mL/1.73m<sup>2</sup>/day of urine, with an empiric increase of as much as 25% in warm weather [10]. Dietary sodium intake influences urinary calcium excretion in children with and without hypercalciuria [35]. Dietary sodium restriction is recommended as is maintenance of calcium intake consistent with the Recommended Daily Allowance (RDA) for children. In addition, a high-potassium, low-oxalate diet is recommended for children with hypercalciuria and urolithiasis. A low-calcium diet is not effective in reducing the risk of stone recurrence and poses a substantial risk to maintenance of bone health [48,49]. In children who have documented urolithiasis, thiazide diuretics are often used in conjunction with high urinary flow rates and dietary sodium restriction. Some attenuation of the hypercalciuric response to thiazide diuretics has been seen after 3 months use [50], and their prolonged use can lead to hypokalemia with resultant hypocitraturia [51]. Consequently, serum potassium must be monitored at regular intervals, and, when supplementation is required, it should be provided as potassium citrate. In patients with hypercalciuria, consideration should be given to monitoring bone density as a proxy for calcium balance.

Hypercalciuria associated with distal RTA is best treated with sufficient potassium citrate to correct the metabolic acidemia and hypokalemia and to normalize urinary calcium and citrate excretions.

Calcium oxalate stones have occurred in immobilized patients confined to bed for as little as 3 weeks, necessitating maintenance of an adequate

Table 1  
Genetics of hypercalciuria

Disorder	Possible Inheritance
Familial idiopathic hypercalciuria	Autosomal dominant
Distal RTA	Autosomal dominant
Bartter's syndrome	Autosomal recessive
Hypercalciuria/hypomagnesemia	Autosomal recessive
Dent's disease	X-linked recessive
X-linked urolithiasis	
Hypercalciuric rickets	
Hypercalciuria with low molecular weight proteinuria	

Data from Thomas SE, Stapleton FB. Leave no "stone" unturned: understanding the genetic basis of calcium-containing urinary stones in children. *Adv Pediatr* 2000;47:199–221.

urine flow rate and monitoring of urinary calcium excretion in such a clinical setting.

### Uric acid urolithiasis

Uric acid is the end product of purine metabolism. As many as 8% of children with metabolic stones have hyperuricosuria [3]. Hyperuricosuria predisposes not only to uric acid precipitation but also to calcium oxalate lithiasis, the latter by epistaxis. Two major factors promote uric acid precipitation: a high urinary concentration of uric acid and a urinary pH of less than 5.8.

Hyperuricosuria may result from uric acid overproduction, or may occur in the presence of normal serum uric acid levels. The presence of urate stones and elevated serum uric acid may be secondary to inborn errors of metabolism, such as Lesch-Nyhan syndrome (hypoxanthine guanine phosphoribosyltransferase deficiency), type I glycogen storage disease, myeloproliferative disorders, or other causes of cell breakdown. Primary gout owing to partial hypoxanthine guanine phosphoribosyltransferase deficiency with uric acid calculi occasionally occurs in older children. Uric acid stones may also be seen in 5% to 10% of children placed on a ketogenic diet for seizure control [52,53]. Children maintained on a ketogenic diet often have evidence of hypercalciuria, acidic urine, or low urinary citrate excretion, which in conjunction with low fluid intake, places these children at high risk (5% to 10% incidence) for uric acid and calcium stone formation [52]. Hyperuricosuria can also occur secondary to excessive dietary purine/protein intake or uricosuric drugs such as sulfipyrazone, high-dose aspirin (>2 g/day), ascorbic acid (>4 g/day), phenylbutazone, and probenecid.

Uric acid excretion is extremely high in the neonatal period and remains substantially higher than adult values throughout early childhood. Unfortunately, total urate excretion, excretion per unit body weight, and fractional excretion of uric acid all vary with age; therefore, age-related normal values rather than a single normal value must be used. A normal value of less than 0.56 mg of uric acid per deciliter of glomerular filtrate may be used after 2 years of age. This value may be calculated by the following formula [54]:

$$\frac{\text{Urine uric acid} \times \text{Plasma creatinine}}{\text{Urine creatinine}} = \text{mg/dL GFR}$$

Primary treatment goals are increased fluid intake and urinary alkalization to a pH of 6.5 to

7.0 with potassium citrate (preferable) or sodium bicarbonate. Reduction of dietary protein to the RDA for height age may be recommended. Use of the xanthine oxidase inhibitor allopurinol is indicated when fluid and urine alkalization fails to prevent stone recurrence, or when hyperuricosuria is present in excess of 1 g/1.73m<sup>2</sup>/day. Patients with myeloproliferative disorders may benefit from decreasing uric acid production with allopurinol. Because hydration and alkalization can lead to dissolution of uric acid stones, more invasive procedures are often not required. Radiographically, uric acid stones are typically radiolucent.

