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Objectives

After completing this article, readers should be able to:

1. Discuss the major risk factors for renal stone disease in children.
2. Perform and interpret the evaluation of a child who has suspected or proven renal stone disease.
3. Provide dietary advice for the child who has renal stone disease, including fluid intake goals.
4. Prescribe potassium citrate or thiazide diuretics appropriately in the treatment of renal stone disease.
5. Recognize the conditions of cystinuria, primary hyperoxaluria, and struvite stones.

Case Presentation

A 9-year-old boy is referred by his primary care physician for evaluation of abdominal pain and blood in the urine after playing on a trampoline. His past medical history is negative for renal disease, and he takes no medications. A complete dietary history reveals that he eats a lot of fast food and drinks about 1 glass of milk daily. His father and grandfather have a history of renal stones. Findings on his physical examination are unremarkable. A serum chemistry profile yields normal results, and the urinalysis shows a specific gravity of 1.030, pH of 6.5, and the presence of a large amount of blood but no protein. Microscopic examination shows numerous eumorphic red blood cells and calcium oxalate crystals. Spiral computed tomography (CT) scan without contrast shows two very dense stones in the pelvis of the right kidney and one stone in the left kidney. There is moderate hydronephrosis on the left, and a 3-mm stone seen in the left ureter is recovered 24 hours later by straining the urine.

Stone analysis shows elements of calcium oxalate, calcium phosphate, and uric acid. Three weeks later, a 24-hour urine collection demonstrates elevated supersaturation for calcium oxalate, low urine volume of 0.84 L, elevated calcium and sodium excretion, and low citrate excretion. Analysis of the boy's diet shows low calcium and high sodium intake. He is placed on a no-added sodium diet and 1 L daily of dairy products. An additional liter of fluid per day is recommended, with one third given at bedtime.

Definitions

Urolithiasis refers to renal stones at any location within the urinary tract; nephrolithiasis denotes stones formed exclusively in the kidney. Nephrocalcinosis is the term describing deposition of calcium salts in the renal parenchyma, including the tubular lumen, tubular epithelium, and interstitium. These deposits usually are either calcium oxalate or calcium phosphate and may be associated with discrete renal calculi. The combination of nephrocalcinosis and nephrolithiasis does not occur in the typical patient who has primary renal stone disease; rather, it suggests that an underlying metabolic disorder, such as primary hyperoxaluria or renal tubular acidosis, is contributing to the formation of stones. (1)

Recognition of Renal Stone Disease in Children

Urolithiasis is an uncommon disease in children, but recent studies have demonstrated an increasing incidence in the pediatric population. One recent article found a fivefold increase in the incidence of pediatric urolithiasis cases over the past decade. The diagnosis of urolithiasis in children accounts for about 1 in 1,000 to 1 in 7,600 hospital discharges in children, a rate that is about 2% to 4% that of adults. (2) The reason for the lower

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incidence in children is unknown, but one possible cause may be higher concentrations of inhibitors of stone formation such as citrate, magnesium, and inhibitory macromolecules in their urine. The reported incidence likely underestimates the true frequency of renal stone disease in children because most children who develop these stones never require hospitalization for their disease. Similar to adults, males are affected more commonly than females, and there is a strong racial propensity in white compared with African American individuals. In the United States, renal stones are located mostly in the renal pelvis or ureters, in contrast to children in certain parts of the world, who often present with endemic bladder stones.

Clinical Presentation

Renal stone disease in infants and children has varied presentations. Symptoms of urolithiasis in younger children usually do not include the classic severe flank pain that radiates to the groin, as in adults. Whereas adolescents present similarly to adult patients, 40% to 75% of younger children who have urolithiasis present with nonspecific pain localized to the abdomen, flank, or pelvis. The younger the child, the less likely he or she will present with pain, which may relate to the lower frequency of stones lodged in the ureters of younger children. Ureteral stones are much more likely to cause obstruction that leads to pain. Infants may present with pain that mimics colic but also can present with urinary tract infections. About 10% of stones, usually those in the lower urinary tract, can present with dysuria and frequency, and urethral stones have been known to cause frank urinary obstruction. Finally, renal stones may be present for years and cause no symptoms.

Urinary findings vary from sterile pyuria to gross or microscopic hematuria in 30% to 90% of children. Gross hematuria has been noted as the presenting symptom in 30% to 55% of children who have stones and may or may not be associated with pain. A common question is the significance of crystals in the urine (crystalluria). Common uric acid, calcium phosphate, and calcium oxalate crystals do not distinguish stone formers readily from nonstone formers, although certain unusual crystals can be significant. In particular, hexagonal cystine crystals and the coffin lid-shaped triple phosphate crystals, especially in highly alkaline urine, are suspicious for cystinuria and struvite stones, respectively. Generally, crystalluria has no significance, but urinary crystals combined with other historical, physical, and laboratory findings can be helpful.

