

Nephrolithiasis in Children

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Objectives After completing this article, readers should be able to:

1. Explain why a careful evaluation for nephrolithiasis is appropriate to help guide treatment and provide prognostic advice.
2. Discuss why patients who have nephrolithiasis should have a thorough metabolic evaluation, ideally while at home, not infected, and consuming their regular diet.
3. Explain how to prevent future stones in a patient who has nephrolithiasis, regardless of cause.
4. Describe the risk of recurrent stones in a patient who has a history of one or more calculi.
5. Discuss the consequences of the presence of urinary calculi.

Introduction

Nephrolithiasis occurs following a complex interaction of environment and heredity. Urinary crystals coalesce and precipitate when physical and biochemical conditions disturb a delicate balance of stone-promoting and -inhibiting factors (Fig. 1). Small urinary calculi may pass unnoticed or appear as sandlike sediment in urine. Larger calculi may cause pain or obstruct urinary flow. The prevalence of urinary stones varies by region, being more common in the southeastern United States. Nephrolithiasis affects boys and girls equally and is identified in 1 in 1,000 to 1 in 7,600 hospital admissions. Stones are found most commonly in Caucasian children and rarely in African-American children.

Clinical Presentation

The classic adult presentation of sudden, debilitating flank pain is uncommon in children. Nonetheless, some form of abdominal, flank, or pelvic pain occurs in approximately 50% of children who have urolithiasis, most often in older children and adolescents. Urolithiasis in infants may mimic colic. Gross or microscopic hematuria is found in 33% to 90% of children who have urolithiasis and occurs equally across age groups. Urinary tract infection frequently is the presenting sign of urolithiasis in preschool-age children.

Causes

Hypercalciuria

Hypercalciuria, the most common metabolic cause of pediatric urinary calculi, is not a single entity but rather a condition associated with many causes (Table 1). Most children who have hypercalciuria and urolithiasis have normal serum calcium concentrations. Primary hyperparathyroidism with hypercalcemia is extremely uncommon in children. The gene responsible for familial idiopathic hypercalciuria, the most common cause of hypercalciuria, has not been identified, but the disease appears to be transmitted as an autosomal dominant trait with incomplete penetrance. Dent disease encompasses multiple X-linked syndromes of hypercalciuria with proteinuria due to a chloride channel mutation. Distal renal tubular acidosis, Bartter syndrome, hypomagnesemia-hypercalciuria, and urinary infections also produce stones and increase calcium excretion. Common iatrogenic causes of hypercalciuria include treatment with loop diuretics (such as furosemide or bumetanide), prednisone, and adrenocorticotrophic hormone.

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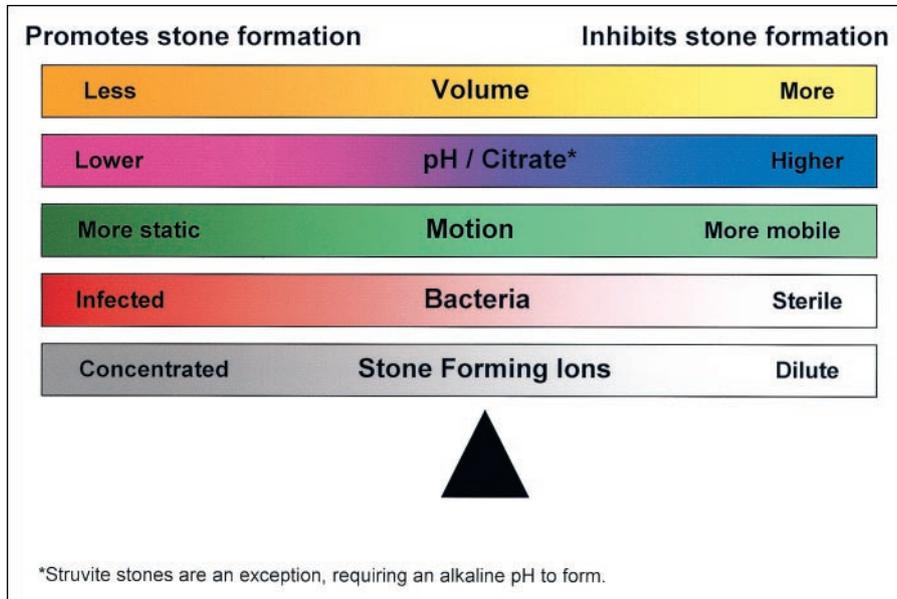


Figure 1. Balance of stone-promoting and -inhibiting factors.

