Renal Stone Disease in Children

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Summary: Renal stone disease has been regarded as an uncommon problem in children compared to adults. However, increased awareness of this problem in children may lead to early intervention preventing long-term consequences on the kidney and the urinary tract. This article reviews the epidemiology, pathogenesis, and the most common etiologies of renal stones in children. The clinical features and diagnostic and therapeutic modalities for the specific etiologies are also outlined. Using these guidelines may be helpful not only in the treatment but also in the prevention of renal stones. *Clin Pediatr.* 1998;37:583-600

Introduction

Renal stone disease (nephrolithiasis, urolithiasis) has generally been regarded as a problem mainly of adults, where it has been estimated that 3–12% will have a stone in their lifetime.[1,2] However, through the years, there has been heightened awareness of this problem in children, especially in certain geographic areas where the prevalence rate is high.[3,4] This is particularly important since knowledge of risk factors and early diagnosis may lead to early intervention preventing stone formation and/or recurrence.

Epidemiology

The incidence of urolithiasis varies according to geographic areas. Several epidemiologic studies have been done in adults and children that show these variations.[3,5-15] Among developed countries such as those in North America and Europe, the reported incidence rate of urolithiasis in children ranges from 0.13 to 0.94 case per 1,000 hospital admissions.[16] In the United States, the incidence varies anywhere between 1 per 1,000 to 1 per 7,600 hospital admissions, depending on the region.[3-4,17] In children, the risk is greatest in southern California[18] and in the southeastern states,[18] which is actually also considered the "stone belt" in the United States in adults.[19]

The etiology also varies according to geographic areas. Bladder stones have been noted to be endemic in developing countries such as those in Southeast Asia, which includes Thailand,[14] Indonesia,[7] and India.[15] The high prevalence of these stones is attributed to the predominantly cereal-based and low-protein diet. In contrast, in developed countries in Europe and North America, upper tract or kidney stones predominate.[5] It has been observed that as industrialization progresses in a geographic area, there tends to be a shift from lower tract to upper tract stones.[5] In the United Kingdom and in certain European countries, approximately 30–90% have infection stones,[18,20] whereas in the United States and Scandinavia, metabolic disorders are the most common cause of kidney stones.[19]

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In contrast to the marked male predominance of urolithiasis in adults, there is equal[8,13] to a slightly higher male preponderance in children.[3,10,17,21] In several series[3,4,8-10,17] of children with urolithiasis, 6–11% are blacks and 72–91% are whites. Recurrence rates reported range from 6.5% to 54% with mean interval to recurrence of 3–6 years.[8,10,17,22]

Mechanism of Stone Formation

Stone formation is a relatively complex process involving the interplay of three main factors, (1) the concentration of the precipitating substances and their urine solubilities, (2) promoters, and (3) inhibitors of crystallization and aggregation.[23]

The concentration of stone-forming ions in the urine is crucial in stone formation. When the concentrations of these ions are excessively high, there is a tendency for their activity product, the product of these free ion concentrations, to increase also. When this product exceeds its urine solubility, there exists a state of supersaturation, and this is the actual driving force for stone formation.[16] However, other conditions affect this process, which will determine whether this state of supersaturation would further progress into what is termed as a metastable state. For instance, urine pH influences the solubility of certain ions. Increasing the urine pH increases the solubility of uric acid, whereas a very high pH decreases calcium phosphate solubility. The pH also affects the availability of inhibitors of crystal formation, thereby influencing the state of saturation of certain stone-forming ions.[24]

Inhibitors of crystallization act by binding certain lithogenic ions, thereby decreasing their concentration in the urine. The complexes formed by this process are more soluble. Therefore, the free ion activity and the saturation for the specific crystal are reduced. Citrate and pyrophosphate are the most commonly known inhibitors and these act by binding to calcium. Magnesium and sodium bind oxalate. Nephrocalcinin inhibits calcium oxalate crystallization by adsorbing to crystal surfaces.[25] Other inhibitors include glycosaminoglycans, uropontin, and Tamm-Horsfall mucoprotein.[16]

Clinical Features

The most common clinical manifestation of urolithiasis is pain, occurring in 40–75% of children.[11,13,16,20,21] The pain varies from nonspecific to vague, dull or sharp abdominal or flank pain, which may be either localized or radiating. The classic renal colic experienced by most adults, described as intermittent, excruciating flank pain usually radiating to the groin, is quite uncommon in children.

Other clinical features include microscopic or gross hematuria, occurring in 30–90% of children.[11,13,16,18,20,21] Symptoms such as urgency, dysuria, frequency, and fever as well as pyuria with or without bacteriuria or documented urinary tract infection (UTI) are noted in approximately 20–50% of patients.[11,16,18] Milliner and Murphy noted that the younger the patient, the more likely that UTI symptoms as well as incidental findings on x-ray film lead to the diagnosis of renal stones, whereas in older children, pain is the most frequent initial symptom[13] (Figure 1). Obstructive symptoms such as urinary retention[9] or, rarely, anuria[26] may also occur, especially in bladder or urethral stones. Other symptoms reported include nausea and vomiting as well as failure to thrive,[4,11,16] which is especially evident in patients with concomitant metabolic disease or in renal tubular acidosis.[27]

Diagnosis

The evaluation of a patient with suspected urolithiasis should start with a complete history to elicit similar signs and symptoms such as those discussed above as well as significant risk factors for stone formation (Table 1). One should inquire about the child's food preferences and medications such as diuretics, corticosteroids, or vitamin D analogues as well as other vitamin supplements. For instance, a diet consisting of large amounts of chocolate, nuts, strawberries, or intake of greater than 0.5–4 g of vitamin C[16,28,29] may predispose a patient to calcium oxalate stones. Other unusual dietary patterns such as ketogenic diets in patients with intractable seizures have been shown to be associated with both urate and calcium stone formation.[30] Recent immobilization, previous urologic procedures, surgery or trauma, and other clinical disorders such as renal tubular acidosis or malignancy, especially with chemotherapy, are all pertinent risk factors for stone formation.[16] A history of recurrent or persistent urinary tract infections, especially if the cultures are positive for *Proteus* sp. or other urease-splitting bacteria, and recurrent or persistent unexplained hematuria are red flags that deserve further evaluation. Family history is positive for stone disease in 20–50% of children with urolithiasis.[3,10,20]