Urolithiasis can present with spontaneous passage of one or more stones in the urine. Depending on their composition, stones can be of different colors. For example, calcium stones often are black, white, or gray; uric acid stones can be reddish-orange; and cystine stones typically appear greenish-yellow. When available, any recovered stones should be sent for analysis to an appropriate laboratory. Renal stones also can be discovered incidentally by imaging procedures such as plain radiography, renal ultrasonography, or CT scan. The ability to see stones by most conventional radiographic procedures depends on stone density, which is determined by its mineral content. Calcium oxalate and calcium phosphate stones are the densest and, thus, are easily detected by imaging studies. Struvite and cystine stones, which contain less mineral, can be more difficult to see, and pure uric acid stones are radiolucent. Ultrasonography can easily miss small stones and ureteral stones.

Another finding that may point to a renal stone-forming diathesis is the presence of hypercalciuria. It has been almost 3 decades since the report of an association between painless, microscopic hematuria and increased excretion of calcium in the urine of children. Since this observation, others have reported that dysuria and urinary frequency also can be associated with hypercalciuria. Approximately 13% to 17% of children who present with hematuria and hypercalciuria subsequently form stones over a 5-year period.

Pathogenesis

A comprehensive discussion of renal stone pathogenesis is beyond the scope of this article, but baseline knowledge is needed to understand the evaluation and medical treatment of affected children. The formation of calcium oxalate kidney stones is determined largely by the product of ionized calcium and oxalate (activity product) in the urine. The concentrations of other compounds in the urine, such as phosphate, citrate, magnesium, and hydrogen (pH), can affect whether calcium oxalate crystals grow, shrink, or form spontaneously. Some substances, such as citrate, magnesium, and certain macromolecules, act as natural inhibitors of crystal formation. As a result, the activity product in the urine at which calcium oxalate crystals no longer shrink is higher than in water. Thus, a relative supersaturation is required for formation or maintenance of calcium oxalate crystals. The complex interaction among all of these factors means that simple concentration measurements do not provide adequate insight into the formation of crystals in the urine; laboratory studies and computer models are needed to evaluate stone risk.

The presence of other substances in the urine can

enhance crystal formation. For example, uric acid lowers the activity product of calcium oxalate needed for spontaneous formation of calcium oxalate crystals. Thus, increased excretion of uric acid in the urine is associated with calcium oxalate stone disease. Also, whereas both stone formers and nonstone formers pass crystals in the urine, recurrent stone formers have a propensity for passing more and larger crystal aggregates. This effect is not sufficient to explain kidney stone formation in patients, however, because even these aggregates are passed into the urine. In actuality, crystals in the urine usually form on the surface of a nidus, which is a fixed particle that allows the formation, growth, and retention of a stone particle at a much lower activity product than otherwise would be needed. The propensity of stone formers to retain stone particles is one more mechanism that appears to separate stone formers from nonstone formers.

What do these facts mean clinically? Urine concentrations of stone-forming substances (hence, relevant activity products in the urine) are influenced by the amounts excreted. These concentrations can be elevated in conditions such as hypercalciuria, hyperoxaluria, and hyperuricosuria. It also is clear that the urine volume plays a direct role in the concentrations and activity products of these substances. Low urine volume is one of the most common risk factors for stone disease, which is why increased fluid intake is the cornerstone of urolithiasis therapy. Urine pH has a powerful effect on the solubility of calcium phosphate as well as on uric acid, which is much less soluble than its urate salt. Citrate has the ability to inhibit crystal growth and aggregation of calcium oxalate. Low urinary citrate excretion, termed hypocitraturia, is an important cause of renal stone disease. In a recent study in children, hypocitraturia was the most common metabolic abnormality detected. Increased uric acid excretion is not significantly associated with uric acid stones (as is low urine pH), as would be expected, but it may enhance calcium oxalate stone formation.

Calcium phosphate crystals can increase the risk for calcium oxalate stone formation. Calcium phosphate also makes up so-called Randall plaques, which may be critical sites of calcium oxalate stone formation. First described by Randall in 1940, these plaquelike deposits on the renal papillae are a focus of intense research in adults, although their role in pediatric stone disease has not yet been investigated. The deposits appear to form as calcium phosphate (apatite) crystals in the basement membranes of the thin loops of Henle fuse into plaques in the interstitium and finally extrude through the urothelium of the renal papillae. Here, they can form a nidus for calcium oxalate crystal formation as well as provide a "fixed particle" for stone formation.

