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Childhood stones

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Encountering a child with a urinary stone is an uncommon and daunting clinical dilemma. Especially in the youngest patients, parental concern over the possible presence of an underlying metabolic condition or a potential lifetime of recurrent painful kidney stones adds to the importance of an accurate diagnosis. Complicating this unusual clinical situation are the unique manifestations of urolithiasis in children and the age-dependent diagnostic criteria. Fortunately, we are now able to successfully diagnose and treat most children with urinary stone disease.

Clinical manifestations

The prevalence of nephrolithiasis in American children varies from 1 in 1000 to 1 in 7600 hospital admissions depending on geographic region [1]. Children in the southeastern United States appear to have the greatest risk for urinary calculi. Urinary stones are found most often in white children and rarely affect African American children; boys and girls appear to be affected equally.

The dramatic presentation of incapacitating flank pain associated with stone passage is uncommon in children. Abdominal, flank, or pelvic pain occurs in approximately 50% of children with urolithiasis [2,3]. In infants, pain from stones may mimic colic. Hematuria, either microscopic or macroscopic, has been reported in 33% to 90% of children with stones. Urinary tract infection may complicate nephrolithiasis, although sterile pyuria is also observed. Dysuria and urinary frequency are manifestations of bladder or urethral calculi. Symptoms of urolithiasis in children vary with age. Urinary tract infections are most commonly associated with stones in preschool children, whereas severe pain is much more common in adolescent patients. The finding of hematuria with urolithiasis, however, is relatively consistent throughout

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childhood [2]. Hematuria may precede stone formation in children with hypercalciuria and, occasionally, with hyperoxaluria or hyperuricosuria [60].

When a stone is available for analysis, its composition often aids in determining the underlying metabolic cause of stone formation. Calcium oxalate accounts for 45% to 65% of stones in children, followed by calcium phosphate (14% to 30%), struvite (13%), cystine (5%), uric acid (4%), and mixed or miscellaneous (4%) [2,4].

Hypercalciuria

Hypercalciuria is defined by a urinary calcium excretion of greater than 4 mg/kg/d while ingesting a routine diet [5–7]. This definition pertains to children from two years through adulthood, although urinary calcium excretion may be minimally higher than these standards during periods of rapid adolescent growth [8]. Neonates and infants have higher calcium excretion and lower creatinine excretion than in older children.

A unique clue to the presence of hypercalciuria has been its association with hematuria in children, particularly in geographic regions with endemic urolithiasis. Hypercalciuria was discovered in 22 of 83 children (27%) with unexplained hematuria in a prospective study [3]. Macroscopic hematuria and a family history of urolithiasis were found more frequently in hypercalciuric children than in hematuric children with normal calcium excretion. Hypercalciuria was not associated with abdominal or flank pain in this group of children, although others have occasionally noted pain as an associated symptom [9]. Boys and girls were represented equally in the hypercalciuric group. When urinary calcium was reduced by hydrochlorothiazide or dietary calcium restriction, hematuria resolved in most children [3]. These findings have been confirmed by additional studies in the United States, Brazil, and Spain [9–11]. Urinary calcium oxalate crystals are frequently observed in children with hypercalciuria and hematuria and may be the cause of bleeding [3,11]. The association of hypercalciuria and hematuria appears to be uncommon in African-American children and has been reported only occasionally in Asian children. Dysuria and urinary frequency are additional symptoms of hypercalciuria in children [12,13]. During infancy, symptoms from hypercalciuria may mimic infantile colic [13].

Although initial studies reported hematuria in children with idiopathic hypercalciuria, this association has also been proposed in children with secondary hypercalciuria from juvenile rheumatoid arthritis, diabetes mellitus, and renal transplantation [13]. A possible relationship between urinary calcium excretion and hematuria was also suggested in children with severe metabolic alkalosis complicating dietary chloride deficiency [13].