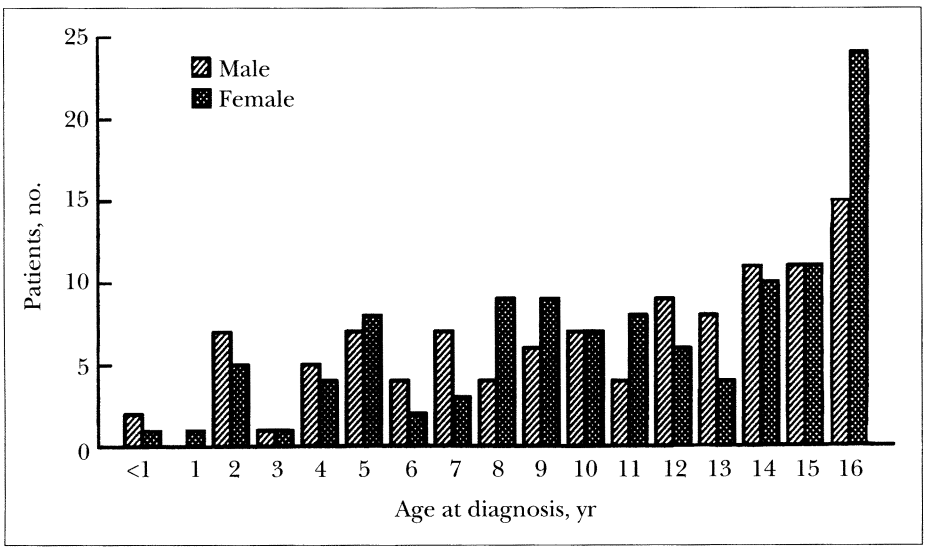

Figure 1. Age and sex distribution of 221 patients with urolithiasis who were examined at the Mayo Clinic between 1965 and 1987. (From Milliner DS, Murphy ME. Urolithiasis in pediatric patients. *Mayo Clin Proc.* 1993;68:242.)

The physical examination is essential in determining whether the patient has other signs of concomitant congenital abnormalities, anatomic abnormalities, systemic disorders, or chronic renal insufficiency. The blood pressure, height, and weight should be included. Findings consistent with stone disease such as abdominal or flank tenderness should be elicited.

Table 1

DIAGNOSIS	
History	
Physical examination	
Urine analysis:	(1) regular urinalysis including pH and microscopic examination (2) urine culture and sensitivity for suspected concomitant UTI (3) spot urine for solute-to-creatinine ratio and/or (4) timed urine collection for creatinine, calcium, phosphorus, magnesium, oxalate, uric acid, sodium, potassium, citrate, cystine, and total volume
Blood:	(1) CBC (2) BUN, creatinine, electrolytes, calcium, phosphorus, alkaline phosphatase, uric acid (3) immunoreactive parathyroid hormone level if serum and urine calcium are abnormally high
Radiographic studies:	(1) Plain abdominal film and/or ultrasound (2) Intravenous pyelogram (3) Voiding cystogram for suspected vesicoureteral reflux (4) CT scan or MRI if needed
Stone analysis	

BUN=blood urea nitrogen, CBC=complete blood count, CT=computed tomography, MRI=magnetic resonance imaging, UTI=urinary tract infection.

Urinalysis as an initial diagnostic tool provides valuable information. This should include the pH and a microscopic examination. Proteinuria may mean underlying renal pathology or renal insufficiency as a result of stone disease or the clinical disorder associated with it. The presence of pyuria and or bacteriuria may indicate an intercurrent infection that should be treated appropriately. The presence and appearance of crystals provide clues to the type of stone (Figure 2), although only the finding of cystine crystals is pathognomonic.[31]

The plain abdominal film and/or ultrasound are very useful in detecting renal stones. Diament and Malekzadeh[32] have shown that the ultrasound was more sensitive than the kidney, ureter, bladder radiograph in visualizing renal stones but that the latter was better with respect to ureteral stones. These noninvasive imaging studies have gained