Causes

Renal stones usually are composed of calcium oxalate, calcium phosphate, uric acid, cystine, or struvite, either separately or in combination (Table 1). The major metabolic abnormalities that can lead to these stones include hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, and cystinuria, with different underlying conditions causing the abnormal excretion of each (Table 2). The most common renal stones are "calcium stones." These can be caused by high calcium, oxalate, and uric acid excretion; low citrate excretion; low urine volume; and high urine pH (calcium phosphate stones), alone and in combination.

Hypercalciuria

Hypercalciuria is the most common abnormality found in stone formers and is seen in 30% to 50% of children who form stones. It may occur as an isolated abnormality or with other stone-forming factors. The classic example is the child who has distal renal tubular acidosis (RTA), which can cause urolithiasis from multiple effects on the urine. In RTA, hypercalciuria results from release of calcium from bone due to buffering of the acidosis. Hypocitraturia is caused by the effects of intracellular acidosis on citrate excretion. Finally, urine pH is elevated due to an inability to acidify the urine. Hypercalciuria is encountered commonly in the child who has nonglomerular hematuria; the risk for stone formation in such patients has been stated to be 4% to 17% over the next 1 to 11 years after diagnosis. The definition has varied, but generally, calcium excretion greater than 4 mg/kg per day in children older than 2 years of age is considered abnormal.

In many children, a 24-hour urine collection is not possible or practical. For them, a calcium/creatinine ratio greater than 0.2 mg/mg or 0.56 mmol/mmol in

Table 1. Frequency of Stone Types in Children

Calcium oxalate: 45% to 65%
Calcium phosphate: 14% to 30%
Struvite: 13%
Cystine: 5%
Uric acid: 4%
Mixed or miscellaneous: 4%

Table 2. **Metabolic Causes of Abnormal Urinary Excretion States**

Condition	Metabolic Causes
Hypercalciuria	• Idiopathic, inherited and sporadic • Hypercalcemia: vitamin D excess, hyperparathyroidism • Metabolic acidosis • Loop diuretics • Immobilization • Tubular disorders: distal renal tubular acidosis, Dent disease • Excess sodium, extracellular volume overload • Medullary sponge kidney • Ketogenic diet
Hyperoxaluria	• Mild, idiopathic • Enteric hyperoxaluria • Primary hyperoxaluria types I and II
Hypocitraturia	• Mild, idiopathic • Metabolic acidosis • Distal tubular acidosis, complete and incomplete • Hypokalemia • Ketogenic diet
Hyperuricosuria	• Mild, idiopathic, familial and nonfamilial • High-protein diet • Metabolic syndrome • Ketogenic diet • Tumor lysis syndrome, malignant proliferative disorders • Lesch-Nyhan syndrome
Cystinuria	• Cystinuria: types I, II, III

school-age children is considered abnormal, although higher values are reported in younger children (Table 3). If the urine calcium/creatinine ratio is less than 0.2 mg/mg in a random sample 2 to 4 hours after a calcium-containing meal, a timed collection is not needed to rule out hypercalciuria. We always recommend calculating a calcium/creatinine ratio on any timed collection; if the 24-hour calcium excretion (mg/kg per day) is significantly different from 20 times the calcium/creatinine ratio (mg/mg), a problem such as an under- or overcollection of urine should be suspected.

Hypercalciuria has many different causes, some of which are associated with hypercalcemia and are not discussed here. Of the normocalcemic causes of hypercalciuria, the most common is idiopathic hypercalciuria. The heritability of this condition has been estimated to be 52%, based on studies of twins, and appears to be autosomal dominant or codominant. Adult patients often have been categorized according to the mechanism of their hypercalciuria, such as increased intestinal absorption, increased renal leak, or increased bone resorption. Children, however, have not been able to be classified reliably into subtypes. Whereas sodium intake plays an important role in determining calcium excretion, calcium intake itself does not alter urinary calcium concentrations significantly in most patients. Therefore, low-calcium diets are not recommended. A number of primary renal tubular disorders are associated with hypercalciuria (Table 2). Distal RTA is the most important, including so-called incomplete distal RTA, in which the basal serum bicarbonate concentration may be normal, but there is an inability to lower the urine pH after an acid load. Dent disease is a condition in which the defect is an abnormal chloride channel, CLCN5. The condition is characterized by hypercalciuria, hypophosphatemic rickets, low-molecular weight proteinuria, nephrocalcinosis, and progressive renal insufficiency.