In a follow-up study of untreated children with hematuria and hypercalciuria, 40% of patients had hematuria and 70% had hypercalciuria one year following diagnosis [14]. In 7 patients studied after 4 years, 4 patients (57%)

had hematuria and 6 children continued to have hypercalciuria. Clearly, the association of hypercalciuria and hematuria identifies a group of children at high risk for subsequent urolithiasis. In 65 children identified as having hypercalciuria with hematuria in a prospective study by the Southwest Pediatric Nephrology Study Group, 8 patients (13%) developed urinary stones within a 1- to 4-year follow-up period [11]. Garcia et al. [14] found that 10 of 58 (17%) children with hematuria and hypercalciuria developed a renal calculus. The mean interval between diagnosis of hypercalciuria and a urinary stone was 13.1 months with a range of 1 to 41 months. No predictive clinical findings have been identified for potential stone formation in this group of patients. Risk for subsequent urolithiasis has specifically not been associated with macroscopic hematuria, urinary calcium excretion, parathyroid hormone, or urinary flow rate [14].

The pathogenesis of idiopathic hypercalciuria is a continuum of increased renal calcium excretion, increased gastrointestinal calcium absorption, and, occasionally, increased bone resorption [1,15–18]. Many children with idiopathic hypercalciuria have a parent or sibling with hypercalciuria; familial hypercalciuria appears to be transmitted as an autosomal dominant condition [19–22]. The genetic basis of idiopathic hypercalciuria is unknown.

In addition to idiopathic hypercalciuria, a number of pathophysiologic or environmental influences may lead to increased urinary calcium excretion (Box 1). For example, an increased filtered calcium load may result from increased bone resorption (hyperparathyroidism, hyperthyroidism, immobilization, acidosis, corticosteroid excess, or osteolytic metastasis), gastrointestinal hyperabsorption (hypervitaminosis D, sarcoidosis, or milk-alkali syndrome). Distal renal tubular acidosis leads to hypercalciuria and stones by increased bone resorption and reducing urinary citrate excretion. Dietary factors, such as high sodium or animal protein intake may also increase urinary calcium excretion [23]. In recent years, children with intractable seizures have been placed on ketogenic diets [24]. This diet increases urinary calcium excretion and decreases urinary citrate excretion. As a result, 5% to 10% of children receiving therapy with a ketogenic diet develop calcium oxalate or uric acid stones.

Seyberth Syndrome Genetics of hypercalciuria

Due to the lack of clarity concerning the pathogenesis of hypercalciuria, the search for the genetic cause of familial hypercalciuria has gone slowly. (Table 1) Initial efforts to link familial idiopathic hypercalciuria with the vitamin D receptor (VDR) gene were unsuccessful [25]. Linkage of a susceptibility gene near the VDR locus on chromosome 12 has been reported [26]. This is the first study to link nephrolithiasis to the VDR gene and will require further verification. Another gene of interest, the 1- α hydroxylase gene, also on chromosome 12, has been excluded as playing a role in idiopathic hypercalciuria [27]. In three families with severe absorptive

Box 1. Selected causes of hypercalciuria and urolithiasis in children

Idiopathic hypercalciuria
Adrenocorticoid excess
Barter's syndrome
CLCN5 chloride channel mutation
Corticosteroid therapy
Diabetes mellitus
Distal renal tubular acidosis
Excessive protein intake
Expansion of extracellular fluid volume
Furosemide
Generalized renal tubular dysfunction
Hyperalimentation
Hypercalcemia
Hyperprostaglandinuria
Hypo/hyperthyroidism
Hypomagnesemia
Hypophosphatemia
Immobilization
Juvenile rheumatoid arthritis
Ketogenic diet
Medullary sponge kidney
Metabolic acidosis
Methylxanthines
Pyelonephritis

hypercalciuria, a gene defect has been mapped to chromosome 1q23.3-q24 [28]. A calcium sensing receptor gene, known to be the cause of autosomal dominant familial benign idiopathic hypercalcemic hypocalciuria has also been excluded as the basis of hypercalciuria and nephrolithiasis [29]. This gene, located on chromosome 3, is linked to aquaporin gene expression and is of teleologic interest. When urinary calcium concentration is high, this gene interacts with the aquaporin gene to reduce water reabsorption and maintain a dilute urine, potentially reducing the propensity for stone formation [30].