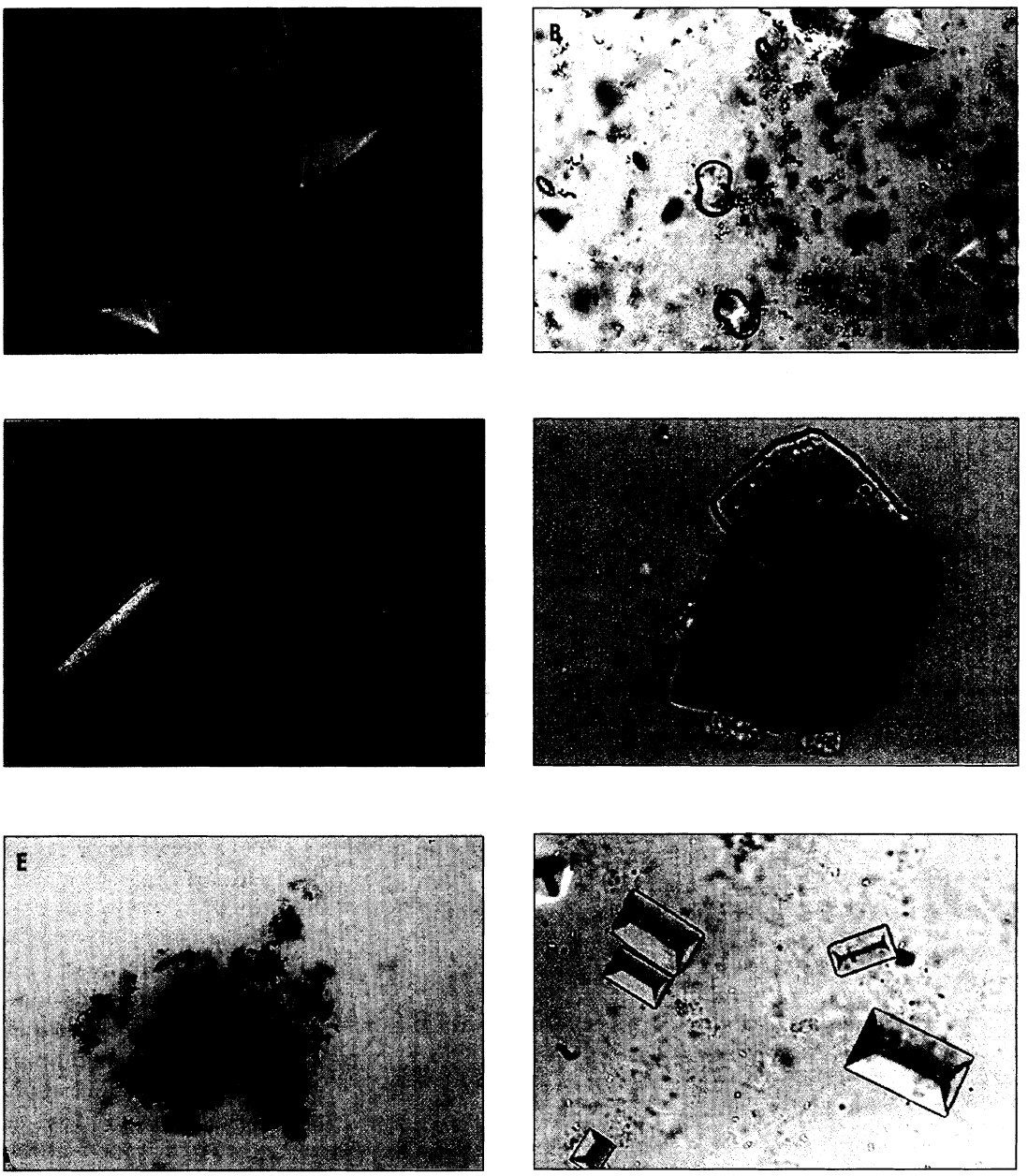

Figure 2. Urinary crystals commonly seen in nephrolithiasis. Calcium oxalate dihydrate crystals are shown in Panel A. Dumbbell-shaped calcium oxalate monohydrate crystals, which are the size of erythrocytes, are shown to the left of the pyramidal dihydrate crystals in Panel B. Elongate, lath-shaped brushite crystals can be seen in Panel C; rhomboidal uric acid crystals, in Panel D; uric acid microcystallites, in Panel E; coffin-lid-shaped struvite crystals, in Panel F; and cystine crystals, in Panel G. (From Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. *N Engl J Med.* 1992;327:1142.)

wide acceptance as initial tests although intravenous pyelography has been considered the gold standard.[16] Studies such as the voiding cystogram should be done in patients with concomitant urinary tract infection once the infection has cleared. Computed tomography (CT) scan or magnetic resonance imaging (MRI) may be done for further evaluation as needed. Radiographically, calcium stones are discrete opaque densities, whereas uric acid stones are radiolucent. Struvite stones are laminated and cystine stones are radiopaque, more rounded, and homogeneous.[16,33]

Recovery of the stone itself either by spontaneous passage or after surgical intervention is of utmost importance. Grossly, calcium stones appear as black, gray, or white; uric acid stones are usually reddish-orange but may also be white. Cystine stones appear flecked and are usually greenish yellow.[16,33] These stones can be sent to special laboratories for chemical analysis. Therefore, further evaluation can be directed based on the type of stone identified (Table 2).

Table 2

TYPE OF STONE	AND ETIOLOGY
Calcium	Idiopathic hypercalciuria
	Secondary hypercalciuria
	Chronic diuretics
	Sarcoidosis
	Primary hyperparathyroidism
	Distal renal tubular acidosis
	Immobilization
	Juvenile rheumatoid arthritis
	Malignancies
	Multiple myeloma
	Milk alkali syndrome
	Vitamin D excess
	Idiopathic hypercalcemia of infancy
	Hypocitraturia
	Hyperoxaluria
	Enteric hyperoxaluria
	Primary hyperoxaluria
Uric acid	Hyperuricosuria
	High purine diet
	Drugs (salicylates, probenecid, etc)
	Obesity
	Alcohol intake
	Inborn errors of metabolism
Cystine	Cystinuria
Struvite	Urinary tract infection with urease-splitting bacteria

Other studies include spot urine for solute-to-creatinine ratios appropriate for the specific etiology suspected (Table 3). These are obtained by sending a fresh urine specimen, preferably a morning sample, to determine the amount of the specific solute desired as well as the creatinine and dividing the former by the latter (usually expressed in mg/mg or mmol/mmol). These ratios are very useful not only for screening but also for follow-up since obtaining a timed urine specimen from small children is often difficult. However, timed urine collections (12–24 hours) for volume and specific solute (calcium, phosphorus, magnesium, uric acid, protein, sodium, creatinine, cystine, oxalate, citrate) excretion often need to be obtained to determine more accurate levels in order to confirm the defect as well as to assess other possible risk factors for other calculi (Table 2). Needless to say, proper collection such as the use of containers with the appropriate preservatives or chemicals as well as ensuring that the true 24-hour volume is obtained affect the accuracy of these levels. A urine creatinine excretion close to 15–20 mg per kilogram per day is reflective of a complete collection.[16] It is also important that these urine studies be done after the treatment of a concomitant urinary tract infection since this can affect accuracy of the solute levels as well. For instance, citrate levels have been shown to be falsely low in patients with concomitant UTI.[13]

Serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, and uric acid should also be obtained to detect other metabolic or tubular defects as well as to evaluate renal function. It is also necessary to determine the immunoreactive parathyroid hormone concentration if the serum and urine calcium concentrations are abnormal to diagnose hyper-

Table 3

		NORMAL VALUES	
Urinary Solute: creatinine ratios			
Calcium: (mg/mg)	infants ≤34 weeks' gestation		<0.81:1[141]
	>34 weeks' gestation		<0.42:1[141]
	child		<0.21:1[70]
Oxalate: (mg/mg)[103-149]	infants <6 months		<0.3:1
	child <4 yr old		<0.15:1
	>4 yr old–adult		<0.1:1
(mmol/mmol)[150]	infants <1 yr old		<0.061:1
	1–5 yr old		<0.036:1
	5–12 yr old		<0.03:1
	>12 yr old		<0.013:1
Uric acid:		<0.53 mg/dL GFR*[142]	
Citrate: (g/g)		0.51:1**[94]	
(mol/mol)[143]	infants	1.9:1 (F)	0.63:1 (M)
	child	0.27:1 (F)	0.33:1 (M)
	adolescent	0.32:1 (F)	0.28:1 (M)
Timed Collections:			
Calcium:	<4 mg/kg/24 hours		
Oxalate:	<40 mg/1.73m²/24 hours or <0.5 mmol/1.73 m²/24 hours[102,144].		
	atomic absorption method: <40 mg [0.45 mmol]/24 hours[145]		
	Olthius method: 20–60 mg [0.23–0.68 mmol]/24 hours[146]		
	immobilization oxalate oxidase method: 10–40 [0.11–0.46 mmol]/1.73 m²/24 hours[147]		
Uric acid:	<815 mg/1.73 m²/24 hours[128]		
Cystine:	<20 mg/24 hours[148]		
Citrate:[95]	>128 mg/g creatinine/24 hours (M)		
	>300 mg/g creatinine/24 hours (F)		