Hyperoxaluria

Oxalate, the other component of calcium oxalate stones, also can be excreted in abundance. There are two primary mechanisms: increased biosynthesis, such as in primary hyperoxaluria (PH), and hyperoxaluria that results from increased gastrointestinal absorption, which can be from increased net absorption or increased oxalate or its precursors in the diet. PH is a rare autosomal recessive disorder of glyoxylate metabolism that shunts glyoxylate to oxalate. Oxalate is the end product of the pathway and, in this disorder, can be excreted in amounts in excess of 100 mg/day, leading to early and severe calcium oxalate stone formation, nephrocalcinosis, and renal failure. After renal failure develops, systemic accumulation of oxalate ensues, resulting in oxalosis.

Two types of PH are described: type 1 is more common, more severe, and the result of abnormal alanine-glyoxylate aminotransferase in liver peroxisomes. In some cases of type I PH, pyridoxine (vitamin B6) is therapeutic in reducing oxalate formation; in most cases, however, the only effective therapy is a combined liver-kidney transplant. Type II PH, which is due to deficient glyoxylate reductase/hydroxypyruvate reductase, is less likely to lead to renal failure. A small number of patients who have primary hyperoxaluria have neither of these enzyme defects.

A more common cause of hyperoxaluria, enteric hyperoxaluria, is due to increased intestinal absorption of oxalate and can result in urinary oxalate excretion in excess of 50 mg/1.73 m^2 per day. Enteric hyperoxaluria

Table 3. **Normal Values for Urinary Excretion of Metabolites**

Metabolite	Age	Random (mmol/mmol)	Random (mg/mg)	Timed (all ages unless specified)
Calcium	0 to 6 months	<2.24	<0.8	<4 mg/kg per 24 hours
	7 to 12 months	<1.68	<0.6	
	>2 years	<0.56	<0.2	
Oxalate	0 to 6 months	<0.325	<0.26	<0.5 mmol/1.73 m^2 per 24 hours or
	7 to 24 months	<0.132	<0.11	<45 mg/1.73 m^2 per 24 hours
	2 to 5 years	<0.098	<0.08	
	5 to 14 years	<0.07	<0.06	
	>16 years	<0.40	<0.32	
Citrate	0 to 5 years	>0.12 to 0.25	>0.2 to 0.42	>0.8 mmol/1.73 m^2 per 24 hours or
	>5 years	>0.08 to 0.15	>0.14 to 0.25	>0.14 g/1.73 m^2 per 24 hours
Cystine	>6 months	<0.018	<0.075	<60 mg/1.73 m^2 per 24 hours
Uric acid	>3 years	<0.03 mmol/dL glomerular filtration rate	<0.56 mg/dL glomerular filtration rate	<815 mg/1.73 m^2 per 24 hours

has been associated with chronic diarrheal disorders associated with fat malabsorption, such as inflammatory bowel disease, celiac disease, and cystic fibrosis. The pathogenesis may be the presence of free fatty acids that bind calcium in the intestinal lumen, resulting in more oxalate being free to be absorbed. Also, there is evidence that free fatty acids and bile acids increase the permeability of the gastrointestinal tract to oxalate. Other comorbidities for stone formation in these disorders include dehydration, low urine volume, and acidosis, resulting in decreased citrate excretion. An interesting debate is over the role of diet and oxalate excretion. Traditionally, only about 10% to 20% of the urinary oxalate is believed to be from dietary sources, and the role of high-oxalate foods has been controversial. An important observation is that adults who have low calcium intake have a greater risk of stone disease, a nonintuitive result that is hypothesized to be due to enhanced oxalate absorption in the presence of restricted calcium diets.

Hypocitraturia

Citrate has been found to be a natural inhibitor of calcium oxalate and calcium phosphate nucleation, crystal growth, and aggregation. Hypocitraturia can be the result of distal RTA and other systemic metabolic acidoses. In general, renal stone formers excrete less citrate in their urine; additional factors such as low potassium and high protein in the diet also can reduce citrate excretion.

Hyperuricosuria, Uric Acid Stones, and Low Urine pH

The relationship among uric acid excretion, uric acid stones, and other renal stones is interesting. Uric acid has a pKa of 5.35 at 37.0°C, and sodium urate is 20 times more soluble than uric acid. Therefore, urine pH is the most important factor in determining the solubility of uric acid, with uric acid stones often being formed at physiologic excretion rates. Urine volume and hyperuricosuria are less important. Uric acid stones classically are associated with excessive purine loads, which can be related to high-protein diets. These diets also are associated with low urinary pH. New research has focused on the role of obesity and insulin resistance, as seen with metabolic syndrome, in the formation of uric acid stones. This association has not been explored adequately in pediatric patients but may become important as clinicians deal with the epidemic of pediatric obesity. Hyperuricosuria, defined as uric acid excretion greater than 815 mg/1.73 m^2 per day, has been associated as much with calcium oxalate stone formation due to the effects of urate on lowering the formation product of calcium oxalate crystal formation as it has been with uric acid stones.