Dent's disease

A large kindred in which men and boys had nephrolithiasis and renal failure was reported in 1991 [31]. Boys with this X-linked recessive nephrolithiasis may present with microscopic hematuria, proteinuria, and

Table 1
Genetic types of hypercalciuria

Disorder	Possible inheritance
Familial idiopathic hypercalciuria	Autosomal dominant
Distal renal tubular acidosis	Autosomal dominant
Bartter syndrome	Autosomal recessive
Dent's disease	X-linked recessive
X-linked urolithiasis	
Dent's disease	
Hypercalciuric rickets	
Hypercalciuria with low molecular-weight proteinuria	
Hypomagnesemia/autosomal recessive hypercalciuria	

hypercalciuria, as well as a history of renal failure and/or nephrolithiasis in male relatives. Increased excretion of low molecular weight proteins (α_2 microglobulin, and retinal-binding protein) is the most consistent abnormality in affected males and in almost all carrier females [32]. Glycosuria, aminoaciduria, and phosphaturia may also occur in affected males [32,33]. The association of hypercalciuria and low-molecular weight proteinuria clinically distinguishes X-linked recessive nephrolithiasis from idiopathic familial hypercalciuria, as does the family history of renal failure.

Previously, Dent and Friedman [34] reported two unrelated boys with rickets, low molecular weight proteinuria, hyperphosphaturia, and hypercalciuria. Subsequently, these individuals and some male relatives developed nephrocalcinosis and renal failure [34,35]. Two other conditions, X-linked recessive hypercalciuric hypophosphatemic rickets and low molecular weight proteinuria with nephrocalcinosis in Japanese children have also been described with similar phenotypes [36]. All are caused by mutations affecting a chloride channel [37]. These X-linked syndromes, including X-linked recessive nephrolithiasis, are now commonly referred to as Dent's disease, acknowledging the original report by Dent and Friedman [34].

Mapping studies established linkage of all forms of Dent's disease to the short arm of the X chromosome (Xp11.22) [38]. A chromosomal microdeletion was detected in one family and led to mapping of the region and identification of a gene encoding a voltage-dependent chloride channel, CIC-5. CIC-5 is expressed predominantly in the thick ascending limb of the kidney [39,56,59]. The CIC-5 gene is a member of a family of genes that encode voltage-gated chloride-channels. Included among these genes is CIC-*Kb*, one of the three mutations responsible for Bartter's syndrome. CIC-5 is expressed in the subapical endosomes of the proximal tubule where it may allow chloride to enter the endosome and dissipate the positive charge generated during acidification by the proton ATPase [38]. Impairment of this channel could limit endosomal acidification, thus causing defective reabsorption of proteins, and might also lead to impaired reabsorption of other solutes if membrane protein recycling were altered [38]. The role of this

channel in the reabsorption of calcium in the thick ascending limb remains to be elucidated. CIC-5 mutations have not been identified in individuals with idiopathic familial hypercalciuria [33].

Another fascinating clinical genetic association for idiopathic hypercalciuria was published by Praga et al. [40] in 1998. These investigators noted a history of urolithiasis among family members with hematuria and familial thin basement membrane nephropathy [40]. An association between hypercalciuria, hyperuricosuria, and thin glomerular basement membranes was identified in these families. Hematuria, a hallmark of thin glomerular basement membrane nephropathy and hypercalciuria, did not resolve with hydrochlorothiazide and allopurinol therapy. These interesting findings suggest a linkage between these two genetic conditions. The genetic basis of thin basement membrane nephropathy is currently unknown. In most instances, it does not appear to be linked to the autosomal dominant form of Alport syndrome [41].

Primary hyperoxaluria

Primary hyperoxaluria type I (PH-I) is inherited in an autosomal recessive fashion, and is a result of a deficiency of peroxisomal alanine-glyoxylate aminotransferase [12,42]. Pyridoxine (B6) is a cofactor for the AGT enzyme; therefore, pyridoxine should be part of the therapeutic regimen. Hyperoxaluria is associated with hyperglycolic aciduria. The less common primary hyperoxaluria type II is also inherited in an autosomal recessive manner, and is associated with a deficiency of cytosolic D-glycerate dehydrogenase (glyoxylate reductase). This disorder is associated with L-glyceric aciduria [22]. With a deficiency of the AGT, excretion of oxalate and glycolate is increased, causing urolithiasis and nephrocalcinosis. If oxalate deposition in the kidneys is extensive, renal failure may ensue, along with resultant oxalate deposition in tissues throughout the body (systemic oxalosis). Both clinical and enzymatic heterogeneity exist in PH-I [12]. In most patients, the first symptoms of urolithiasis occur in childhood. However, initial presentation may be in the first few months of life or, occasionally, late in adulthood. Infantile oxalosis is the most severe form of primary hyperoxaluria type I. Infants with primary hyperoxaluria may present with acute renal failure. Most often, this condition comes to medical attention due to recurrent calcium oxalate stones.