Nephrocalcinosis refers to a generalized deposition of calcium throughout the renal parenchyma. Among children, nephrocalcinosis is most common in term and preterm infants who have complicated hospital courses. Multiple risk factors are associated with nephrocalcinosis, most commonly hypercalcemia, metabolic acidosis, or the use of loop diuretics.

Infection

Improvements in urologic surgical options for children have reduced the incidence of stones due to urinary tract infections. Specific infections are associated especially strongly with stones and include those caused by most isolates of *Proteus* sp and *Providencia* sp and some strains of *Klebsiella* sp, *Pseudomonas* sp, and enterococci. These organisms contain urease, an enzyme that catalyzes the hydrolysis of urea. This initiates a complex biochemical cascade that creates a unique urinary milieu that is highly favorable to struvite (magnesium ammonium phosphate) stone formation. Struvite stones also may contain carbonate apatite, and they tend to branch and enlarge, often filling the renal calyces and producing a “staghorn” appearance. Struvite stones form only in the setting of infection because urease is exclusively a bacterial product that is not present in sterile urine. Early studies identified infection as the most frequent cause of urolithiasis in children. However, clinical studies now suggest that most nonstruvite calculi develop from metabolic abnormalities, with infection being a complication of the stone more often than a cause.

Hyperuricosuria

Relatively few childhood stones are composed purely of uric acid. Determining whether uric acid excretion is abnormal in children can be a challenge. Uric acid excretion is highest in infancy and remains high, relative to adult values, until adolescence. Reference values are age-specific, but in children 2 years of age or older, normal uric acid excretion adjusted for glomerular filtration rate (GFR) is constant at less than 0.56 mg/dL fractionated by GFR (Table 2). Normal levels of urinary uric acid are so high in infants that crystals may precipitate in diapers and be misidentified as blood.

Idiopathic hyperuricosuria is an uncommon cause of urolithiasis and hematuria in children. Approximately 12% to 40% of children who have idiopathic hyperuricosuria have coexistent hypercalciuria. High purine intake, uricosuric drugs, renal tubular disorders, cyanotic congenital heart disease, hemolysis, and myeloproliferative disorders also may result in hyperuricosuria. Conditions associated with excess production of urate include Lesch-Nyhan syndrome (hypoxanthine-guanine phosphoribosyl transferase deficiency) and type I glycogen storage disease (glucose-6-phosphatase deficiency). Some individuals who have normal uric acid metabolism and excretion develop uric acid calculi; this type of idiopathic uric acid lithiasis often is familial, and affected persons tend to have acidic urine.

Hyperoxaluria and Oxalosis

The primary hyperoxalurias, types I and II, are rare autosomal recessive disorders caused by defects in specific hepatic enzymes that result in overproduction of oxalate. Secondary hyperoxaluria occurs with excessive intake of oxalate precursors (ethylene glycol, ascorbic acid, methoxyflurane), increased absorption of oxalate (inflammatory bowel disease, extensive bowel resection), or deficiency of cofactors in oxalate metabolism (pyridoxine deficiency). Oxalosis develops as calcium oxalate precipitates in multiple organs and joints. Oxalate deposition in the kidneys impairs renal function, further elevating serum oxalate levels.

The clinical presentation of oxalosis includes nephro-

Table 1. Selected Causes of Hypercalciuria

Increased Intestinal Calcium Absorption

- Vitamin D excess

Renal Tubular Dysfunction

- Renal tubular phosphate leak
- Impaired renal tubular calcium absorption
- Type 1 (distal) renal tubular acidosis
- Dent disease
- Bartter syndrome

Endocrine Disturbances

- Hypothyroidism
- Adrenocorticoid excess
- Hyperparathyroidism

Bone Metabolism Disorders

- Immobilization
- Rickets
- Malignancies
- Juvenile rheumatoid arthritis

Other

- Familial idiopathic hypercalciuria
- Drugs (certain diuretics, corticosteroids)
- Urinary tract infection
- Williams syndrome
- Increased renal prostaglandin E₂ production
- Hypercalcemia
- Hypophosphatemia
- Glycogen storage disease

calcinosis and nephrolithiasis. More advanced cases may exhibit features of chronic renal insufficiency such as growth failure, malnutrition, and uremia. Primary hyperoxaluria type I appears to have a more severe phenotype; renal failure is uncommon in type II.