Cystinuria

Cystinuria is a rare autosomal recessive defect in renal and intestinal transport of cystine and the dibasic amino acids (ornithine, arginine, and lysine), which is the source of 2% to 7% of pediatric stone disease. Despite similarities in name, cystinuria must be distinguished from cystinosis, a lysosomal disorder leading to Fanconi syndrome and renal failure in children. Because the solubility of cystine is much lower (240 mg/L at pH 7) than the other amino acids affected, only cystine stones form. Two genetic defects have been identified: *SLC3A1*, which encodes for rBAT and is associated with type 1 cystinuria, and *SLC7A9*, which encodes for bo+AT and accounts for most patients who have types II and III cystinuria. Cys-

tine stones can be characterized by their ability to form very large calculi that can fill the collecting system (staghorn calculi) by late childhood or early adolescence. Cystinuria can be screened for by the cyanide-nitroprusside test, and quantitative tests are available to help guide therapy.

Struvite Stones

Struvite stones refer to an unusual type of stone that develops following the change in urinary composition caused by urease-producing bacteria that catalyze the following reaction:

$$\text{Urea} \Rightarrow NH_3 + H_2O \Rightarrow NH_4^+ + OH^-$$

The result is a very alkaline urine that has high concentrations of ammonium. In response to the high urine pH, carbonate and trivalent phosphate ions are formed that combine to form struvite: $MgNH_4PO_4 \cdot 6H_2O$. *Proteus* is the most common urease-forming bacterial species, but *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Citrobacter*, and *Morganella* also can produce urease. Struvite stones can grow quickly and form large staghorn calculi, with the bacteria becoming trapped in the stone. Children who have neurogenic bladders, urinary diversions, and recurrent urinary tract infections are at greatest risk for developing struvite stones. Management is very difficult, and these stones are associated with significant morbidity and mortality.

Evaluation

The purposes of the evaluation of the child suspected of having renal stone disease are to confirm the diagnosis, establish the underlying cause, and direct therapy. Even with a common calcium oxalate stone, many different metabolic causes and risk factors may be present in a single patient. Successful identification of these factors likely can determine the ability to prevent future stone formation. The evaluation of a child who has proven or suspected stone disease is a several-step process (Table 4).

History

The initial evaluation should start with a complete history focused on clinical symptoms such as pain; dysuria; frequency; and passage of blood, stones, or gravel as well any other sign of stone disease. The history also should inquire about any renal disease or anatomic malformations, metabolic disease, gastrointestinal disease, or medications. A dietary history is important and can be augmented by a 3-day food record focused on the intake of calcium and dairy products, sodium, oxalate, and protein. A family history, which may be positive in 20% to 50% of children who have stones, is important. Because most adults who have renal stone disease do not undergo a comprehensive evaluation, it is unusual to obtain a clear picture of the underlying stone disease from the family history. A physical examination also is indicated to look for signs of renal or other metabolic diseases such as spina bifida, RTA, Dent disease, or Lesch-Nyhan syndrome.

Table 4. Clinical Evaluation of the Child Suspected of Having Urolithiasis

Initial Visit	• History: gross hematuria, pain, passage of stones, malabsorption, medications, recurrent urinary tract infections, diet, family history • Physical examination: growth, evidence of spina bifida, metabolic disease • Laboratory tests: serum electrolytes, blood urea nitrogen, creatinine, uric acid, calcium, phosphorus, urinalysis with microscopic examination, spot urine calcium and creatinine
Studies Ordered after Initial Visit	• Two 24-hour urine collections on regular diet for comprehensive analysis of stone risk that include calcium, oxalate, citrate, uric acid, creatinine, sodium, phosphate, pH, volume, qualitative test for cystine excretion • Three-day food record for dietary analysis on regular diet • Renal ultrasonography (noncontrast spiral computed tomography scan in symptomatic patients) • Stone analysis by infrared spectroscopy or x-ray diffusion on any stone captured • Parathyroid hormone if hypercalcemia is present on initial evaluation
Second Visit	• Review 24-hour urine results and dietary analysis, make dietary recommendations • Order additional investigations based on initial studies
Follow-up Visit at 6 Months	• Review clinical course for signs of active renal stone disease • Repeat 24-hour urine collection for stone risk analysis and renal ultrasonography; evaluate effectiveness of conservative management • Consider medication for active or recurrent renal stone disease

