Kidney Stone

Kidney Stone

- **Kidney stone** disease, also known as **nephrolithiasis or urolithiasis**, is a disorder in which urinary solutes precipitate to form **aggregates of crystalline material in the urinary space.**

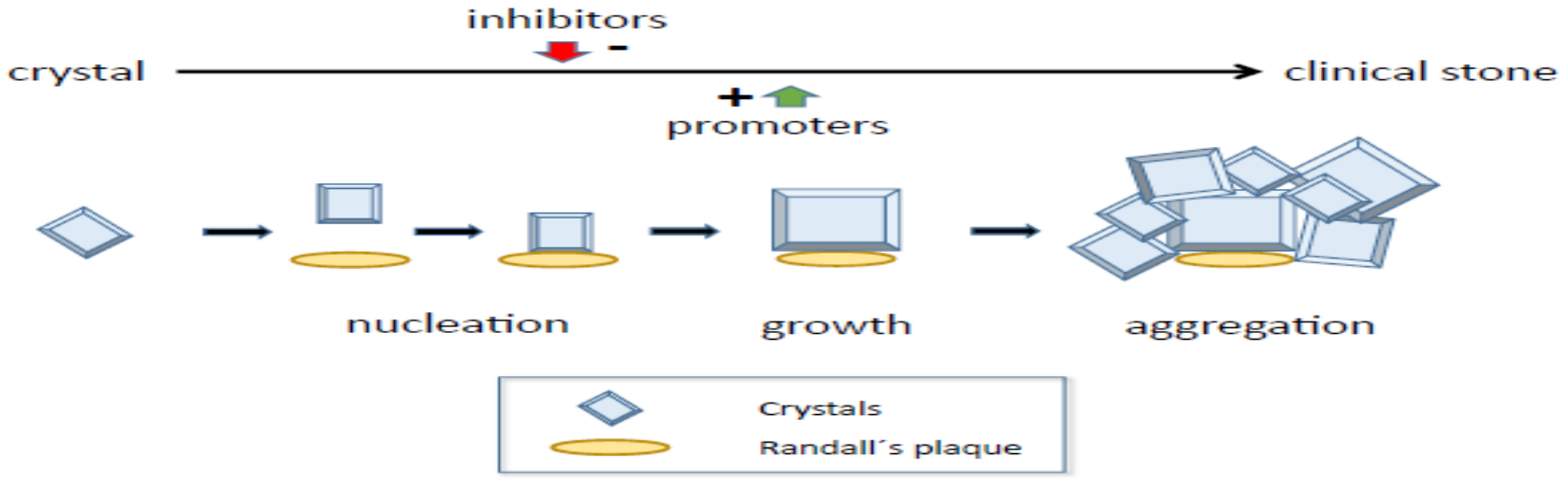

Figure 2. Mechanisms of stone formation.

Kidney Stone

- The medical community's perspective on nephrolithiasis has gradually shifted from viewing it as a **primarily urologic illness** to a **chronic medical condition requiring long-term surveillance and management.**

- kidney stone disease is best addressed by **a team led by nephrologists and urologists** with input from multiple other health professionals including **dietitians, endocrinologists,interventional radiologists, and endocrine surgeons**.

- Nephrolithiasis is now recognized as a marker for **systemic disease** and a predictor of **metabolic and cardiovascular complications**.

Epidemiology

- Nephrolithiasis is common, affecting approximately 1 in 11 people. By age 70, 19.1% of men and 9.4% of women report ever having a kidney stone.

- with the National Health and Nutrition Examination Survey noting an increase in the self-reported prevalence of kidney stones, from 3.2% in 1980 to 8.8% in 2014.

- The male-to-female ratio has decreased from 3:1 to about 2:1 in the past 2 decades, attributed to an increasing prevalence of obesity. Obesity and diabetes are strongly associated with a history of kidney stones in multivariate models, particularly for women.

Epidemiology

- Racial and ethnic differences are also evident, with the prevalence of nephrolithiasis being higher in White male patients, intermediate in Asian patients, and less common in Black patients.

- The highest risk of stone formation is reported in men in the United Arab Emirates and Saudi Arabia.