Cystinuria

Cystinuria is an autosomal recessive disorder of renal tubular transport, the genetic basis of which has been studied extensively. Affected individuals have excessive excretion of the dibasic amino acids cystine, arginine, lysine, and ornithine. Colorless, flat, hexagonal crystals found in urinary sediment are diagnostic, but are identified in only 19% to 26% of individuals homozygous for the disease. Recurrent nephrolithiasis and its complications are the only clinical manifestations of cystinuria. Cystinuria rarely may be associated with calcium oxalate stones. It should be emphasized that cystinuria is distinct

from cystinosis, a lysosomal storage disease, not customarily associated with nephrolithiasis.

Other Causes

Patients who have cystic fibrosis (CF) have an increased risk of nephrolithiasis, most commonly due to calcium oxalate stones. The mechanisms are not fully understood but appear to be associated with hypercalciuria, hyperoxaluria, and hypocitraturia. Tubular dysfunction from cotrimoxazole and ceftazidime therapy may play a role in children who have CF. Certain drugs may produce stones. Protease inhibitors, notably indinavir, may form stones that do not appear on standard imaging. Other drugs directly or indirectly leading to stones include sulfamethoxazole, furosemide, acetazolamide, and allopurinol.

Patients who have surgically augmented bladders also are at high risk for developing bladder stones, most commonly those composed of struvite. Augmentation using intestinal segments presents a much higher risk than use of gastric segments. Paradoxically, the grafted gastric mucosa inhibits stone formation by secreting acid into the bladder. Although acidic urine facilitates formation of most types of stones, struvite stones require an alkaline environment. Gastric acid may help to inhibit bacterial growth.

Urolithiasis has been reported as a presenting complaint in Munchausen syndrome by proxy. In some cases, parents have submitted alleged urinary stones found to be of nonurinary minerals such as quartz.

An important emerging cause of childhood stones is the ketogenic diet, with an incidence of urologic stones as high as 10%. Used for refractory seizures, this diet also is promoted in the lay press for weight loss. A high-protein, low-carbohydrate, low-fluid dietary regimen is associated with hypercalciuria, hyperuricosuria, hypocitraturia, and low urine volume.

Diagnosis

Initial Evaluation

Evaluation begins with a detailed history and physical examination, including careful inquiry regarding any family history of nephrolithiasis, arthritis, gout, or renal disease. Acute or chronic urinary tract infection must be excluded. Identification of stone composition greatly facilitates diagnosis and management. The patient should be asked to strain his or her urine and submit any stone or fragment for analysis. Urinary strainers are available from medical supply companies; cheesecloth or fine mesh nets may be improvised if needed. A suggested scheme for evaluating possible nephrolithiasis is shown in Figure 2.

Table 2. Normal Urinary Values in Children Based on Random Urine Collection

	Age	mg/mg	Age	mmol/mmol	
Calcium/Creatinine	0 to 6 mo	<0.8	0 to 6 mo	<2.24	
	6 to 12 mo	<0.6	6 to 12 mo	<1.68	
	2 to 18 y	<0.2	2 to 18 y	<0.56	
Oxalate/Creatinine	0 to 6 mo	<0.3	<1 y	<0.061	
	6 mo to 4 y	<0.15	1 to 5 y	<0.036	
	>4 y to adult	<0.1	5 to 12 y	<0.03	
			>12 y	<0.013	
Cystine/Creatinine	All ages	<0.02	All ages	<0.01	
Citrate/Creatinine	All ages	<0.51	Male	Female	
			Infant	<1.9	<0.63
			Child	<0.27	<0.33
			Adolescent	<0.32	<0.28
Uric Acid/Glomerular Filtration Rate calculated as: $\frac{\text{urine uric acid} \times \text{serum creatinine}^*}{\text{urine creatinine}^*}$	≥ 3 y	<0.56 mg uric acid/dL of glomerular filtrate	≥ 3 y	<0.03 mmol uric acid/dL of glomerular filtrate	

*All values in same units: mg/dL or mmol/L.