Laboratory Studies

The initial laboratory examination should include screening procedures such as a urinalysis and urine culture and basic blood chemistry studies. The urinalysis can be helpful in providing evidence of low urine output by noting high specific gravity, urine pH (<6 for uric acid stones, >7 for calcium phosphate stones, and >8 for struvite stones), nonglomerular hematuria, or urinary tract infection. As mentioned, the presence of urinary crystals is interesting, but only cystine and certain crystals caused by medications such as indinavir are diagnostic. Triple phosphate crystals are significant in the presence of a urine pH greater than 8 and signs of a urinary tract infection. Electrolyte analysis can identify RTA, blood urea nitrogen and creatinine concentrations evaluate overall renal function, and calcium and phosphorus abnormalities identify disorders of divalent ion metabolism such as hypercalcemia or hypophosphatemia in Dent disease. Uric acid measurement may identify rare disorders of uric acid metabolism. Measurements of parathyroid hormone rarely are indicated in the presence of normal calcium and phosphorus concentrations. A spot urine test for calcium and creatinine concentrations can serve as an initial screen for hypercalciuria.

Unlike recommendations for adults, all children who have urolithiasis should undergo a full metabolic evaluation. Any stones passed or retrieved at surgery should be sent for analysis, preferably by infrared spectroscopy or radiograph diffraction and not by chemical stone analysis. The use of a urine strainer is useful in helping the child having a stone episode to catch small stones. Usually, the composition is identified as mixed or predominantly calcium oxalate, which may not point to a single metabolic cause but still is helpful. Cystine and struvite stones point to a particular pathogenesis, and predominant calcium phosphate stones suggest the possibility of RTA.

To characterize the cause of urolithiasis further, two consecutive 24-hour urine samples should be sent for comprehensive analysis. Two commercial companies that offer this service are Litholink Corporation (http://www.litholink.com) and Mission Pharmacal (http://missionpharmacal.com). It is important to evaluate the data with respect to weight, body surface area, or creatinine excretion to provide meaningful numbers for pediatric patients and to compare the results to published pediatric normative data (Table 3). The 24-hour urine collections should be performed when the patient is eating a regular diet to obtain a true assessment of the risks for stone formation. A repeat 24-hour urine collection should be performed 6 to 12 months after dietary modifications are initiated and after medications are started to evaluate for compliance and effectiveness of the treatment plan. In addition to the stone-forming substances such as calcium, oxalate, phosphate, and uric acid, the amount of the inhibitors citrate and magnesium also should be measured. An initial evaluation for cystine excretion with the cyanide-nitroprusside test should be performed if cystinuria is a possibility.

The 24-hour urine volume and the urine pH are important. Urine creatinine excretion is useful for comparing with other metabolites and should equal 15 to 25 mg/kg per day in a complete 24-hour collection. Creatinine excretion that differs significantly from this value can indicate either over- or undercollection. Finally, the calculation of the degree of supersaturation of calcium oxalate, calcium phosphate, and uric acid should be performed using an appropriate computer program.

Imaging

Imaging of the urinary system in patients who have renal stone disease is important for initial diagnosis, evaluation of acute stone episodes, and monitoring of therapy. As already discussed, renal stone disease often is diagnosed with the discovery of one or more stones in a patient presenting with pain, hematuria, or other signs and symptoms of urolithiasis. The most common modality is renal ultrasonography, and it is recommended that all new patients have an imaging study to look for stone burden and any evidence of renal malformations or obstruction. A stone detected by ultrasonography usually is hyperechoic, and there should be evidence of "shadowing" behind it. Ultrasonography has the advantage of using no ionizing radiation and can detect large renal stones and urinary tract obstruction readily. Small renal stones and most ureteral stones are poorly visible on renal ultrasonography. For the patient who presents with acute pain or gross hematuria, the standard of care is CT scan without radiographic contrast media using a spiral technique. This study can detect most stones of significant size in the kidney and lower urinary tract and can provide information about the stone's composition by its density in Hounsfield units. CT scan has the disadvantage of delivering a significant radiation dose. Certain low-density stones such as uric acid, indavir, or matrix stones are difficult to see by any modality.

Management

Diet and Fluid Intake

There is clear evidence for the role of diet as a risk factor for urolithiasis, which makes it a clear target for therapy. (3) The greatest risk factors for calcium kidney stone

formation are low fluid and high sodium intake. The choice of fluid is not as important because coffee, tea, beer, wine, and soda are not associated with increased risk, but the overall daily volume of fluid intake is crucial. The recommendations for calcium and dairy products have changed from avoidance of these items to encouraging their consumption at the Recommended Dietary Allowance (RDA) for the population after three adult studies showed increased risk of stones with low calcium intake. The hypothesis is that reduced calcium in the diet allows more absorption of oxalate, an outcome that may have even greater effects on calcium oxalate stone formation than intake of calcium alone.