Secondary hyperoxaluria may accompany gastrointestinal disorders, such as inflammatory bowel disease, pancreatitis, and small bowel resection. The increased oxalate excretion caused by both the increased bowel wall permeability to oxalate and by complexing of calcium by fatty acids that frees oxalate for absorption [1]. Other causes of acquired hyperoxaluria are ethylene glycol poisoning, hepatic cirrhosis, renal tubular acidosis, sarcoidosis, Shwachman's syndrome, cystic fibrosis, pyridoxine deficiency and following ingestion of large amounts of vitamin C [1].

Diagnosis of hyperoxaluria requires a 24-hour urine collection. Normal oxalate excretion is less than 50 mg/1.73m²/day. Urine oxalate excretion is higher during infancy [43].

Cystinuria

Cystine stones account for five percent of pediatric urinary calculi. Cystinuria is a group of inherited transport disorders characterized by excessive urinary excretion of cystine and the dibasic amino acids arginine, lysine, and ornithine. It results from an abnormality in a specific membrane transport system located in the brush-border membrane of the renal proximal straight tubule and the small intestine [44,45]. Children with this disorder often have renal colic in the second or third decade of life. Cystine crystals are characteristically flat, hexagonal, and colorless. Cystine crystals are diagnostic, but appear in only 19 to 26 percent of homozygous cystinuric patients [45]. Cystine stones are radioopaque on plain film. In some patients, the disease is caused by mutations in the SLC3A1 gene, which is located on the short arm of chromosome 2 and encodes a renal/intestinal transporter for cystine and the dibasic amino acids [46,57]. In some populations, cystinuria maps to the long arm of chromosome 19 [57,58].

Children with cystinuria present with urinary calculi as their sole manifestation due to the limited solubility of cystine, and children with this disorder may suffer from recurrent urinary calculi in childhood and into adulthood. Cystinuria infrequently has been associated with hyperuricemia, uric acid urolithiasis, hemophilia, retinitis pigmentosa, muscular dystrophy, muscular hypotonia, mental retardation, trisomy 21, and hereditary pancreatitis.

The diagnosis of cystinuria is confirmed by the recovery of a cystine stone or cystine excretion with dibasic aminoaciduria. Occasional children with cystinuria will have stones that are composed primarily of calcium oxalate through the process of epitaxy. Normal individuals excrete less than 60 mg of cystine per 1.73 m² body surface area (BSA) per day, whereas patients who are homozygous for cystinuria often excrete more than 400 mg/1.73² BSA per day [1]. Patients with nonspecific proximal renal tubule aminoaciduria may excrete as much as 200 mg cystine per 1.73 m² per day. Cystine crystals may be observed in the urine as flat, hexagonal, colorless crystals. Crystalluria may be absent in dilute or alkaline urine.

Uric acid calculi

Uric acid calculi are responsible for three to four percent of urinary calculi in pediatric patients. Uric acid lithiasis can be associated with overproduction of uric acid, hyperuricosuria, and may be familial or idiopathic. Hereditary disorders associated with overproduction of uric acid include inborn errors of metabolism such as Lesch–Nyhan syndrome (Hypoxanthine-guanine phosphoribosyl transferase deficiency), and Type I glycogen

storage disease (glucose-6-phosphatase deficiency) [47]. Hyperuricosuria may be the result of a high purine intake or uricosuric drugs or from tubular defects such as an isolated defect in renal tubular urate reabsorption, or from generalized tubular dysfunction [47].