Imaging

Many clinicians use plain abdominal radiography as the initial study. Ultrasonography reveals many types of stones, including some radiolucent stones, and may yield other clinically important findings such as urinary obstruction or nephrocalcinosis (Fig. 3). One study has demonstrated that all renal calculi identified on plain radiographs also were observed on ultrasonography (see Smith in Suggested Reading). Previously, ultrasonography had largely supplanted intravenous pyelography (IVP) in the evaluation of children who had suspected urolithiasis due to concerns about radiation exposure and the risks associated with contrast agents. More recently, studies have suggested that nonenhanced helical computed tomography (CT) is superior to IVP in the evaluation of urolithiasis (Fig. 4). This study requires no contrast agents and offers a high sensitivity and specificity (96% to 98% in adult studies), the ability to image very small stones, and a greater potential to identify alternative diagnoses.

CT evaluates total stone burden efficiently and can localize ureteral stones with great precision as well as detect obstruction or subtle hydronephrosis. The radiation exposure during CT varies widely due to differences in equipment and institutional protocols and may exceed that of IVP, particularly in smaller children. Physicians can minimize radiation doses through judicious ordering of studies and by ensuring that scanning parameters are

adjusted for patient size and weight and study type, particularly if the study is performed at a facility in which there is limited experience in imaging children. Table 3 compares various imaging modalities.

Metabolic Evaluation

Metabolic evaluation ideally is performed while the patient is at home, consuming his or her regular diet, and free of infection. Although 24-hour urinary collections form the criterion for most urinary measurements (Table 2), obtaining such collections from small children can be difficult or impossible. Standards based on single specimens have been developed (Table 4).

If no stone is recovered or analysis reveals a stone of calcium oxalate or calcium phosphate, a broad evaluation is required. Evaluation should begin with two 24-hour urine collections, if possible, including measurement of volume, calcium, creatinine, oxalate, uric acid, sodium, and citrate. Urinary cystine levels should be obtained with the first specimen. Commercial laboratories offer panel tests for urinary stone risk factors, but the results may require conversions to interpret according to units used in pediatric reference ranges. Serum levels of uric acid, potassium, creatinine, calcium, phosphorus, and bicarbonate should be obtained. Measurement of serum parathyroid hormone levels is indicated if the patient has hypercalciuria, hypercalcemia, or hypophosphatemia.