- Heat-related increases in urinary concentration from nonrenal water losses, geographic differences in diabetes and obesity rates, and other environmental and genetic factors likely explain these variances.

Nephrolithiasis has been associated with significant morbidity

- the risks of end-stage kidney disease, late-stage CKD, and doubling of serum creatinine were significantly higher among participants with 1 or more episodes of nephrolithiasis.

- especially in women and those younger than 50 years. Struvite stone-formers with staghorn calculi and patients with cystinuria are at especially high risk for CKD.

Am J Kidney Dis. 2016;68(6):973-985

Nephrolithiasis has been associated with significant morbidity

- One analysis revealed a 31% increase in risk for myocardial infarction in those with a history of nephrolithiasis despite adjusting for known risk factors for cardiovascular disease.

- Nephrolithiasis is also associated with an increased risk of cardiovascular disease. Studies reveal a greater prevalence of hypertension and possibly increased carotid wall thickness in stone patients, even when controlling for major atherosclerotic risk factors.

- the link between kidney stones and reduced bone mineral density and fractures is particularly robust The skeleton commonly serves as a source for the excessive urinary calcium excretion rates that frequently predispose individuals to stones.

Am J Kidney Dis. 2016;68(6):973-985

risk of stone

- The factors that predispose individuals to kidney stone formation can be **genetic, metabolic, and environmental.**

- **genetic component** **to recurrent stone formation has been recognized for decades. Studies have confirmed the heritability of patterns of urinary excretion of calcium,citrate, oxalate, and uric acid.**

- **Monogenic** **causes of nephrolithiasis do exist and include cystinuria, primary hyperoxaluria, and Dent's disease.**

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risk of stone

- **Anatomic abnormalities such as medullary sponge kidney, polycystic kidney disease are associated with an increased risk of kidney stones.**

- **medullary sponge kidney**

- **It manifests with nephrocalcinosis, UTIs, and recurrent kidney stones. Due to the anatomic feature of the disease, the dilatation of the collecting ducts can cause urinary stasis and enhance the precipitationof poorly soluble substances.**

- **Furthermore, affected patients may present with any of several established stone risk factors such as hypercalciuri and hypocitraturia.**

Am J Kidney Dis. 2016;68(6):973-985

risk of stone

- dietary habits:
  - **Low fluid intake** leads to high concentrations of lithogenic substances in urine
  - **potassium-rich foods**
  - **high animal protein intake**
  - **A diet high in salt** **increases urinary calcium**
- **Inflammation**
- **Obesity and diabetes**

Am J Kidney Dis. 2016;68(6):973-985

Drug-induced nephrolithiasis

- **Drug-induced nephrolithiasis is rare and represents 1% to 2% of all renal calculi.**

Two major mechanisms whereby drugs may promote stone formation are :

(1) direct crystallization

(2) altering the supersaturation

Drug Nephrolithiasis

Sulfadiazine crystalluria

Predisposing Factors

- High-dose therapy with offending medications
  - Allopurinol
  - Ceftriaxone
  - Ephedrine
  - Fluoroquinolones
  - Guaifenesin
  - Magnesium trisilicate
  - Phenazopyridine
  - Protease inhibitors (eg, indinavir, atazanavir) and efaviren
  - Sulfonamides
  - Triamterene

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Drug-induced nephrolithiasis