The role of dietary oxalate in stone formation is controversial because only 10% to 20% of urinary oxalate is derived from the diet. Thus, limiting intake to a modest amount of high-oxalate foods such as leafy vegetables, nuts, chocolate, star fruit, and dark tea seems prudent. Excessive animal protein intake can result in increased calcium and uric acid excretion and lower citrate excretion and should be avoided. All children being evaluated for renal stone disease benefit from a comprehensive dietary analysis with evaluation for risk factors.

Medical Treatment (Table 5)

For the patient who has calcium stones and hypercalciuria, treatment can be nonspecific or guided by the results of the diet assessment and 24-hour urine collection. The first recommendation is to increase fluid intake, which increases the urine output. The recommended daily urine outputs based on age are: infants, 750 mL or more; small children younger than age 5 years, 1,000 mL or more; children between ages 5 and 10 years, 1,500 mL or more; and children older than age 10 years, 2,000 mL or more. The recommended daily intake must be about 50% greater than the targeted output to account for other losses. Specific advice should be given to the patient and family regarding suggested servings, including 8 to 20 oz at bedtime to avoid low urine volumes overnight. Increased urine output alone can decrease the risk of stones in adults by up to 50%, the so-called stone-clinic effect.

The second recommendation for most children who have hypercalciuria is to reduce sodium intake to a "no added salt" diet. Other recommendations include adequate potassium intake and no more than a moderate amount of animal protein consumption. For the patient who has hyperoxaluria but who does not have a primary cause, such as enteric hyperoxaluria, the first step is to ensure adequate calcium intake to the RDA level. High-fat diets also should be avoided because they may bind enteric calcium and promote oxalate absorption. Moderate restriction of high-oxalate foods generally is recommended. Finally, avoidance of excess vitamin C, which is metabolized to oxalate in the body, is suggested.

For children in whom dietary therapy is ineffective in controlling stone formation, pharmacologic therapy is warranted, which is guided best by the results of the analysis of a 24-hour urine collection. A thiazide diuretic often is needed for the child who has hypercalciuria and

Table 5. Medical Management of Pediatric Urolithiasis

Condition	Dietary	Pharmacologic
Hypercalciuria	• High fluid intake • Restricted sodium • RDA for calcium • Moderate animal protein	• Hydrochlorothiazide (1 to 2 mg/kg per day) • Amiloride (0.625 mg/kg per day for children <20 kg or 5 to 10 mg/d for children >20 kg) • See below
Hypocitraturia	• High fluid intake	• Potassium citrate (2 to 3 mEq/kg per ÷ BID or 30 to 80 mEq/d in older children)
Hyperoxaluria	• Very high fluid intake (PH) • Moderate oxalate restriction • Low-fat diet (EH) • RDA for calcium	• Potassium citrate (2 to 3 mEq/kg per day ÷ BID or 30 to 80 mEq/d in older children) • Pyridoxine (5 to 10 mg/kg per day) for PH
Hyperuricosuria	• High fluid intake • Moderate animal protein	• Potassium citrate (2 to 3 mEq/kg per day ÷ BID or 30 to 80 mEq/d in older children) • Allopurinol (200 to 300 mg/m^2 per day ÷ BID)
Cystinuria	Very high fluid intake	• Potassium citrate (2 to 3 mEq/kg per day ÷ BID or 30 to 80 mEq/d in older children) • Tiopronin (starting dose of 100 mg BID)

BID=twice a day, EH=enteric hyperoxaluria, PH=primary hyperoxaluria, RDA=Recommended Dietary Allowance
Recommended intake (RDA) of calcium by age: 1 to 2 years: 500 mg, 3 to 8 years: 800 mg, 9 to 18 years: 1,300 mg

does not respond to a restricted sodium diet. The usual recommendation is hydrochlorothiazide 1 to 2 mg/kg per day. To avoid hypokalemia, add amiloride, which is potassium-sparing and has an added hypocalciuric effect. For the child who has low citrate excretion, potassium citrate at a dose of 2 to 3 mEq/kg per day for infants or younger children or 30 to 80 mEq/day for older children and adolescents can be added in two divided doses, with the second dose at bedtime. This regimen can be useful in preventing hypokalemia in the child who also is receiving a thiazide diuretic. Potassium citrate also is indicated to alkalinize the urine in children who have RTA and calcium phosphate stones as well as for the more unusual patient who has low urine pH and uric acid stones.