Identification of stones composed of struvite, cystine,

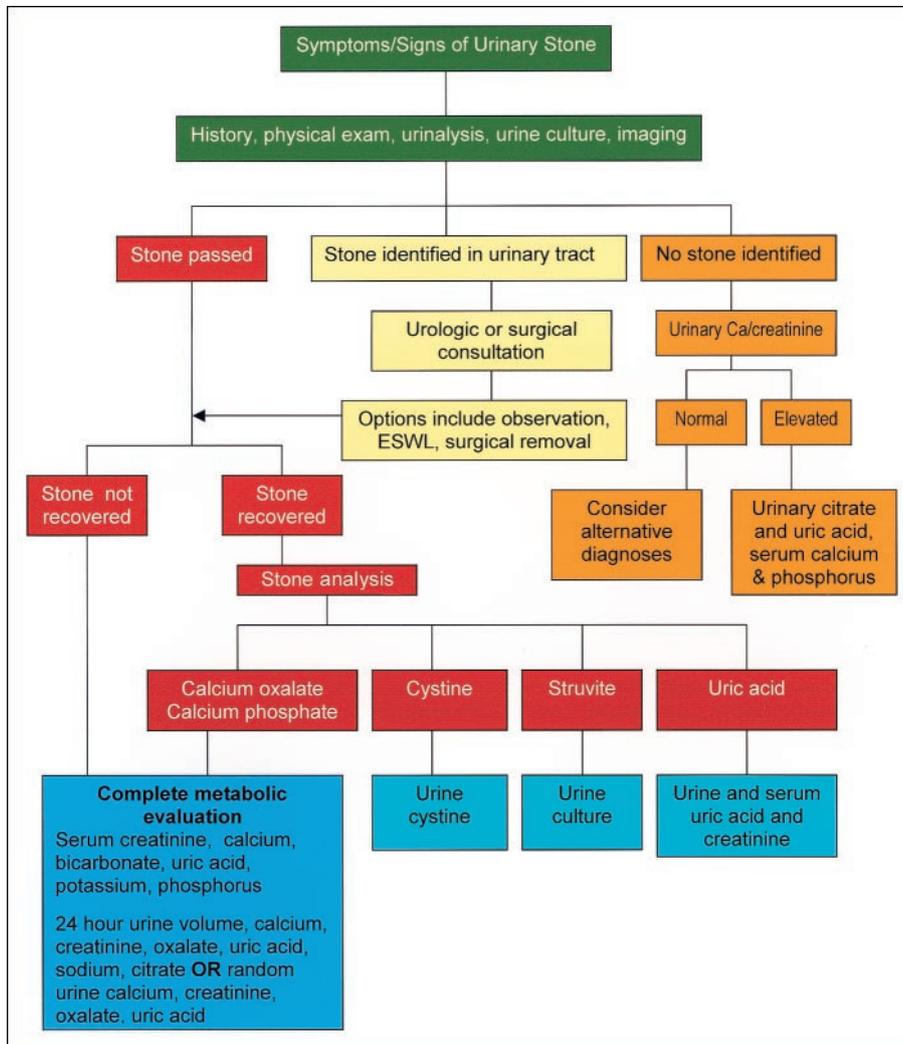


Figure 2. Suggested algorithm for evaluating possible nephrolithiasis.

or uric acid narrows the differential diagnosis, allowing a more focused evaluation. Struvite stones always are associated with infection by a urea-splitting organism. Alternatively, the finding of a nonstruvite stone in the setting of infection suggests that the infection was secondary, and the search for a primary cause of urolithiasis should continue. Calcium excretion increases during pyelonephritis, so metabolic studies should be performed after any infections are resolved.

Treatment

All Causes

Adequate fluid intake is a key to treatment regardless of the cause of stones. High fluid intake increases urinary

volume and dilutes stone-forming compounds, making them less likely to precipitate. Brisk urinary flow also helps expel small crystals and bacteria before they become clinically significant. Patients should increase fluid intake even more during hot weather or strenuous exercise. Water is preferable; use of other beverages may lead to undesirable increases in caloric or caffeine intake. Due to the risk of urinary obstruction or infection, patients should be reminded to seek medical assistance promptly if they develop pain or fever.

Hypercalciuria

Good fluid intake and a low-sodium diet constitute first-line therapy for hematuria or stones due to hypercalciuria. Thiazide diuretics, such as chlorothiazide or hydrochlorothiazide (Table 5) may be added if these measures fail. Thiazide drugs reduce calcium excretion by stimulating calcium reabsorption in the distal tubule. Adverse effects include hypokalemia and elevated serum lipid levels. Some patients may benefit from a combination of thiazide diuretics and amiloride. Loop diuretics have no role because they increase calcium excretion. Patients should avoid vitamin C and D supplements. Citrate supplementation (Table 5) helps prevent stones in patients who have renal tubular acidosis or hypocitraturia.

Other dietary interventions may prove helpful in selected cases. High protein intake increases calcium excretion. Patients who eat excessive amounts of protein should reduce their consumption, but all patients should receive 100% of the United States Recommended Dietary Allowance for age to supply adequate substrate for growth and development. Similarly, any unusual excess of calcium intake should be curtailed, but calcium restriction is not recommended because of the risk of osteopenia. Adult studies suggest that grapefruit juice increases