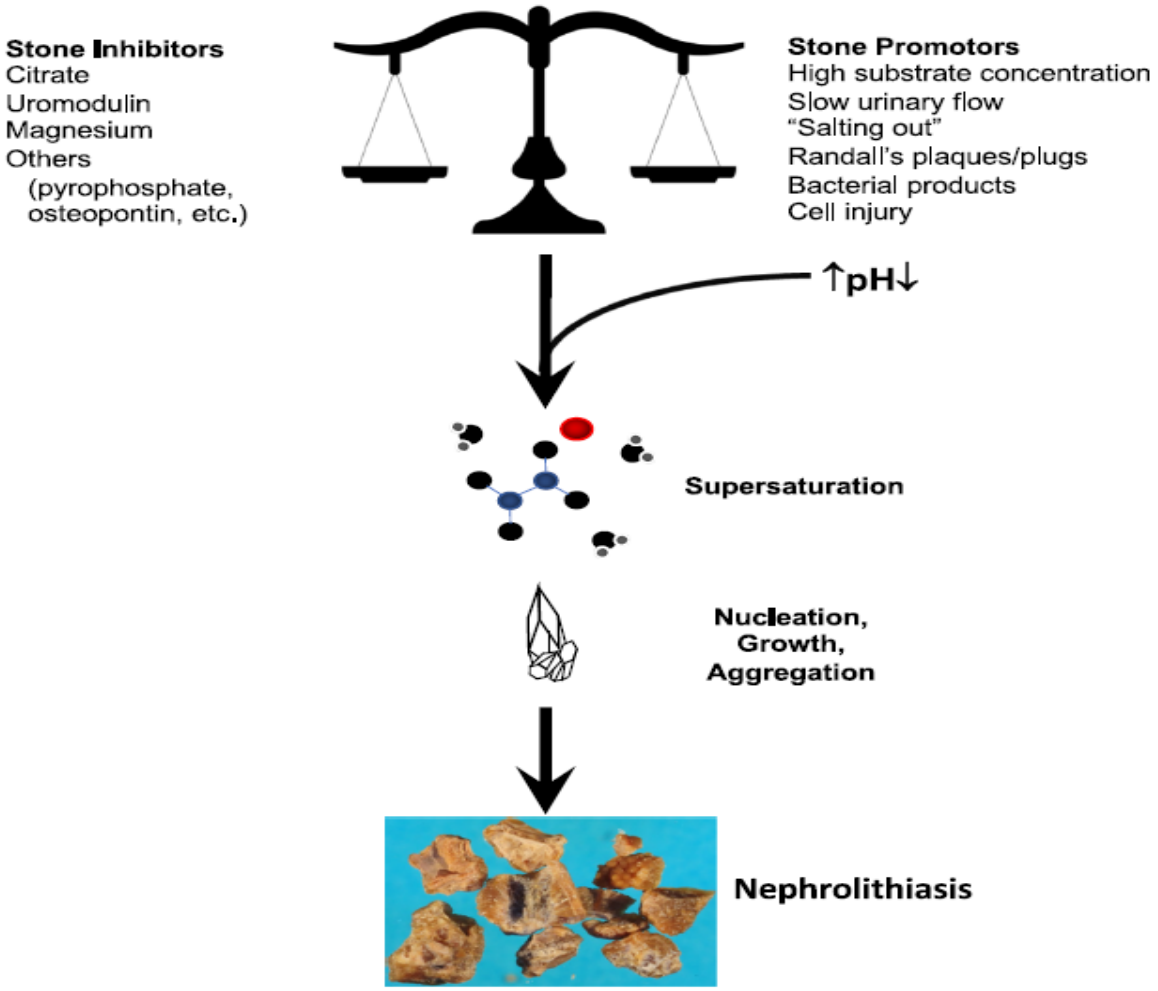
Table III. The most common drug-induced urinary stones [25-28].

Class of drugs	Drugs examples	Primary stone composition	Rationale for stone development
		Drug-containing stones	
Sulfonamides	sulfadiazine	sulfadiazine, N-acetylsulfadiazine	The basic premises for these types of stones development are: (1) The long-term treatment involving the administration of high doses of drug excreted by the kidney; (2) The administered drug and its metabolites are poorly soluble in urine; (3) There is the co-existence of the patient-dependent risk factors for the development of urinary stones.
	sulfaguanidine	N,N-diacetylsulfaguanidine	
	sulfamethoxazole	N-acetylsulfamethoxazole	
	sulfasalazine	N-acetylsulfapyridinine	
Antibiotics	aminopenicillins	ampicillin trihydrate amoxicillin trihydrate	
	cephalosporins	calcium ceftriaxonate	
Quinolones	pipemidic acid	pipemidic acid	
	ciprofloxacin	ciprofloxacin magnesium salt	
	norfloxacin	norfloxacin magnesium salt	
Other antibacterial drugs	nitrofurantoin	nitrofurantoin	
Protease inhibitors	indinavir	indinavir monohydrate	
	nelfinavir	nelfinavir	
	atazanavir	atazanavir	
Antacids	magnesium trisilicate	amorphous silica	
	aluminium hydroxide	aluminium magnesium potassium urate	
Various drugs	triamterene	triamterene, hydroxytriamterene sulfate	
	allopurinol	oxypurinol	
	ephedrine	ephedrine, norephedrine, pseudoephedrine	
	acyclovir	acyclovir	