Uric acid excretion is extremely high in the neonatal period (fractional excretion $40 \pm 10\%$) and remains substantially higher than adult values through early childhood [47]. Unfortunately, total urate excretion, excretion per unit body weight, and fractional excretion of uric acid all vary with age, and age-related normal values rather than a single normal value must be used [48]. In children older than 2 years of age, however, the amount of uric acid excreted per deciliter of glomerular filtrate does not vary with age in either early morning urine or 24-hour samples [13]. 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:

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

Infection-related stones

Infections have been found to account for 13% of pediatric cases of urolithiasis [4]. Urinary infections produce calculi composed of struvite (magnesium-ammonium-phosphate) and carbonate apatite. On microscopic analysis, struvite crystals have a coffin-lid shape. These stones form as a result of the bacterial enzyme urease, which hydrolyzes urinary urea to ammonia and carbon dioxide. This produces an alkaline urinary environment and favors the formation of struvite calculi. Organisms known to produce urease include *Proteus*, *Klebsiella*, *Pseudomonas*, *Staphylococcus*, *Serratia*, *Candida*, and *Mycoplasma*. *Escherichia coli* does not produce urease [43]. Struvite calculi may also be associated with congenital anomalies that cause stasis of urine. Urinary tract infections may be the primary cause of calculus formation, or may occur because of stones from other metabolic causes. In most children, stones related to infections are first discovered before the child is 5 years old. All races are affected, and boys account for 80% of the population [43]. These infection-related stones often form large radiopaque upper-tract stones called staghorn calculi. Infections may also produce a soft radiolucent mucoid substance called, “matrix concretion” that may calcify rapidly and account for the rapid formation of some infection-related calculi. Because of their size, struvite calculi may be associated with obstruction, pyelonephritis, and urosepsis.

Despite recent advances in non-invasive technology, most struvite calculi in children are still removed surgically. Urease inhibitors have had limited use because of side effects, and are not approved for use in children.

It is advisable to delay detailed metabolic evaluation of children with infection-related calculi because urinary calcium excretion is markedly

increased during acute pyelonephritis. Calcium excretion returns to normal after the stone is removed and the infection is cleared.

Miscellaneous causes of childhood stones

Hypocitraturia has been found in 10% of children with urolithiasis [49]. Mean urinary citrate excretion in children with hypercalciuria and in pediatric patients with idiopathic calcium oxalate stones is not statistically different from that of control children, however [49]. In normal children and in children with hypercalciuria, girls had greater urinary citrate excretion than did boys, and an inverse relationship between urinary citrate excretion and age was observed. Urinary citrate excretion was reduced most often in older children with hypercalciuria. It is possible that chronic hypercalciuria results in renal tubular injury, which secondarily reduces citrate excretion. Hypocitraturia is seen routinely in children ingesting a ketogenic diet.

Hypouricemia (serum uric acid concentration less than 2 mg/dl) in the presence of decreased uric acid excretion and urinary calculi should suggest the rare condition of xanthinuria [43]. Xanthinuria results from a deficiency in xanthine oxidase, and thus, xanthine is not converted to uric acid. Radiolucent xanthine stones form in acidic urine. Secondary xanthinuria with xanthine stones is an unusual complication of allopurinol therapy.

A deficiency of the purine enzyme adenine phosphoribosyl transferase (APRT) has been associated with urolithiasis [43]. The metabolic defect is inherited as an autosomal recessive trait. Calculi in this condition are composed of 2,8-dehydroxyadenine and are radiopaque [22]. Special techniques, such as isotachopheresis or high-performance liquid chromatography (HPLC), are required to distinguish these stones from uric acid. Moreover, alkalization of the urine, which is indicated for urate calculi, decreases the solubility of 2,8-dehydroxyadenine. Allopurinol, which exhibits xanthine oxidase, is effective therapy for this condition, and a low-purine diet is also recommended [43].

Orotic aciduria is a rare inborn error of pyrimidine metabolism that is recessively inherited and associated with urolithiasis. This disorder is characterized by onset during early infancy, growth failure, developmental delay, hypochromic anemia, and excessive urinary excretion of orotic acid (an intermediary in uridine synthesis) [22].