### Struvite stones

Infection-related stones account for 2% to 24% of children with nephrolithiasis [3,5–7,12] and as many as 75% of stones in European children. Infection stones are more common in males and are usually detected before the age of 6 years. More than half of all children with infection-related stones have genitourinary anomalies [3]. Affected children have persistent pyuria, bacteriuria, and struvite crystalluria.

Infection stones consist of an organic matrix of Tamm-Horsfall glycoprotein, struvite (Mg-NH<sub>4</sub>-PO<sub>4</sub>), and triple phosphate and apatite (CaPO<sub>4</sub>). Most of the components of struvite stones (calcium, phosphate, magnesium, and urea) are present in adequate concentrations for stone formation in normal urine. Infection by urea-splitting bacteria results in an increased, markedly elevated urinary pH owing to large amounts of NH<sub>4</sub> production and increased urinary magnesium ammonium phosphate, conditions favoring the formation of struvite and carbonite apatite crystallization. The resultant stones, which have a tendency to grow rapidly and form staghorn calculi, are contaminated intrinsically by bacteria. *Proteus* species are isolated from more than 70% of all patients with infected stones, although *Pseudomonas*, *Klebsiella*, *Streptococcus*, *Serratia*, *Providencia*, *Staphylococcus*, *Candida*, and *Mycoplasma* species may also produce urease.

Successful management of infection stones requires the elimination of urinary stones and fragments, the correction of anatomic or functional obstruction, and sterilization of the urine. Eradication of the stones is often difficult given the tendency of struvite crystals toward rapid growth and the formation of staghorn calculi. Long-term suppressive, culture-specific antibiotic therapy

(particularly if there are residual stone fragments) is often necessary. Lavage chemolysis, urease inhibitors, acetohydroxamic acid (AHA), and urinary acidification are adjunctive therapies to be considered.

Because ureolysis is the primary cause of struvite stones in humans, inhibition of urease retards the growth of existing stones and most likely lessens the risk of new stone formation. There is good clinical and experimental evidence to support the use of urease-inhibiting drugs [55]. Urease inhibitors may have a role in palliation, as opposed to actual treatment, of infection stones. The combination of urease inhibitors and antibiotics is synergistic. The difficulty associated with urease inhibitors is related to their toxicity. The greatest experience is with AHA, which is more potent than the other available urease inhibitor hydroxyurea. As many as 30% of adults are unable to tolerate AHA because of gastrointestinal and neurologic symptoms. Although urinary acidification, in theory, should be beneficial to increase the solubility of struvite and carbonate apatite, long-term studies of successful urinary acidification are lacking.

### Cystinuria

Cystinuria accounts for 2% to 7% of children with metabolic urolithiasis in industrialized countries [3, 5]. Cystinuria is an incompletely recessive autosomal disorder characterized by failure of tubular reabsorption of four basic amino acids: cystine, ornithine, lysine, and arginine. It occurs with a frequency of approximately 1 case per 15,000 population in the United States. Only cystine has poor solubility in the normal urinary pH range. The solubility of cystine in urine is about 250 mg/L up to pH 7 but sharply rises with higher pH, up to 500 mg/L or more above pH 7.5. Urinalysis reveals the characteristic flat hexagonal cystine crystals in 26% of patients. A positive nitroprusside test indicates a level of greater than 75 mg/dL of urinary cystine, and this result needs to be confirmed by a 24-hour collection. Because the genetic transport defect exists from birth, stone formation begins in the first decades of life, with 25% of affected patients passing their first stone in childhood. The permanent excretion of excessive amounts of cystine is spontaneously associated with the relentless formation of stones, which can have a staghorn development. Because cystine stones are poorly fragmented by extracorporeal shock wave lithotripsy (ESWL), regular medical

treatment is of particular importance in affected patients.