Drug-induced nephrolithiasis

Drug-induced "metabolic stones"			
Calcium-containing supplements	many commercially available	calcium oxalate, calcium phosphate	These drugs enhance an intestinal calcium absorption, leading to the hypercalcemia and the hypercalciuric state.
Vitamin D-containing supplements	many commercially available		
Loop diuretics	furosemide		
Anhydrase inhibitors	acetazolamide zonisamide topiramate	calcium phosphates, mainly carbapatite	These drugs inhibit bicarbonate reabsorption and hydrogen ion excretion in proximal tubules, leading to systemic metabolic acidosis, an increase in urinary pH and decrease of urinary citrates.
Corticosteroids	cortisol	calcium oxalate, calcium phosphate	These drugs promote the release of calcium from bones and lead to the hypercalcuria and hyperphosphaturia state.
Ascorbic acid (vitamin C)	many commercially available of dietary supplements	calcium oxalate	The excess of vitamin C is metabolized to oxalates and it increases the urinary oxalates excretion. Moreover, high doses of vitamin C also contribute to urinary acidification.
Xanthine oxidase inhibitors	allopurinol	xanthine, oxypurinol	The drug inhibits the biotransformation of hypoxanthine into xanthine and final synthesis of uric acid, leading to the formation of xanthine-containing purine stones.
Uricosuric drugs	benzbromarone probenecid	uric acid	These drugs reduce hyperuricemia by enhancing urinary uric acid excretion, leading to the formation of uric acid-containing purine stones.

Overview of Pathogenesis



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stone inhibitors

- **Low urine volume increases the concentration of lithogenic solutes, thus predisposing them to crystallization.**

- **Known inhibitors include :**
  - **citrate**
  - **pyrophosphate**
  - **magnesium**
  - **uromodulin**
  - **Osteopontin**

stone inhibitors

Stage of lithogenesis	Inhibitors
Nucleation	nephrocalcin osteopontin urinary prothrombin fragment-1 bikunin glycosaminoglycans
Crystal growth	nephrocalcin osteopontin urinary prothrombin fragment-1 bikunin histone-lysine N methyltransferase alpha – 2HS glycoprotein chondroitin sulphate heparin sulphate human urinary trefoil factor 1 glycosaminoglycans citrate pyrophosphate magnesium
Aggregation	nephrocalcin osteopontin albumin urinary prothrombin fragment-1 alpha-1-microglobulin bikunin fibronectin
Retention	osteopontin bikunin crytal adhesion inhibitor fibronectin glycosaminoglycans

Wiad Lek. 2020;73(9 p. II):2031-2039

risk of stone recurrence

- **The risk of stone recurrence is high, with a relapse rate of 50% in 5-10 years and 75% in 20 years.**

- **Risk factors for recurrent stones include multiple prior stone episodes:,**

- **younger age of onset**
- **male gender**
- **family history of kidney stones**
- **higher body mass index (BMI)**

risk of stone recurrence

- **Stone characteristics which predict recurrence include :**

- **the presence of 2 or more stones across both kidney**

- **the presence of stones in the renal pelvis or lower kidney pole.**

- **a stone composition consisting of uric acid, struvite, or calcium phosphate**

Diagnosis

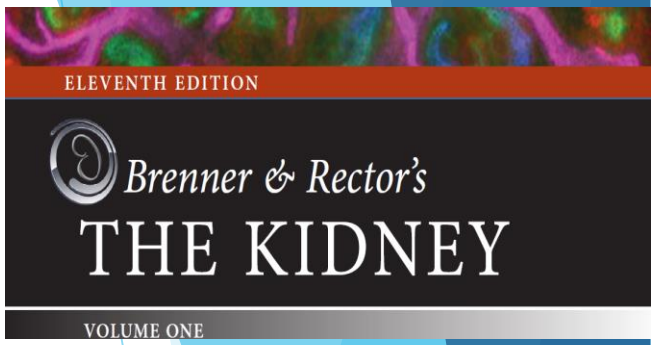
- **The diagnosis of nephrolithiasis involves a thorough assessment, including a detailed medical history and physical examination, consideration of the patient's risk factors and concurrent medical conditions, and an evaluation of the probability of a significant alternative diagnosis.**