Surprisingly, passage of urinary calculi may be a manifestation of Munchausen's syndrome. An example is a child whose mother observed a stone to pass from the penile urethra. No metabolic or infectious etiology for a calculus was discovered. Analysis of the stone revealed its composition to be quartz. Careful scrutiny of the child's development revealed marked behavioral problems. When no etiology of urolithiasis is defined or when abnormal family dynamics are present, factitious disease should be considered. Analysis of the stone, if possible, may assist in this diagnosis.

Diagnosis of a child with urolithiasis

The initial evaluation of a pediatric patient with urolithiasis may suggest the diagnosis through a complete history and physical exam. The patient's age at presentation may provide clues to a particular metabolic cause. Attention to a family history of urolithiasis, hematuria, or renal failure is especially important. The physical exam should include an evaluation of growth and development, bone development, and blood pressure. A dietary history should be obtained with inquiries concerning any dietary excesses or deficiencies, vitamins, medications, and fluid intake. The urinary sediment should be examined for crystalluria and a thorough medical, metabolic, and radiographic evaluation performed. If a stone is available, its content should be analyzed.

If a stone analysis reveals a cystine, struvite, or uric acid calculus, the metabolic work-up initially may be more focused. Finding a calcium phosphate or calcium oxalate stone requires a broader metabolic evaluation. A 24-hour urine collection should be performed while the patient is healthy, eating their customary diet, and after urinary infections have been treated. In general, the urine should be analyzed for calcium, cystine, uric acid, sodium, oxalate, and citrate. Normal values in school age children are listed in Box 2. These values may differ during infancy or adolescence. Oxalate, citrate, uric acid, and calcium excretion are considerably higher during the first one to two years of life. Abnormal values should be verified with a repeat collection. In children with repeated calculi and normal urinary values, a second urinary collection may be useful in arriving at the appropriate diagnosis. Appropriate serum studies include calcium, magnesium, phosphorus, creatinine, bicarbonate, and uric acid. Urinary infection should be excluded. Intact PTH levels should be determined in children with hypercalciuria or hypophosphatemia. Reduced urinary citrate excretion requires investigation of renal acidification ability, and may suggest the diagnosis of distal renal tubular acidosis.

Hypercalciuria

Normal calcium excretion during childhood is less than 4 mg/kg per day while eating a routine diet [5,7,50]. Calcium excretion does not appear to dif-

Box 2. Normal urinary values for school age children

Calcium	<4 mg/kg/day
Uric acid	<0.56 mg/dL GFR
Oxalate	<50 mg/1.73 m ² /day
Cystine	<60 mg/1.73 m ² /day
Citrate	>400 mg/g creatinine
Volume	>20 mL/kg/day

fer on the basis of gender; no racial differences have been identified during childhood. Geographic location may influence urinary calcium excretion. For example, urinary calcium excretion is somewhat higher in Taiwanese children than in children from the United States [8]. Use of the ratio of urinary calcium to creatinine (mg/mg) has been offered as a means of screening for hypercalciuria [51,52]. In school-aged children, normal values for the urinary calcium/creatinine ratio in 24-hour urinary calcium collections are less than 0.2. Use of random urinary collections may be misleading [13]. The urine calcium to creatinine ratio may increase by 40% to 0.28 following a meal [52].

Urinary calcium excretion is greater during infancy than in school-age children. In term infants, calcium excretion has been studied primarily by measuring the ratio of urinary calcium to creatinine. Urinary calcium to creatinine (mg/mg) ratios are substantially higher during infancy, with normal values up to 0.8 during the first six months of life and as high as 0.6 from six months to one year [6,53,54]. Although creatinine excretion is lower in infants, it appears that urinary calcium excretion is increased independently. Urinary calcium excretion is influenced by the source of milk or formula. Babies fed human milk have the highest urinary calcium excretion, whereas soy-based formulae produce the lowest calcium excretion [53].

Whenever possible, the diagnosis of hypercalciuria should be made on the basis of 24-hour urinary calcium excretion. Once an abnormal value is discovered, it should be reconfirmed and examined in relationship to urinary sodium excretion. A careful dietary history should be obtained in all children with hypercalciuria to ascertain if dietary factors might account for the finding. Diagnostic studies for hypercalciuria should be deferred if the patient has a urinary infection, as pyelonephritis increases urinary calcium excretion. In young children, timed urinary collections may be impractical or impossible. Urinary calcium excretion in younger children is estimated by use of the ratio of urinary calcium to creatinine. A first-morning fasting collection along with a postprandial sample can provide considerable information. If only a single random sample is available, it would be desirable to collect a sample two to four hours following a meal in which milk is given. In such a sample, if the ratio of urinary calcium to creatinine (mg/mg) is less than 0.2, further evaluation for hypercalciuria is not necessary. The oral calcium-loading test is not recommended in the routine evaluation of hypercalciuria in children.