For many years, cystinuria was considered a genetically homogeneous disorder, and the three different phenotypes, which are distinguished by the degree of derangement in intestinal amino acid transport, were thought to be caused by allelism of the same gene. Recent genotypic and phenotypic correlation data, combined with linkage results, have provided strong evidence for the presence of genetic heterogeneity in cystinuria. Type I cystinuria is associated with an amino acid transporter gene on chromosome 2p. More recently, the identification of the cystinuria type III locus on the long arm of chromosome 19 has been reported, and preliminary data suggest that type II families share the same locus. There may be additional unidentified genetic defects. Patients with type I/I cystinuria have the highest risk for nephrolithiasis. Concomitant hypercalciuria, hyperuricuria, and hypocitraturia owing to a renal tubular acidification defect have been reported in adults with cystinuria, predisposing these individuals to calcium and uric acid urolithiasis as well.

The goal of treatment in patients with cystinuria is to obtain solubilization of cystine excreted in the urine. This goal can be accomplished in three ways: (1) dietary measures allowing reduction of cystine production (by decreasing methionine intake), urinary excretion (by low sodium intake), or both; (2) conservative measures directed at decreasing cystine concentration (by hyperdiuresis) with or without increasing its solubility (by alkalization); and (3) treatment with chelating agents (sulfhydryl compounds) that convert cystine to a more soluble disulfide, reducing excretion of the poorly soluble free cystine.

Treatment goals include maintaining urinary flow rates of 50 mL/kg/day, dietary protein and sodium restriction, and urinary alkalization with potassium citrate to maintain a urinary pH above 7.5. The daily intake of fluid and alkali should be sufficient to maintain urinary cystine concentration below 300 mg/L. The fluid intake should be distributed throughout the day and night. Fruit juices (citrus or orange) are useful, because they contain citric acid and potassium, increasing diuresis and alkali load. Lowering daily sodium intake to 50 µg can markedly reduce cystine excretion, although the mechanism by which this occurs is incompletely understood. A substantial decrease in cystine excretion on a low-sodium diet has been seen in adults and children [56]. Methionine, an essential amino acid, is the precursor of

cystine. Reduced methionine intake lowers cystine production but cannot be lower than the physiologic requirement, that is, 1200 to 1400 mg/day. Most authorities believe that such dietary restriction is not advisable for children. Alkali is best given as potassium citrate. Unlike bicarbonate, citrate interferes with the calcium oxalate crystallization that may result from urinary alkalinization and from the idiopathic hypercalciuria or hypocitraturia that are simultaneously present in some patients.

The chelating agents D-penicillamine and  $\alpha$ -mercaptopyropionyl glycine (Thiola) are also used as adjunctive therapies. Both compounds are sulfhydryls that cleave cystine into two cystine moieties to form a mixed disulfide 50 times more soluble than cystine itself. Half the daily dose of chelating agents should be given at bed time, because cystine concentration in urine is maximal during the night. Side effects have developed in as many as 50% of patients receiving D-penicillamine and include fever, rash, nephrosis, pancytopenia, hypogeusia, and epidermolysis. Side effects with  $\alpha$ -MPG are seen in 65% to 76% of those treated but are less severe than the effects seen with D-penicillamine.

Conflicting results have been reported regarding the effect of captopril on cystine excretion. Captopril contains sulfhydryl groups leading to the formation of captopril–cystine complexes that are 200 times more soluble than cystine alone (and three to four times more soluble than the disulfides formed with penicillamine and tiopronin). Results in children have been less encouraging [57–59].

Disappearance of cystine crystals in the first-morning urine is an excellent index of treatment efficacy. Cystine stones are radiopaque owing to their sulfur content but are usually not as dense as calcium-containing stones; therefore, they may be missed on abdominal flat plate imaging. Cystine stones are often resistant to ESWL; therefore, percutaneous surgery or ureteroscopy are often preferred methods of stone extraction.

Cystinuria is a different disorder from cystinosis, which is an autosomal recessive disorder of lysosomal cystine transport that results in excessive intracellular accumulation of free cystine, leading to Fanconi syndrome and progressive renal failure but not urolithiasis.

### Hyperoxaluria

Oxalate is a product of human metabolism produced in the liver and excreted primarily by

the kidney. Oxalate is also absorbed from the diet, and renal excretion reflects the combined endogenous and exogenous oxalate loads. Hyperoxaluria accounts for a small but significant portion of pediatric stone disease.