*Calculated as $\frac{\text{urine uric acid} \times \text{serum uric acid}}{\text{urine creatinine}}$

**Mean.
GFR=glomerular filtration rate.

parathyroidism, which is treatable.[16] It is also recommended that all children with suspected urolithiasis be screened for cystinuria by means of the cyanide nitroprusside test.[8,16,34] This test has been proven to be a reliable screening qualitative test for cystine,[34] and it is inexpensive and simple to do. However, its reliability for detecting heterozygotes has been questioned.[34,35] Therefore, if there is a very high index of suspicion for cystinuria; i.e., recurrent urolithiasis with onset from early childhood with a positive family history for cystinuria or urolithiasis as well as cystine crystalluria, the 24-hour urine collection to determine cystine quantitatively is preferred since it is more reliable.

Medical Management

Initial medical management (Table 4) is directed at relieving pain, which may require narcotics, and treatment of intercurrent infection. Promoting passage of the stone if possible by adequate hydration with approximately 1.5 to 2 times maintenance requirements to increase urine

Table 4

MEDICAL MANAGEMENT OF RENAL STONES

Acute Management	Long-Term Management
Pain relief with analgesics or narcotics	Maintain adequate oral fluid intake with the goal of keeping a high urinary volume with low specific gravity
Oral or parenteral hydration, approximately 1.5 to 2 times maintenance requirements to increase urine output by at least 2–3 times	Dietary modifications such as low sodium and oxalate, normal calcium, moderate protein, and high potassium intake
Treatment of concomitant urinary tract infection	Prevent urinary tract infection
	Maintain normal levels of known inhibitors of stone formation, e.g., citrate, pyrophosphate, magnesium, etc. based on urine levels monitored at periodic intervals
	Specific medications (see Table 5)

output by two to three times is also needed, provided the patient does not have renal insufficiency or any form of urinary tract obstruction.[16] Stones ranging from 2 to 6 millimeters have been passed spontaneously.[4,8,33]

Subsequent measures are taken to prevent further stone formation by maintaining adequate fluid intake with the goal of at least the calculated maintenance requirements equal to at least 1,400 mL/1.73 m^2/day of urine output.[16] This is the mainstay of therapy in all types of urolithiasis. With a low urine volume, the concentration of all stone-forming ions increases, predisposing to stone formation.

Dietary modifications should be done to eliminate dietary excesses or correct dietary deficiencies. These include decreasing sodium intake, especially in patients with hypercalciuria. It has been suggested that patients with calcium stones are more sensitive than the general population to the calciuric effect of sodium.[36] The hypercalciuric effect of a high sodium diet is attributed to an inhibition of sodium and calcium reabsorption in the proximal tubule and along the loop of Henle.[37]

A low oxalate diet is also recommended, especially in calcium oxalate stone formers and in patients with enteric hyperoxaluria. Protein intake should also be moderate because a high intake enhances urinary excretion of calcium,[38,39] uric acid,[38] and oxalate and causes a decrease in urine pH and urinary citrate excretion.[38,40,41] A low calcium (and low oxalate) diet has been shown to be helpful only in adults with dietary dependent absorptive hypercalciuria.[42] This type accounts for only 3.9–17.2% of adults with idiopathic hypercalciuria.[43] Furthermore, whereas most of the adults are reported to have absorptive hypercalciuria, the majority of children have the renal type.[44] Generally, a normal to high calcium diet is recommended.[28,38,40,41,45-48]

Potassium administration has been shown to decrease urine calcium excretion in healthy adults as well as in those with urinary stone disease.[49-51] The mechanism for such an effect has been postulated to be secondary to changes in extracellular fluid volume, potassium-mediated changes in renal tubular phosphate transport, and renal synthesis of 1,25 $(OH)_2$ vitamin D.[49] Potassium administration as well as a high potassium diet has also been shown to be beneficial in hypercalciuric children,[52] where a decrease in their urine sodium-to-potassium ratio and, consequently, a decrease in their urine calcium-to-creatinine ratio was noted. There was also marked improvement in their symptoms.

Normal levels of known inhibitors of crystallization such as phosphate, citrate, magnesium, etc. should be maintained because of their roles, as previously discussed. This may be accomplished by replacement therapy or supplementation following determination of their urine levels.

In addition to these conservative measures, specific medications (Table 5) may be added to the therapeutic regimen as will be discussed later.

Table 5

MEDICATIONS

	Medication	Dosage	Comments
Idiopathic hypercalciuria	Thiazide	1–2 mg/kg/day divided b.i.d.[16]	
Distal RTA hypocitraturia	Potassium citrate	1–4 meq/kg/day divided q.i.d.[95]	
Hyperoxaluria	Pyridoxine	5 mg/kg/day divided b.i.d.[107]	Very high doses (>1 gram/day) may cause neurologic symptoms
	Orthophosphate	30 mg/kg/day divided t.i.d.-q.i.d.[107]	
	Magnesium hydroxide	3–6 mg elemental magnesium/kg/day divided t.i.d.-q.i.d.	Monitor serum and urine magnesium with dosage changes
Hyperuricosuria	Allopurinol	10 mg/kg/day divided t.i.d.-q.i.d.	
	Potassium citrate	1–4 meq/kg/day divided q.i.d.	Keep urine pH between 6.5–7[129]
Cystinuria	Thiol:		
	D-penicillamine	15–40 mg/kg/day[34] divided t.i.d.-q.i.d.	Titrate to maintain urine cystine <200 mg/g creatinine
	MPG	10–30 mg/kg/day[34] divided t.i.d.-q.i.d.	
	Captopril	0.5–1 mg/kg/day	
	Potassium citrate	1–2 meq/kg/day divided q.i.d.	Maintain pH between 7.5–8.0[34]

Nonmedical Management

Surgery is recommended when there is evidence of persistent obstruction anywhere in the urinary tract increasing the risk for renal damage. Persistent UTI associated with the continued presence of the stones as well as intractable pain are also indications for surgery.[8,10]

Surgical lithotomy has traditionally been the most common form of nonmedical intervention. This is usually done when the stone disease is associated with a congenital anomaly in the urinary tract, which can be corrected simultaneously, minimizing the risks of repeated general anesthesia.