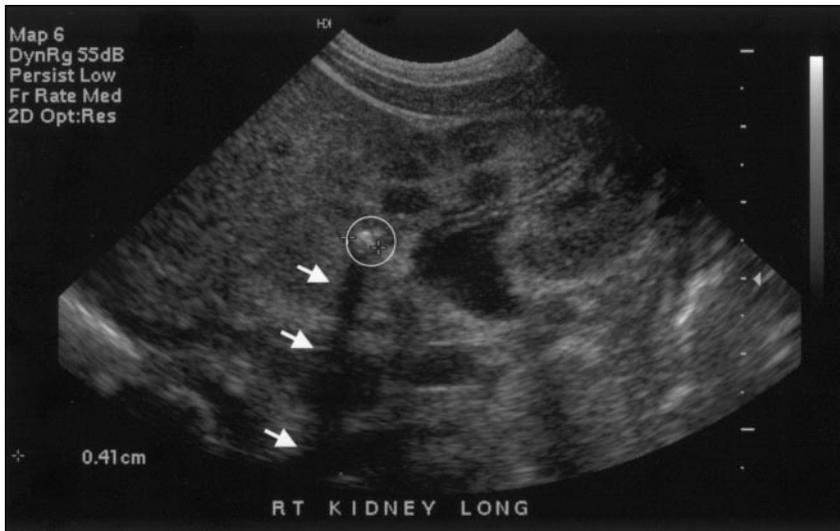


Figure 3. Ultrasonographic appearance of renal calculi. Many renal calculi do not appear as prominently as the one circled, but they still can be identified by the hypoechoic "shadow" they produce, as shown by the arrows.

the risk of urinary stones; other citrus juices have not been implicated. Because potassium depletion increases calciuria, patients should receive adequate dietary potassium, particularly if they are taking diuretics.

Hyperoxaluria and Oxalosis

Treatment of primary hyperoxaluria is difficult, and all affected patients should be followed closely by clinicians who have expertise in the disorder. Reducing sodium intake to 2,000 to 3,000 mg/d and limiting or avoiding high-oxalate foods such as spinach, rhubarb, nuts, tea, wheat bran, and strawberries is recommended. Supplemental citrate, magnesium, and phosphorus may help decrease urinary oxalate crystallization. Calcium intake should not be restricted because this can increase intestinal calcium absorption. Oral citrate has been suggested as adjunctive therapy. Hydrochlorothiazide reduces calcium excretion in patients who have concomitant hypercalciuria. Approximately 10% to 40% of patients respond to pyridoxine supplementation, but vitamin C and D supplements should be avoided. Dialysis does not remove oxalate ade-

quately. Combined liver and kidney transplantation remains the only definitive therapy.

Uric Acid Lithiasis

Limiting dietary sodium intake may decrease urinary uric acid (and calcium) excretion. If these measures fail or if patients have recurrent symptoms, base supplementation with citrate or bicarbonate may be indicated. The resulting elevation in urinary pH increases the solubility of uric acid. Patients who have known disorders of uric acid metabolism should receive appropriate therapy for the primary disease. Allopurinol decreases uric acid synthesis by inhibiting xanthine oxidase and is useful in disorders associated with excess uric acid pro-

duction. For patients who have very high production of uric acid, allopurinol increases urinary xanthine, which may precipitate into secondary xanthine stones. Dietary purine restriction is of limited value; most children do not consume significant quantities of purine-rich foods, such as anchovies, mussels, goose, brain, kidney, and liver. Counseling patients to avoid unusual amounts of purine intake is appropriate.

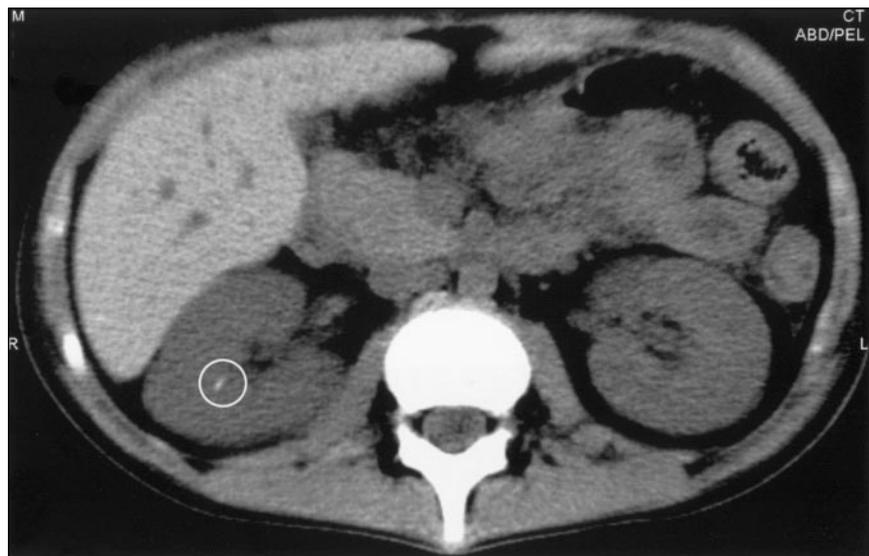


Figure 4. Renal calculus on unenhanced computed tomography (CT). With judicious use, noncontrast helical CT may be helpful in identifying renal calculi (such as the one circled) as well as nonrenal causes of abdominal symptoms.