Primary hyperoxaluria usually presents as calcium oxalate stone formation or nephrocalcinosis during childhood. Some patients never have clinical stone disease; rather, they experience progressive loss of renal function owing to calcium oxalate deposits in the renal interstitium. Approximately 50% of children with primary hyperoxaluria have symptoms by age 5 years. Primary hyperoxaluria is usually diagnosed by the finding of elevated urinary oxalate on a 24-hour urine collection, with hyperoxaluria in children defined as exceeding 1.0 to 1.5 mmole/1.73m<sup>2</sup>/24 hours. Oxalate excretion in childhood varies with age, with infants normally excreting four to five times more oxalate than preschool children. Most endogenously produced oxalate is derived from glyoxylate. Any alteration in glyoxylate metabolism that leads to increased hepatocyte glyoxylate levels will lead to increased oxalate production. One of the critical enzymes regulating this process is alanine glyoxylate transferase (AGXT), a hepatic enzyme located specifically in peroxisomes in humans that converts glyoxylate to glycine.

Type 1 primary hyperoxaluria (PH1) accounts for most oxalosis and for approximately 1% of chronic renal failure in childhood. In patients with PH1, there is a reduction or absence of alanine glyoxylate aminotransferase (AGT) activity that leads to increased glyoxylate levels with a resultant increased conversion to oxalate. Multiple mutations of the gene for AGT, located on chromosome 2, have been found to cause PH1. Because AGT is expressed predominantly in the liver, definitive diagnosis of the disease requires liver biopsy to assess AGT catalytic activity and immunoreactivity. Reduced or absent AGT activity leads to excessive build-up and urinary excretion of oxalate and glycolate, with the formation and deposition of insoluble crystals primarily in the urinary tract and renal parenchyma, leading to recurrent urolithiasis, nephrocalcinosis, and, ultimately, renal failure and systemic oxalosis. There is considerable phenotypic, enzymatic, and genetic heterogeneity within PH1, with manifestations of the disease occurring between infancy and the seventh decade. Diagnosis can be suspected in the presence of elevated urinary oxalate and glycolate levels. Increased urinary glycolate occurs in 70% to 75% of patients with PH1. In children with PH1, the

plasma oxalate and plasma CaOx saturation are elevated even with normal renal function. The level of plasma calcium oxalate supersaturation is thought to be the major determining factor leading to calcium oxalate crystal deposition.

In addition to measuring glyoxylate metabolites in the urine and plasma and performing an enzymologic assay on liver tissue, DNA analysis offers an additional tool in the diagnosis of PH1. Mutational analysis of the gene for AGXT has been used in lieu of liver biopsy to confirm the diagnosis [60]. Genetic analysis can also be used in the prenatal diagnosis of PH1; however, owing to the large number of rare mutations, genetic diagnosis requires family linkage analysis.

Primary hyperoxaluria type 2 (PH2) is characterized by a less severely affected phenotype and results from a deficiency of hydroxypyruvate reductase activity and glyoxylate reductase. Both forms of the disease are autosomal recessive. Children with PH2 usually do not present until their second or third decade of life, and the diagnosis is made following documentation of elevated urinary oxalate and L-glycerate levels. The GRHPR gene has been localized to chromosome 9.

PH1 is more common than PH2, although accurate prevalence rates are difficult to obtain, because many early studies did not carefully segregate the two forms of the disease. The Mayo Clinic found that 20% of their patients with primary hyperoxaluria had PH2. In a comparison of the clinical features of PH1 and PH2, Milliner et al [61] found that the average age of onset and age of diagnosis were similar. Urinary oxalate was higher in the PH1 group, but there was considerable overlap between the populations. Although PH2 has a less severe clinical course, rare cases can progress to chronic renal failure.

Finding elevated urine glycolate (PH1) or glycerate levels (PH2) in the presence of severe hyperoxaluria is diagnostic of primary hyperoxaluria. Unfortunately, neither test is 100% sensitive, because approximately 25% to 30% of patients with PH1 documented by liver enzyme analysis have normal urine glycolate levels. Although liver biopsy is the gold standard for diagnosis, it is not clear that every patient suspected of having primary hyperoxaluria needs a liver biopsy. Therapy to prevent stones will not be altered by classifying the type of primary hyperoxaluria. The decision to pursue a liver biopsy is based on the risk versus benefit of a liver biopsy, patient interest in a definitive diagnosis,

and the availability of facilities to analyze the liver biopsy properly. Certainly, if a liver transplant is considered as therapy, a definitive diagnosis is required [62].