When idiopathic hypercalciuria is confirmed, the next step is to assess whether dietary manipulations can normalize calcium excretion. If the urinary collections suggest a high dietary sodium intake, a third collection following two to four weeks of sodium restriction (2–3 g sodium/day) is indicated. Urinary citrate excretion should be determined, as well as serum calcium, phosphorus, bicarbonate, magnesium, and parathyroid hormone concentrations in all children with hypercalciuria. Decreased urinary citrate excretion should alert the clinician to the possibility of distal renal tubular acidosis.

While many genetic studies remain investigational and are not available in commercial laboratories, genetic diagnoses will be increasingly important. A web-based directory of genetic laboratories screening for specific genes or genetic disorders can be accessed at <http://www.genetests.org> [55].

Preventive medical therapy

A high fluid intake is critical in preventing supersaturation of the urine regardless of the cause of urolithiasis. In addition, a reduced sodium, high potassium, and low oxalate diet is recommended for children with hypercalciuria, oxaluria, and idiopathic stones because of the well-known calciuric effect of high dietary sodium intake. For children with hypercalciuria unresponsive to dietary sodium restriction, hydrochlorothiazide (1–2 mg/kg/day) and/or citrate therapy may be helpful. All children with hypercalciuria should be advised to ingest a diet rich in potassium. Increased potassium intake may reduce urine calcium excretion [37]. If a child is receiving excessive amounts of protein, the diet should be adjusted to the recommended daily allowance. Intake of supplemental vitamin C and/or D should be discontinued. Citrate therapy (potassium citrate) is helpful in patients with reduced urinary citrate excretion and hypercalciuria and should be considered, if hypercalciuria does not respond to other anticalciuric measures. Dietary calcium restriction is not recommended for children with hypercalciuria, especially in light of reports of osteopenia in some children [13]. Preventive therapies for urinary stones, other than hypercalciuria, should address either the underlying overproduction of the lithogenic ion and/or increase the solubility of solutes in the urine. Medical therapy for uric acid calculi includes efforts to maintain an alkaline urinary pH (>6.0), and a high urinary flow rate. Urinary alkalinization may be achieved with sodium bicarbonate or potassium citrate. Therapy with allopurinol (5–10 mg/kg/day) also should be considered.

Management of cystinuria requires promoting a large fluid intake and urinary alkalinization. When patients suffer from recurrent nephrolithiasis despite these measures, Tiopronin or D-Penicillamine may be used. Both compounds interact with cystine to form a thiol-disulfide exchange with cystine, which is more soluble in urine [43]. Captopril also has been shown to form a thiocysteine mixed disulfide that is more soluble in urine than cystine, although trials in children are not available.

Primary hyperoxaluria requires vigorous management and careful follow-up [12]. Therapy includes promoting a high urinary flow rate 24 hours a day and restricting dietary oxalate. In children with coexistent hypercalciuria, use of hydrochlorothiazide (1–2 mg/kg/day) may be beneficial. Restriction of dietary calcium can result in increased oxalate absorption via the gastrointestinal tract and should be avoided. Inhibitors of crystal growth, including magnesium, citrate, and phosphate supplements are beneficial. If renal insufficiency is present, the use of phosphate supplements is

contraindicated. Some patients with PH-1 respond to pyridoxine. Occasionally, urinary oxalate returns to normal values with pyridoxine therapy. More often, the response is partial, with reduced, but still abnormal, oxalate excretion. The initial dose of pyridoxine is 25 mg with a maximum of 250 mg/day. Urinary oxalate levels are followed as the dose is increased. Neurologic toxicity has been attributed to high doses of pyridoxine (1000 mg) [12]. The ultimate therapy for primary hyperoxaluria is combined liver-kidney transplantation.

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