- **The diagnosis varies depending on the type of calculus. Typically, laboratory tests are conducted, encompassing hematological and urinary analyses.**

- **For the diagnosis, it is necessary using imaging techniques.**
- **The current guidelines include a suggestion for stone analysis in individuals forming stones for the first time,**
- **as well as in some recurrent high-risk stone formers. Standard techniques for stone analysis include polarization microscopy on grain preparations.**

Int. J. Mol. Sci. **2024**, 25, 3075

LABORATORY EVALUATION SERUM CHEMISTRY



- **All kidney stone formers require the determination of full fasting serum chemistries :**

❑electrolytes, including calcium and phosphorus, renal function, uric acid and PTH.

❑Fasting glucose and a full lipid panel are also justified considering the high prevalence of diabetes and metabolic syndrome in stone formers.

A serum 25(OH)D measurement is helpful in patients with high or high-normal PTH levels and mild hypercalcemia to exclude vitamin D deficiency as a cause of the high PTH level

LABORATORY EVALUATION 24-hour urine samples

- Samples **should not** be obtained during an acute **UTI, obstruction, or following a recent urologic intervention**. To avoid misinterpretation, measurement should be obtained in a steady state **1 to 3 months after a last stone.**

e

During the collection, patients are advised to maintain their **usual diet and fluid intake**

Two measurements are recommended in order to obtain representative results

Am J Kidney Dis. 2016;68(6):973-985

LABORATORY EVALUATION 24-hour urine samples

- When the decision has been made to initiate medical kidney stone prevention by reversing a defined metabolic abnormality (eg, hypercalciuria), 24-hour urine samples should be repeated to monitor the response of therapy.

❖ We recommend repeating 24-hour urine testing at 6 to 12 weeks after a mdical or dietary intervention has been initiated and monitoring treatment goals at month 6 and then annually.

24-hour urine samples

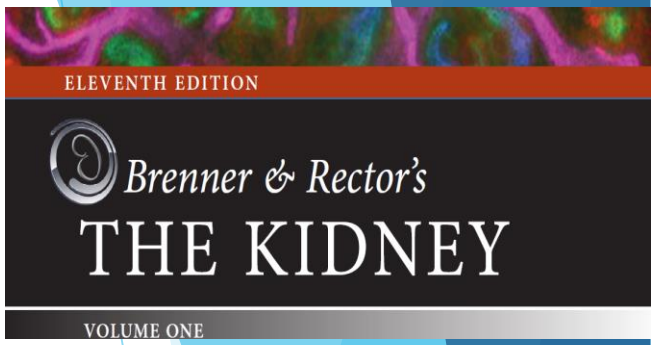
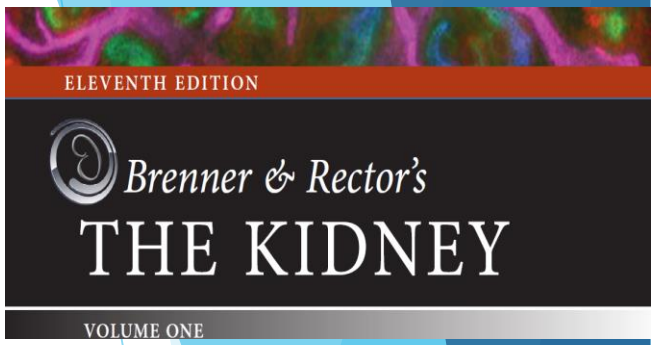


Table 38.8 Simplified Ambulatory Metabolic Evaluation and Interpretation of Urinary Parameters[a]