Table 3. Appearance of Stones on Urinary Tract Imaging

Stone	Radiography	Ultrasonography	Unenhanced CT
Calcium Oxalate	●	●	●
Struvite	●	●	●
Uric Acid	○	●	●
Cystine	●/○*	●	●
Indinavir	○	○	○

● Visible
○ Not visible
* Stones are faintly radio-opaque or radiolucent

Cystinuria

Treatment of cystinuria includes creating abundant urinary flow (>1.5 L/m² per day) and urinary alkalini-zation. The goal of fluid therapy should be to maintain a urinary concentration of cystine of less than 250 mg/dL. D-penicillamine, tiopronin, and alpha-mercaptopyropionylglycine, agents that bind cystine and form highly soluble complexes, may help in refractory cases. These drugs are associated with significant risks and toxicities and should be used cautiously and in consultation with a specialist familiar with their use. Studies evaluating captopril as a therapy for cystinuria have yielded conflicting results; more research is needed before recommendations can be made.

Struvite

Prevention of struvite stones rests on prevention of infection. The evaluation and management of recurrent urinary tract infections are beyond the scope of this review, but affected patients should receive a thorough evaluation and appropriate medical, surgical, or behavioral therapy to minimize the risk of infection. Urease

inhibitors such as acetohydroxamic acid have been studied in adults, but these agents are palliative at best and are associated with substantial toxicities. Theoretically, urinary acidification should prevent struvite stones, but no practical, well-tolerated technique has been developed for humans.

Complementary and Alternative Therapies

Herbal therapies now command widespread public interest. Chocolate vine (Mu Tong, *Akebia quinata*) and Gotu Kola (*Centella asiatica*) originate from traditional Chinese medicine. Kamala (*Mallotus philippinensis*) and cumin (*Cuminum cyminum*) are popular treatments in India, although cumin may be of concern in pregnancy because it also is used as an abortifacient. Other plants include cleavers (*Galium aparine*) and burdock (*Arc-tium lappa*). Most of these agents are believed to have mild diuretic effects, which may reduce stone formation by increasing urinary flow and volume. *Aloe vera* and yellow dock (*Rumex crispus*) contain calcium binders that reduce crystal growth rate, but the high levels of oxalate in yellow dock may negate any beneficial effect. Acupuncture and acupressure are used to treat nephrolithiasis in China and other areas.

Stone Removal

Extracorporeal shock wave lithotripsy (ESWL) uses shock waves to fracture stones. The resulting fragments may pass spontaneously or be removed endoscopically. Anesthesia or sedation is indicated primarily for nonco-operation; older children and adults frequently undergo ESWL without medication. Complications of ESWL include skin bruising and hematuria, which are almost universal but transient. Early concerns about possible damage to the growing kidneys in children treated with ESWL have not been validated in long-term follow-up studies. Most stones respond well to ESWL, but cystine stones frequently require surgical extraction because of their pasty consistency, which renders them relatively resistant to shock waves.

Stones may be removed by using rigid or flexible endoscopes passed through the urethra into the bladder or ureter. This technique allows for simultaneous placement of a ureteral stent or performance of cystourethrography, if indicated. Renal calculi also may be removed percutaneously; the resulting instrument tract may serve for urinary drainage before or after removal of an obstructing stone. The previously noted modalities can treat most children successfully, but open surgical lithotomy remains an option if other techniques fail or are not appropriate. Endoscopic laser fragmentation of stones is

Table 4. Normal Urinary Values in School-age Children Based on 24-hour Urine Collection

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

Table 5. Selected Medications Used in the Treatment of Nephrolithiasis

Chlorothiazide

- <6 mo: 10 to 40 mg/kg per day in 1 or 2 divided doses
- 6 mo to 12 y: 10 to 20 mg/kg per day in 2 divided doses (maximum, 40 mg/kg per day)
- >12 y: 500 to 2,000 mg/d in 1 or 2 divided doses