Percutaneous nephrolithotomy (PNL) subsequently gained wide acceptance in adults because patients need not be subjected to general anesthesia. However, this advantage was not evident in children. Furthermore, the size of the instruments was not appropriate for the body size of the pediatric age group. More recently, smaller instruments have been developed, enabling the application of this procedure to children. PNL is done when the stone is not amenable to either extracorporeal shock wave lithotripsy or ureteroscopy, or when there is a large stone burden; i.e., large sized or multiple stones.[53]

Ureteroscopy or cystoscopy with stone extraction had a similar disadvantage initially, i.e., inappropriate instrument size. Through the years, this procedure has been applied to children with good success rates without residual reflux, strictures, trauma, or renal damage.[54] However, these procedures are indicated depending on stone size and location; i.e., they are usually recommended mainly for stones in the lower third of the ureter.

Nephrectomy may be required on rare occasions, especially when permanent renal damage has occurred from persistent infection or obstruction causing unremitting infection or uncontrolled hypertension.

The evolution of extracorporeal shock wave lithotripsy (ESWL) is a major breakthrough in the treatment of urolithiasis. ESWL[53,55] uses an underwater electrical discharger producing high-energy shock waves that originate at a single focus (F1) of an ellipsoidal reflector. These shock

waves expand radially and are redirected by the reflector, subsequently causing convergence at a second focus (F2). It is in this focus where the stone is placed by proper positioning of the patient in the water bath. The delivery of the shock wave is synchronized with the patient's heart rate as monitored by an electrocardiogram in order to avoid cardiac arrhythmias. The shock wave generated passes through the water then into human tissue, subsequently reaching the stone at F2.[53] Thereafter, the stone gradually disintegrates owing to the high energy released from the different acoustic impedance between the stone and water contained by human tissue, urine, etc. The goal is to break the stone into small enough fragments to pass spontaneously. The patient's position, body size, and cooperation are essential for the success of the procedure. Therefore, it is not surprising why this has had limited use in small children initially. With the recent development of new-generation lithotripters, as well as various modifications in techniques, some of these problems have been overcome such that more centers are now using ESWL in children and have success rates ranging from 79% to 98.5%.[21,56-62] Results are noted to be better if the stone is in the renal pelvis and composed of calcium oxalate or uric acid, which are noted to disintegrate well.[53] Cystine stones respond poorly to ESWL. Percutaneous lithotripsy is preferred for these stones.[53] This involves using an electrohydraulic or ultrasonic lithotripter introduced into the body through a nephroscope via a percutaneous approach. This procedure as well as pulsed dye laser for lithotripsy are newer modalities currently being employed for the management of urolithiasis especially in adults.

Complications of ESWL include bruising, fever, perirenal hematomas, pain when the fragments are passed, and a condition called steinstrasse (literally meaning stone street), which is the accumulation of the retained stone fragments in the ureter.[56] Long-term studies by Nijman[56] showed a recurrence rate of approximately 10% after 2 years. However, this high rate of recurrence was attributed to the complex urologic conditions of their patients.[60] Others report a 0% recurrence rate[10] after a mean follow-up of 22 months. Surgical intervention after ESWL has been reported to occur in less than 9% of patients.[16] Long-term results of renal function and growth after ESWL have not been fully determined.

Extracorporeal shock wave lithotripsy is not suitable for neonates and generally children less than 3 years of age although there have been some few successful cases.[21,55-58, 61-67] It is also not recommended for patients with marked bony deformities, those who had stone removal at the time of corrective surgery for a congenital urinary tract abnormality,[8] or any form of obstruction that might prevent the passage of the stone.[63] ESWL is also not indicated for treatment of lower ureteral stones where ureteroscopy basket extraction or ultrasonic lithotripsy is preferred.[53] ESWL is also not advisable for women of childbearing age if the stone is located in the true pelvis since the gonads may be at risk for damage by the shock waves.[63]

Etiology

Metabolic Stones

Calcium Stones and Hypercalciuria. Hypercalciuria is the most common metabolic etiology attributed to urolithiasis in both children and adults. It is defined as a urinary calcium excretion more than 4 mg/kg/day or a random urine calcium-to-creatinine ratio of greater than or equal to 0.21. There are several causes of hypercalciuria, the most common of which is idiopathic hypercalciuria (IH).

IH has originally been classified into either absorptive (AH) or renal (RH) hypercalciuria. excretion. Recent studies[33,68] suggest that AH and RH may actually constitute a spectrum of the disorder rather than exist as separate types.

IH is more common in whites and affects both sexes but with slightly more male preponderance in children.[69] Family history is positive for urolithiasis in 52% of children with IH,[70] and an autosomal dominant pattern has been suggested.[71,72]

The most common clinical feature of hypercalciuria is gross or microscopic hematuria, which may occur with or without urolithiasis.[70,73,74] Back or flank pain is also a frequent symptom as well as dysuria, frequency, and enuresis.[75,76] A random morning urine sample should be sent for urine calcium-to-creatinine ratio, and if it is greater than or equal to 0.21, a timed urine collection for calcium should be done. Within 3–5 years of the onset of the hematuria, without therapy, the risk for urolithiasis is estimated to be 15–18%.[18]

Hydrochlorothiazide at an initial dose of 1–2 mg/kg/day is given, especially if the urine calcium levels are markedly or persistently high despite good compliance with the conservative measures previously discussed. This drug acts by promoting calcium reabsorption in the distal renal tubule[77] and decreasing intestinal calcium absorption.[78]