Glycolate oxidase, another hepatic enzyme contributing to glyoxylate synthesis, a key precursor step of endogenous oxalate, is a candidate for a third form of inherited hyperoxaluria.

Therapy for primary hyperoxaluria is directed at reducing oxalate excretion or increasing the solubility of calcium oxalate in urine. High water intake is a cornerstone of therapy. To avoid exacerbating hyperoxaluria, patients should be instructed to avoid high-oxalate foods, although most excreted oxalate is endogenously produced. The only pharmacologic intervention known to reduce urinary oxalate in primary hyperoxaluria is pyridoxine supplementation. Pyridoxine is a cofactor for AGT-mediated conversion of glyoxylate to glycine. Approximately 25% to 30% of PH1 patients can lower urinary oxalate excretion significantly with the administration of pyridoxine. Patients with residual AGT function on liver biopsy tend to be more likely to have a response to pyridoxine. Pyridoxine is not effective in PH2 but should be given in a trial to all patients with PH1 and any patient in whom classification of primary hyperoxaluria is not clear.

Neutral orthophosphate in combination with pyridoxine has been used as long-term therapy at the Mayo Clinic for the treatment of primary hyperoxaluria [63]. Orthophosphate reduces calcium oxalate crystallization by (1) reducing intestinal calcium absorption by suppressing calcitriol production, which leads to lowered calcium excretion; (2) increasing excretion of pyrophosphate, an inhibitor of calcium crystallization; and (3) reducing calcium oxalate supersaturation by providing more phosphate in the urine to complex calcium. The combination of orthophosphate and pyridoxine is the best-documented long-term therapy for primary hyperoxaluria.

Potassium citrate complexes urine calcium and is a direct inhibitor of calcium oxalate crystallization. Citrate has been shown in children with primary hyperoxaluria to decrease urinary calcium oxalate supersaturation rates and to reduce the frequency of stone events [64]. Magnesium oxide, which forms a soluble complex with oxalate in urine, has also been shown to reduce stone formation rate.

The definitive therapy for PH1 is liver transplantation, although the timing of transplant and the selection of appropriate subjects remain

controversial [65]. Because PH2 has an overall better prognosis than PH1, there is no role for a pre-emptive transplant in PH2.

Hyperoxaluria can be caused by defects in oxalate metabolism, overabsorption of dietary oxalate secondary to bowel disease, or consumption of diets rich in oxalate or oxalate precursors. Secondary hyperoxaluria accounts for 50% of stones in children owing to hyperoxaluria and is the result of conditions not dissimilar to those seen in adults. Enteric hyperoxaluria is caused by intestinal (mostly colonic) hyperabsorption, most frequently seen in Crohn's disease or a state in which disease or resection of the small bowel leads to malabsorption of fat and bile acids. In the setting of malabsorption and steatorrhea, dietary calcium is bound by the free fatty acids in the intestinal lumen. Less calcium is available to bind oxalate, resulting in increased amounts of free oxalate for absorption. Patients with inflammatory bowel disease and malabsorption who have had their colon resected do not have significant elevations of urine oxalate. In addition to enteric hyperoxaluria causing calcium oxalate stone disease, as is true in primary hyperoxaluria, the urinary oxalate excretion can be high enough to cause renal damage and renal insufficiency.

Enteric hyperoxaluria is typically evident based on the clinical history or the finding of intestinal malabsorption and varies widely with dietary changes. Other secondary forms of hyperoxaluria include dietary oxalate excess and increased gastrointestinal absorption not owing to gastrointestinal disease or resection. Recent evidence suggests a role for the oxalate-degrading gut flora *Oxalobacter formigenes*, an anaerobic bacteria that colonizes the colon, in the latter form of hyperoxaluria. Intestinal absorption of oxalate ranges between 5% to 15% of dietary intake and is dependent on the amount of free oxalate present in the intestinal lumen. A decrease in the amount of oxalate available for absorption within the colonic lumen as a result of the oxalate-degrading ability of these bacteria is postulated to account for the observed reduction. Significant overlap of oxalate excretion rates between colonized and noncolonized subjects suggests that *O. formigenes* colonization status is just one of many factors determining oxalate excretion [66]. The role of probiotics in the treatment of stone disease is still under investigation, but early studies are promising. A recent study of six adult hyperoxaluric stone formers treated with lactobacillus for 4 weeks showed a reduction of oxalate excretion of 40%.