Hydrochlorothiazide

- <6 mo: up to 3.3 mg/kg per day in 2 divided doses
- 6 mo to 12 y: 2 to 2.2 mg/kg per day in 2 divided doses
- >12 y: 25 to 100 mg daily or divided bid

Urinary Alkalinization

- Children: 2 to 3 mEq HCO₃/kg per day in 3 to 4 divided doses
- Adolescents and adults: 30 to 60 mEq HCO₃ 3 to 4 times daily

Alkalinizing Agents

- Potassium citrate: 2 mEq HCO₃/mL
- Sodium citrate/citric acid: 1 mEq HCO₃/mL
- Sodium bicarbonate intravenous solution: 8.4%=1 mEq HCO₃/mL (given orally): 4.2%=0.5 mEq HCO₃/mL
- Baking soda: 1 tsp=42 mEq HCO₃

gaining popularity for adult treatment, but its role in children remains undefined. Treatment should be selected on an individual basis in consultation with a pediatric urologist or surgeon.

Prognosis

The prognosis for nephrolithiasis depends on the primary diagnosis and adherence to therapy, but recurrence rates generally are high when the condition is left untreated. Patients who have hyperuricosuria may continue to have symptomatic or asymptomatic calculi. Primary hyperoxaluria type I remains progressive and debilitating, even with optimal therapy; type II has a more favorable prognosis, rarely leading to renal failure. For

patients who have cystinuria, recurrent nephrolithiasis and obstruction may impair renal function. One study found a recurrence rate of 0.64 per patient year. Population studies in adults suggest that patients who have cystine stones develop higher serum creatinine levels over time and are more likely to undergo nephrectomy.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

12. A 3-year-old boy has had severe abdominal pain and cloudy urine. On microscopic examination his urinalysis demonstrates red blood cells too numerous to count (TNTC), white blood cells TNTC, and bacteria. He subsequently has passed what you suspect is a struvite renal stone. The cause of his urinary tract infection and this stone is *most* likely due to an infection with:
 - A. *Clostridium difficile*.
 - B. *Enterococcus* sp.
 - C. *Escherichia coli*.
 - D. *Proteus* sp.
 - E. *Staphylococcus aureus*.

13. A 4-year-old boy has had an extensive resection of his small bowel after being diagnosed with a malrotation and volvulus at age 6 months. He has required home intravenous hyperalimentation but is able to take some foods and fluids orally. He now presents with flank pain, hematuria, and dysuria. You suspect a renal stone. The *most* likely cause of his renal stone is:
 - A. Cystinosis.
 - B. Hypercalciuria.
 - C. Hyperoxaluria.
 - D. *Proteus* sp urinary tract infection.
 - E. Uric acid.

14. A 10-year-old girl presents with vomiting and pain radiating into her groin. Her urinalysis reveals red blood cells TNTC. You suspect a urinary tract stone. The *most* effective radiographic method of detecting this stone and its location is:
 - A. Abdominal ultrasonography.
 - B. Helical nonenhanced computed tomography.
 - C. Intravenous pyelography.
 - D. Plain abdominal radiography.
 - E. Voiding cystourethrography.

15. One of the most common causes of renal calculi is hypercalciuria. Which of the following will reduce the risk of stone formation in children who have hypercalciuria?
 - A. Avoidance of rhubarb.
 - B. Furosemide therapy.
 - C. Increased protein consumption.
 - D. Increased sodium intake.
 - E. Increased water consumption.

16. Each child who is diagnosed with either a calcium oxalate or calcium phosphate stone should receive a metabolic evaluation that includes urine studies measuring calcium, creatinine, oxalate, uric acid, sodium, and citrate. In addition, blood studies should be performed and include which of the following measurements?
 - A. Acid phosphatase, cystine, oxalate.
 - B. Calcium, uric acid, creatinine.
 - C. Homocystine, galactose-1-phosphate uridylyltransferase, biotin.
 - D. Magnesium, ammonia, blood urea nitrogen.
 - E. Thyroxine, 25-hydroxycholecalciferol, total bilirubin.