Random 24-Hour Urinary Profile	Expected Values (per day)	Interpretation
Total volume	≥2.5 L	Indicative of daily fluid intake (minus insensible losses); diminishes with low fluid intake, sweating, and diarrhea
pH	5.9–6.2	<5.5—increases risk of uric acid precipitation; commonly found in idiopathic uric acid stone patients, subjects with intestinal disease and diarrhea, and in those with intestinal bypass surgery >6.7— increases risk of calcium phosphate precipitation; commonly found in patients with dRTA, primary hyperparathyroidism, alkali, and carbonic anhydrase treatment >7.0–7.5— indicates urinary tract infection from urease-producing bacteria.
Creatinine	15–25 mg/kg body weight (0.13–0.22 mmol/kg body weight)	Assessment of completeness of collection: 15–20 mg/kg body weight (0.13–0.15 mmol/kg body weight) in females, 20–25 mg/kg body weight (0.15–0.22 mmol/kg body weight) in males; valid only in steady state of constant serum creatinine concentration with time
Sodium	100 mEq (100 mmol)	Reflects dietary sodium intake (minus extrarenal loss); much lower than dietary intake in diarrhea and with excessive sweating; high sodium intake is major cause of hypercalciuria
Potassium	40–60 mEq (100 mmol)	Reflects dietary potassium intake (minus extrarenal loss); much lower than dietary intake in diarrhea states; gauge of dietary alkali intake because most dietary potassium accompanied by organic anions

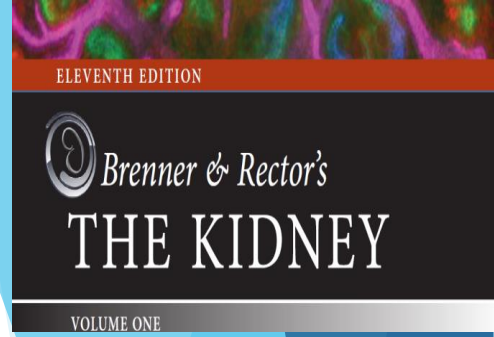
Brenner. Section V — Disorders of Kidney Structure and F unction

24-hour urine samples



		potassium accompanied by organic anions
Calcium	≤250–300 mg (≤6.24–7.49 mmol)	A higher value expected in males; in states of zero balance, urinary calcium excretion is net gut absorption minus net bone deposition; secondary causes should be ruled out before making the diagnosis of idiopathic hypercalciuria
Magnesium	30–120 mg (1.23–4.94 mmol)	Low urinary magnesium detected with low magnesium intake, intestinal malabsorption (small bowel disease), and following bariatric surgery; low magnesium may increase risk of calcium stones.

Brenner. Section V — Disorders of Kidney Structure and F unction

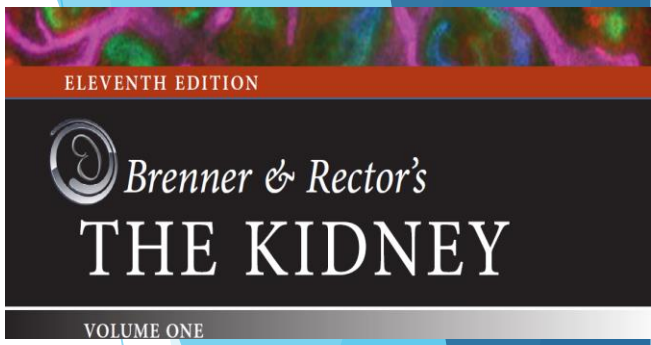


24-hour urine samples

		magnesium may increase risk of calcium stones.
Oxalate	≤45 mg (≤0.51 mmol)	Commonly encountered with intestinal disease with fat malabsorption, such as inflammatory bowel disease and following bariatric surgery; values >100 mg/day (1.14 mmol/day) suggest primary hyperoxaluria (PH); the diagnosis of PH I and PH II is further established with high urinary glycolate and L-glycerate levels.
Phosphorus	≤1100 mg (35.5 mmol)	Indicative of dietary organic and inorganic phosphorus intake and absorption; a higher excretion may increase the risk of calcium phosphate stone formation.
Uric acid	600–800 mg (3.57–4.76 mmol)	Hyperuricosuria is encountered with overproduction of endogenous uric acid or overindulgence of purine-rich foods such as red meat, poultry, and fish; mainly a risk factor for calcium oxalate stones when UpH is >5.5 but is a risk factor for uric acid stone when UpH < 5.5.