Previously, it has been recommended that calcium should be limited in the diet of patients with IH. However, many studies[33,48] demonstrate increased risk for stones in patients with calcium-restricted diets as well as negative calcium balance and bone loss,[79] which occurs by the stimulation of vitamin D3 secretion, causing increased intestinal absorption of calcium and increased bone resorption of calcium[80] and thus increasing serum calcium and subsequently calcium excretion. Several studies[81-83] indicate the increased frequency of bone loss in adults with stones and IH as demonstrated by bone mineral density studies. The increased risk for stone formation of a low-calcium diet is attributed to increased oxalate absorption as a result of the low intraluminal calcium, and this is thought to be more important in stone formation than a decrease in calcium intake.[47] Normally, free intraluminal calcium and oxalate bind and form a complex that is excreted in the gastrointestinal tract. Thus, if there is a decrease in calcium in the gut, there is more oxalate capable of being absorbed and subsequently excreted in the urine. A study in adults by Galosy et al[84] did not demonstrate any changes in oxalate excretion with calcium restriction to 400 mg/day. Reusz et al demonstrated significantly greater oxalate excretion in children with absorptive hypercalciuria on calcium-restricted diets.[85] In a prospective study by Curhan et al[48] on more than 45,000 adult males, a high dietary calcium intake decreased the risk of urolithiasis. Based on these findings, calcium restriction is no longer recommended.

A low-sodium diet of approximately 2–3 meq/kg is mandatory to avoid the hypercalciuric effect of sodium as previously discussed.[47] A high-potassium diet has also been shown to be beneficial.[52]

Other clinical conditions that may cause increased urine calcium excretion (secondary hypercalciuria) include the following:

Chronic diuretic use, especially of furosemide. This is particularly evident in preterm infants with chronic lung disease[86,87] or patients with congestive heart failure[88] who are on prolonged furosemide therapy. These patients have increased frequency of nephrocalcinosis and nephrolithiasis, the occurrence of which may be minimized by substituting furosemide with thiazides.

Sarcoidosis, a chronic granulomatous disorder the cause of which is still unknown, may also cause hypercalcemia and stone formation. This is attributed partly to the renal damage by the granulomas but mainly to the hypercalcemia and hypercalciuria.[89]

Primary hyperparathyroidism is characterized by increased serum parathyroid hormone concentrations, which increase calcitriol production, causing increased intestinal absorption, tubular reabsorption, and bone resorption of calcium.[33] These cause markedly increased serum and urine calcium concentrations. In hyperparathyroid stone formers, surgical removal of the parathyroid glands is indicated.

Distal renal tubular acidosis (RTA) is a disorder caused by a defect in the production and maintenance of the hydrogen ion gradient in the distal tubule. It is characterized by normal anion gap acidosis with hyperchloremia. The risk for stone formation is attributed to (1) increased urine pH promoting precipitation of calcium phosphate stones, (2) increased calcium excretion, and (3) low urine citrate.[90] The low urine citrate is attributed to multifactorial causes including a defect in renal citrate metabolism, acidosis, low glomerular filtration rate, and hypokalemia. The suggested cause of the hypercalciuria is mainly the metabolic acidosis. When a state of chronic acidosis exists, the body buffers retain hydrogen ions in bone. Consequently, calcium salts are dissolved from bone and tubular calcium reabsorption decreases, causing increased urine calcium excretion.[90] Treatment is via administration of potassium citrate to neutralize endogenous acid production and increase urine citrate excretion. Note that patients with IH may later develop distal RTA, probably as a result of papillary calcification.[91] When this occurs, the drug of choice is a thiazide rather than potassium citrate.[91]

Immobilization, even as short as 3 weeks,[10,16,17] may cause hypercalciuria, which in other literature is classified as resorptive hypercalciuria. This is attributed to increased calcium mobilization from bone leading to increased calcium excretion. These are usually the chronically ill bedridden patients, those with significant fractures, or those with severe neurologic disorders. Early ambulation or mobilization as soon as feasible as well as increasing fluid intake are important in preventing stone formation.

Other disorders causing calcium urolithiasis include vitamin D excess, especially if accompanied by large doses of oral calcium, milk-alkali syndrome, multiple myeloma, malignancies especially with metastatic bone disease, juvenile rheumatoid arthritis, and idiopathic hypercalcemia of infancy.[16,18,89]

Hypocitraturia. Hypocitraturia occurs in approximately 19–63% of adults and children

with urolithiasis.[92] Normal urine citrate is approximately 40–60 mg/dL in adults depending on sex; i.e., females have higher levels than males.[93] In children, the mean citrate-to-creatinine ratio is 0.510 in normal subjects,[94] and the mean urine citrate excretion is 457 mg/g creatinine in boys and 681 mg/g creatinine in girls.[95] Decreased levels of this inhibitor occur in distal RTA as well as in disorders with acquired metabolic acidosis such as chronic diarrhea from inflammatory bowel disease or after gastrectomy. Diuretic therapy, potassium depletion, and active urinary tract infection[92] may also cause this problem. Other studies have shown that a high sodium intake as well as high amounts of meat products in the diet may decrease urine citrate levels.[92] Therapy is mainly through replacement using potassium citrate or a relatively new drug, potassium magnesium citrate.[96] Initial dosage depends on the severity of the hypocitraturia. Usually 1–4 meq/kg/day of potassium citrate divided two to four times daily is recommended and then adjusted accordingly based on follow up urine citrate levels.[95]

Hyperoxaluria. Oxalate is one of the end products of normal metabolism. Its main route of excretion is through the kidneys with normal urine levels approaching 15–40 mg per day in adults and children.[97] The majority of urine oxalate is derived from endogenous metabolism with ascorbate and glyoxylic acid as the main precursors.[97] Only approximately 10–20% of urine oxalate is derived from diet.[97] Examples of oxalate-rich foods are spinach, rhubarb, swiss chard, peanuts, sweet potato, baked beans, blackberries, strawberries, chocolate, cocoa, and tea. However, most of the oxalate ingested is bound to free calcium ions in the gut, forming a calcium oxalate complex, which is subsequently excreted through the gastrointestinal route.[98] Thus, oxalate absorption is normally only less than 10% of the entire dietary intake.[97]

Hyperoxaluria accounts for less than 2–3% of children with calcium urolithiasis.[22] Certain clinical disorders may cause malabsorption, promoting increased oxalate absorption, and these comprise what is known as enteric hyperoxaluria. Absorption of oxalate is increased by decreased intraluminal calcium and free fatty acids[99] as well as by increased permeability of the gastrointestinal mucosa to oxalate[100] caused by small bowel disease such as ileal resection, pancreatic diseases, and severe fat malabsorption.