For the less common forms of urolithiasis, special treatment is required. In PH type 1, a very high urine output of more than 3 L/1.73 m^2 should be established and pyridoxine (vitamin B6) at a starting dose of 5 mg/kg per day should be tried in case the patient is pyridoxine-sensitive (30% to 50% of cases). Other therapeutic measures include potassium citrate, magnesium, and neutral phosphate. Unfortunately, the only definitive therapy is liver and kidney transplantation. The initial therapy for cystinuria also is a high fluid intake to try to decrease the concentration of cystine to a soluble level. Raising the urine pH to 7 with potassium citrate is recommended, but higher pH levels, which increase the risk of calcium phosphate stones, or sodium-containing agents that can increase cystine excretion should be avoided. In cystinuria, the sulfhydryl agent alpha-mercaptopropionylglycine (tiopronin) can be effective by binding cystine in the urine and forming more soluble dimers, but it often is not tolerated. The safety and effectiveness of tiopronin in children younger than age 9 years have not been established.

Infection-related (struvite) stones pose a serious therapeutic challenge due to their typically large size (staghorn calculi) and propensity to recur if removal is less than complete. The current recommendation is to combine surgical and medical therapy. Medical therapy centers on appropriate antibiotic therapy. Acidification of the urine mostly has been ineffective, and the novel use of urease inhibitors has been largely abandoned due to adverse effects.

Surgical Treatment

It is rare today that the classic open lithotomy is required for children who have renal stones. Most stones smaller than 5 mm pass spontaneously in children and do not require any surgical intervention. However, stones that are larger than 5 mm may require percutaneous nephrolithotomy (use of endoscopy to enter the kidney), extracorporal shockwave lithotripsy, or retrograde endoscopic lithotripsy by using a holmium:yttrium aluminum perovskite laser to disrupt the stones. With new instruments and new techniques, stones in children now can be removed much more precisely and safely.

Summary

- Although renal stones are much less common in children than in adults, the incidence is rising in the pediatric population.
- Findings associated with renal stones include gross and microscopic hematuria, sterile pyuria, and pain. Adolescents present with pain patterns similar to those of adults, but the younger the child, the less likely pain will be present, and the pain can be nonspecific. Renal stones can cause no symptoms for years.
- Renal stones are most likely to be composed of calcium oxalate, calcium phosphate, uric acid, cystine, or struvite, either separately or in combination. The major metabolic abnormalities that can lead to these stones include hypercalciuria (most commonly idiopathic), hyperoxaluria, hypocitraturia, hyperuricosuria, and cystinuria. Factors that influence stone formation are urine volume, urine pH, and the concentration in the urine of substances that encourage (calcium, uric acid) or prevent (citrate, magnesium) the formation of stones.
- Diagnosis is accomplished through history, including dietary history, and physical examination, as well as by urinalysis, basic blood chemistries, urine calcium/creatine ratio, and metabolic evaluation. Analysis of the stones themselves can add important information, as can comprehensive analysis of 24-hour urine collections. Ultrasonography is a valuable imaging tool, as is serial CT scan.
- Therapy of renal stone disease begins with increasing the urinary volume through increased intake of fluids. Reduction of dietary sodium is helpful in children who have hypercalciuria. A thiazide diuretic can be helpful, and specific agents may be useful in treating renal stones in specific circumstances.
- Although many stones pass spontaneously, endoscopic surgical removal or lithotripsy involving shockwaves or lasers might be necessary.

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PIR Quiz

Quiz also available online at http://pedsinreview.aappublications.org.

1. Among the following, which type of renal stone is *least* likely to be visible on imaging studies?

   A. Calcium oxalate.
   B. Calcium phosphate.
   C. Cystine.
   D. Struvite.
   E. Uric acid.

2. Hypercalciuria is the most common abnormality found in people who tend to form renal stones. Each of the following plays a role in calcium excretion in the urine *except*:

   A. Calcium intake.
   B. Serum calcium concentration.
   C. Sodium intake.
   D. Thiazide diuretics.
   E. Urine pH.

3. In the evaluation of a 7-year-old girl who has probable urolithiasis and presents with abdominal pain, the imaging study of first choice to identify whether this pain is due to an acute renal stone episode is:

   A. Computed tomography scan without contrast.
   B. Magnetic resonance imaging.
   C. Plain radiography.
   D. Ultrasonography.
   E. Voiding cystourethrography.

4. Among the following, the *most* important dietary treatment in the management of renal stone disease is to:

   A. Avoid caffeinated beverages.
   B. Avoid dairy products.
   C. Increase animal protein intake.
   D. Increase fluid intake.
   E. Increase leafy vegetable intake.

5. The upper size limit at which renal stones usually pass spontaneously in children is:

   A. 3 mm.
   B. 4 mm.
   C. 5 mm.
   D. 6 mm.
   E. 7 mm.

Renal Stone Disease

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