### Box 3. Selected causes of clinical disorders associated with urolithiasis

#### *Calcium lithiasis*

##### Hypercalciuria

- Normocalcemic hypercalciuria

- Idiopathic hypercalciuria

- Absorptive

- Renal

- Distal RTA

- Diuretic-induced (furosemide)

- Secondary to diet: sodium, calcium, vitamin D

- Barter's syndrome

- "Chloride shunt" syndrome

- Juvenile rheumatoid arthritis

##### Hypercalcemic hypercalciuria

- Associated with calcium resorption from bone

- Immobilization

- Primary hyperparathyroidism

- Hyperthyroidism

- Adrenocorticosteroid excess

- Adrenal insufficiency

- Osteolytic metastases

- Associated with gastrointestinal hyperabsorption

- Vitamin D intoxication

- Idiopathic hypercalcemia of infancy

- Sarcoidosis

##### Hyperoxaluria

- Primary hyperoxaluria types 1 and 2

- Enteric hyperoxaluria

##### Hyperuricosuria

##### Hypocitraturia

- Metabolic acidosis/distal RTA

- Thiazide diuretics

- Hypokalemia

#### *Uric acid lithiasis*

##### Familial

- Chronic volume depletion

- Ketogenic diet

- Overproduction of uric acid

- Increased purine biosynthesis

- Lymphoproliferative and myeloproliferative disorders

- Polycythemia

- Inborn errors of metabolism

- Hypoxanthine guanine

- phosphoribosyltransferase deficiency

- Complete: Lesch-Nyhan syndrome

Partial: gout  
 Type I glycogen-storage disease  
 Hyperuricosuria  
 High purine intake  
 Uricosuric drugs  
  
*Struvite lithiasis*  
*Inborn errors of metabolism associated with lithiasis*  
 Cystinuria  
 Hereditary xanthinuria  
 Adenine phosphoribosyltransferase deficiency  
 Orotic aciduria  
*Developmental anomalies of the urinary tract*

Treatment of diet-dependent hyperoxaluria consists of restriction of high-oxalate foods and maintenance of a normal calcium intake to limit intestinal oxalate absorption and, possibly, avoidance of excessive protein consumption. Foods rich in oxalate, in order of decreasing content, include rhubarb, spinach, soy burgers, beetroot, almond, tofu, pecans, peanuts, okra, chocolate, collard greens, and sweet potatoes. Dietary calcium and protein intake are important factors determining urine oxalate excretion and stone formation in adults. Dietary calcium restriction has been shown to increase the stone formation rate in patients with idiopathic hypercalciuria owing to increased urinary oxalate excretion [67]. Use of calcium and magnesium supplements with meals increases intestinal binding of oxalate and reduces absorption. Cholestyramine can be added to bind bile acids, which may reverse the increased permeability in the colon and, in addition, bind oxalate.

The role of ascorbic acid supplements, which can be broken down to oxalate, as a cause of hyperoxaluria remains controversial and is complicated by technical problems encountered in the measuring of oxalate in the presence of ascorbate. Although high-dose vitamin C has been associated with extreme hyperoxaluria, the role of ascorbic acid seems to be minimal in routine kidney stone disease in adults.

Traditionally, urinary oxalate excretion has been considered to be abnormal if greater than 50 mg/1.73 m<sup>2</sup>/day. This value is clearly inappropriate for infants, in whom urinary oxalate excretion may be four to fivefold greater than in preschool

children [68]. Oxalate excretion is higher in formula-fed infants than in those fed human milk.

### Hypocitraturia

A decrease in the excretion of urinary inhibitors of crystal formation can promote the development of stones. A principal inhibitor of stone formation is citrate. Hypocitraturia can occur in isolation or in association with hypercalciuria, hyperuricosuria, or hyperoxaluria. Citrate excretion can be limited by chronic metabolic acidosis, induced by chronic diarrhea, RTA, or a high-protein diet, as well as hypokalemia.

Clinical disorders associated with urolithiasis in children are listed in Box 3 [10].

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