Primary hyperoxaluria (PH), a rare genetic disorder with an autosomal recessive mode of inheritance, is an inborn error of glyoxylate metabolism. There are two types, PH I and PH II, both of which cause marked increase in oxalate biosynthesis from glyoxylate that accumulates behind the metabolic block.[101] PH I is due to a deficiency of the hepatic peroxisomal alanine:glyoxylate aminotransferase (AGT) and PH II is due to a deficiency of glyoxylate reductase.

PH I, which is much more common than PH II, is characterized by recurrent urolithiasis and nephrocalcinosis, which later progress to renal insufficiency as well as oxalosis, which is the systemic deposition of oxalate more commonly in the liver, eyes, and bone marrow.[102] The exact incidence of this disorder is unknown, although estimates of at least 30 new patients developing end-stage renal disease from PH in the United States per year have been reported.[103] The preliminary results of the French National Survey[104] reported an incidence rate of 0.12 per 10 million per year and an average prevalence rate of 1.04 per 10 million. Approximately 50% are diagnosed at less than 10 years of age with a male-to-female ratio of 1.33:1. End-stage renal disease is reached by age 15 years in 50% of patients.[104]

A high index of suspicion for PH should be maintained in patients with nephrocalcinosis or calcium oxalate urolithiasis. Urine oxalate-to-creatinine ratio is a very helpful screening test. Normal values are adjusted for age.[102] Results, especially if abnormal, have to be confirmed by a 24-hour urine collection. The upper limit of normal in children is estimated to be 0.46 mmol/1.73 m^2/day.[102] Percutaneous liver needle biopsy for AGT assay is another helpful diagnostic test.[105,106]

Intensive therapy should immediately be administered to retard early progression of the disease. A low-oxalate, low-sodium, and normal calcium diet is recommended. High fluid intake needs to be maintained. Inhibitors of calcium oxalate such as citrate, magnesium hydroxide, and orthophosphate are also given. Diuretics, especially thiazides, may be helpful, not only by increasing urine output but also by decreasing calcium excretion. Since pyridoxal phosphate is a cofactor of AGT, pyridoxine at a dose of 5 mg/kg/day should be given.[107,108] The study by Milliner et al[107] in 25 patients evaluating long-term treatment of PH with orthophosphate and pyridoxine suggests that these medications decrease calcium oxalate formation and appear to preserve renal function in patients treated before the onset of renal failure.

They reported an actuarial rate of end-stage renal disease of 26% after 20 years of treatment with orthophosphate and pyridoxine and reported only one death. Untreated patients or those who do not respond to medical therapy subsequently progress into end-stage renal disease and develop systemic deposition of oxalates requiring dialysis and kidney and/or liver transplantation to prolong survival.[104]

Cystinuria. Cystinuria is a genetic disorder with autosomal recessive transmission characterized by abnormalities in the renal and intestinal transport mechanisms of cystine, ornithine, lysine, and arginine. There is increased urine excretion of these dibasic amino acids with normal or decreased plasma levels. This defect is of no clinical consequence per se except that once the solubility limit is exceeded, cystine stone formation occurs. This process is pH dependent; i.e., solubility is higher at a urine pH equal to or greater than 7.5.[109,110] Cystine stones account for 6% of urolithiasis in children[3,8,10,13,17,111-113] in the United States and approximately 1% of all patients with urolithiasis.[31] Such stones can occur anytime from infancy to adulthood, although the mean age of occurrence is in the second and third decade of life with both sexes being equally affected.[34] Hypercalciuria, hyperuricosuria, and hypocitraturia may be associated.[114] Other clinical disorders associated are hemophilia, retinitis pigmentosa, Down syndrome, muscular dystrophy, and hereditary pancreatitis, as well as mental illness and retardation.[16,18,34]

This disorder is diagnosed in patients with very early onset of recurrent renal stones as well as a positive family history for cystinuria. Urinalysis reveals the characteristic flat hexagonal cystine crystals in 26% of patients.[115] A positive nitroprusside test indicates a level of greater than 75 mg/dL of urine cystine, and this needs to be confirmed by a 24-hour urine collection.[16] Quantitative cystine excretion can also be done by amino acid analyzers or high-pressure liquid chromatography.[116] Urine cystine excretion of more than 75 mg and usually more than 200 mg/g creatinine is diagnostic of cystinuria.[16,34] However, chemical stone analysis provides the more definitive diagnosis.

Strict dietary restriction of methionine-rich food such as red meat, poultry, fish, and dairy products has generally been recommended in adults since methionine is the precursor of cystine. Not only is compliance difficult but also this diet may be detrimental to growing children, and hence, it is not advised in children.[34] A low-sodium diet, which has been shown to decrease urine cystine levels in children,[117] is recommended in the therapeutic regimen of cystinuric patients.

The need for increased fluid intake and urinary flow rates throughout the day and night cannot be overemphasized. Alkalinization of the urine with potassium citrate to a goal of a urine pH between 7.5 and 8.0 is done to increase cystine solubility.[34] Beyond pH 8, there is an increased risk for calcium phosphate stones.[31]

When this regimen fails and stones recur, chelating agents are added to the therapy. These form a complex with cystine, which is more soluble in the urine. D-penicillamine has been the most widely used drug and has been shown to produce a marked decrease in urine cystine excretion.[16,34,116] However, it is coupled with several serious side effects such as agranulocytosis, thrombocytopenia, nephrotic syndrome, pemphigus, polymyositis, etc.[16,34,116] This renders it relatively intolerable, thereby limiting its use. α-Mercaptopropionylglycine (MPG) has the same mechanism as D-penicillamine with a lower incidence of toxicity. However, its side effects such as emesis, skin rashes, nephrotic syndrome, myopathy, and oral ulcers are very common. Captopril, an angiotensin converting enzyme inhibitor, which is commonly used as an antihypertensive, has been shown to decrease urine cystine excretion by approximately 60–90% without any accompanying side effects.[118,119] It forms a thiol-cysteine mixed disulfide, which is 200 times more soluble than cystine[119] and three to four times more soluble than the D-penicillamine and MPG complexes.[120,121] Hypotension is not a significant concern, especially since this may be overcome by volume expansion from vigorous hydration.[120] Current studies on this drug are mostly on adults, and varying results have been reported.[108,119,120,122-126] Coulthard et al[122] reported a small decrease in urinary cystine excretion in their study of five cystinuric children . However, this was not statistically significant. Similar findings were reported by Michelakakis et al[124] in their experience with two siblings with cystinuria. A recent study by Chow and Streem[126] in 16 patients (age range 1.5–49 years) concluded that captopril does not appear to be as effective as D-penicillamine or α-MPG in decreasing stone formation rate and that it does not clearly add clinical benefit to these thiols. More studies need to be done to determine the value of this drug in the treatment of cystinuria.

Uric Acid Stones. Uric acid is the end product of purine metab-

olism, which is handled by the kidney and partly by the gastrointestinal tract. It is a weak acid whose solubility is highly dependent on urine pH; i.e., solubility increases with a higher pH.[16,127] In children, mean uric acid excretion is approximately 520 ±147 mg/1.73 m^2/day.[128]

Uric acid stones account for 5% of stones in children.[8,10,16] Their formation occurs with low urine pH as well as low urine volume. Urate stones may also occur with increased urine ammonium concentration, which may be secondary to UTI, dehydration, or starvation.[129]

Hyperuricosuria is the greatest predisposing factor and this can occur with a high-purine diet, intake of drugs (salicylates, probenecid, sulfinpyrazone etc), obesity, and alcohol intake.[129] Primary gout, myeloproliferative disorders, and other hematologic diseases such as pernicious anemia and polycythemia are also associated disorders. Hereditary diseases causing hyperuricemia such as Lesch Nyhan syndrome, where there is a deficiency of hypoxanthine guanine phosphoribosyl transferase (HGPRT), and superactivity of phosphoribosylpyrophosphate synthetase (PRPP) also cause marked hyperuricemia, uricosuria, and uric acid stones.

Alkalinization with potassium citrate to keep the urine pH between 6.5 and 7 together with vigorous hydration and dietary restriction of purine-rich food are important. Allopurinol is the drug of choice in decreasing hyperuricemia and is very effective in decreasing the risk for stone formation.[16,129]

Infection Stones

Infection stones comprise 24% of the total number of urolithiasis in North American children[8,10,22] compared to 54% in European children.[16] Two-thirds of patients with infection stones are less than 5 years of age at the time of diagnosis. There is also some male predominance.[20] This type of stones also have a predominantly renal location noted in 70% of patients.[20] Thirty-three percent of patients have anatomic lesions that probably contribute to stone formation. These include ureteropelvic junction obstruction, neuropathic bladder, and obstructed megaureter. Vesicoureteral reflux is noted in 12% of patients.[20]

These calculi are primarily struvite (magnesium ammonium phosphate) or carbonate apatite, although mixed stones have also been noted. Urease-splitting bacteria especially *Proteus* sp. are responsible for forming these stones. Other bacteria include *Klebsiella, Pseudomonas, Providencia, Enterococci,* but very rarely *E. coli.*[4,130,131] The mechanism by which stones are formed involves the release of ammonia when the urease from the bacteria acts on urea in the urine. This increases urine pH and urine ammonium, which subsequently binds with phosphate and magnesium ions, forming struvite stones. These stones can increase in size, filling the pelvicaliceal system, forming a staghorn configuration, which often requires some form of surgical removal or rarely even nephrectomy. Bacteria may be interspersed within the structure of the stone, making antibiotic penetration difficult, thus making infection recurrent or persistent. This is the reason why it is essential not only to treat aggressively with the appropriate antibiotic but also to ensure complete removal of all stone fragments.[131,132] The recurrence rate following initial management is 14%, and in those associated with anatomic abnormalities, the median interval to recurrence following initial surgery was 1 year (range 4 months to 13 years).[20] Therefore, close follow-up is also essential. Currently, several modes of nonsurgical therapies are being evaluated such as direct instillation of medications onto the stones and the use of urease inhibitors.[133]

Anatomic Stones

As previously discussed, urinary tract anomalies in association with other risk factors predispose patients to urolithiasis by promoting stasis of urine and heterogeneous nucleation. Infection developing in stones other than struvite or carbonate apatite are said to be infection-associated[134] and are not classified as infection stones per se. Infection may lead to some injury to the uroepithelial lining. The resultant bacterial and inflammatory cellular debris acts as a nidus for stone formation and growth at lower solute concentrations and in effect hastens the process of crystallization.[17,20] This is what is referred to as heterogeneous nucleation. Neurogenic bladder and ureteropelvic junction obstruction are the most common anomalies associated in children. Urinary diversions are also considered risk factors.[8,16] Among patients with ileal loops, large loop residuals, and hyperchloremic acidosis, ureteral dilatation causing stasis are presumed to be the risk factors for stone formation.[135] Medullary sponge kidney disease, which is characterized by cysts in the collecting ducts, is another common anomaly that presents with renal stones, although it is uncommon in children. Most patients are asymptomatic, although some may have hematuria or recurrent

UTI. Diagnosis is made by intravenous pyelography.[133] It is important to remember that not all patients with anatomic anomalies will ultimately develop calculi but that it is the presence of concomitant risk factors that determines whether stone formation will eventually occur.[22,136]

Factitious Calculi

A few patients have undergone extensive evaluation with normal results and unidentifiable stone type. Some were cases of Munchausen-by-proxy. In 19 children aged 4 months to 7 years,[137] hematuria was reported in 7 children. Blood was reportedly generated by the mother by adding her own blood to the child's urine. In one case, a mother stirred a vaginal tampon (during menstruation) into the child's urine specimen.

In older children and adults, reported cases were attributed to Munchausen syndrome. For instance, a 10-year-old boy presenting with colicky pain and hematuria claimed to have passed black specks of stones, which were analyzed as small water-worn pebbles of quartz lightly stained with iron oxide.[138] Other patients reported genuine renal stones factitiously passed, although these were mostly adult patients.[139,140]

Conclusion

The diagnosis and management of urolithiasis involves careful examination of the individual factors that predispose the patient to stone formation. The classification of the particular stone composition for a patient may not be as distinct since mixed types may occur as well as underlying metabolic abnormalities. The main point to remember is that the underlying defects should be corrected as soon as possible; concomitant infection should be treated aggressively; and increased oral intake of fluids should always be emphasized. Close follow-up should also be done to assess the adequacy of therapy and to prevent any recurrence.

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