Brenner. Section V — Disorders of Kidney Structure and F unction

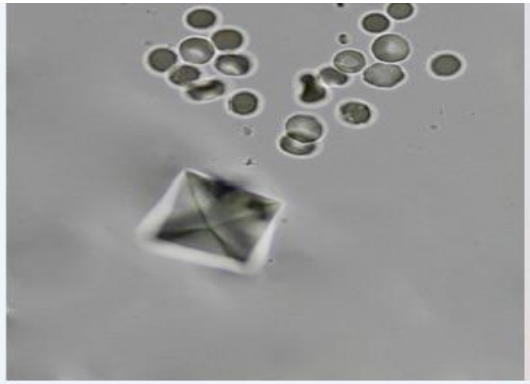
24-hour urine samples



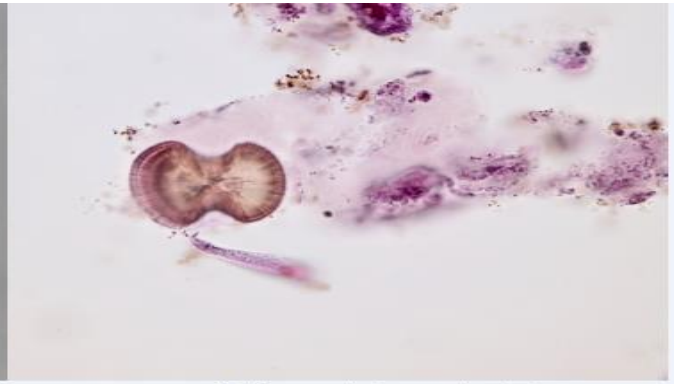
Sulfate	≤20 mmol	Sulfate is a marker of dietary acid intake (oxidation of sulfur-containing amino acids).
Citrate	≥320 mg (≥1.67 mmol)	Inhibitor of calcium stone formation; hypocitraturia is commonly encountered in metabolic acidosis, dRTA, chronic diarrhea, excessive protein ingestion, strenuous physical exercise, hypokalemia, intracellular acidosis, with carbonic anhydrase inhibitor drugs (e.g., acetazolamide, topiramate, zonisamide), but rarely with ACE inhibitors
Ammonium	30–40 mEq (30–40 mmol)	Ammonium is a major carrier of H^+ in the urine; its excretion corresponds with urinary sulfate (acid load); a higher ammonium-to-sulfate ratio indicates GI alkali loss.
Chloride	100 mEq (100 mmol)	Chloride varies with sodium intake.
Cystine	<30–60 mg (<0.12–0.25 mmol)	Cystine has a limited urinary solubility, at 250 mg/L.

Brenner. Section V — Disorders of Kidney Structure and F unction

calcium oxalate



Calcium oxalate dihydrate



Calcium oxalate monohydrate

Predisposing Factors

- Low urine volume
  - Inadequate intake
  - Extrarenal fluid losses (diarrhea, sweating)
- Hypocitraturia
  - Metabolic acidosis
  - Potassium depletion
  - Excess animal protein intake
- Hypercalciuria
  - Idiopathic hypercalciuria
  - High sodium intake
  - Primary hyperparathyroidism
  - Vitamin D excess states
  - Osteolytic conditions
  - Metabolic acidosis
  - Excess simple sugar consumption
  - High animal protein intake
  - Dent's disease
  - Thick ascending limb defects (Bartter syndrome, familial hypomagnesemia with hypercalciuria)
  - Cadmium toxicity
- Hyperoxaluria
  - Fat malabsorption
  - Dietary excess
  - Primary hyperoxaluria
  - Reduced colonic *Oxalobacter*
  - Vitamin C excess
  - Excess glycine intake
- Medullary sponge kidney
- Polycystic kidney disease

Hypercalciuria

- **High urine calcium** is the **most common** metabolic abnormality found in recurrent calcium stoneformers, being present in **30% to 60%** of such individuals.

- The definition of hypercalciuria in the context of kidney stones is controversial. Some define it as a 24-hour urinary calcium excretion that exceeds **200-300 mg/day or 4 mg/ kg/day (0.1 mmol/kg/day)**.

In a **cross-sectional study of 3,350 patients**, the risk of stone formation progressively increased with increasing urinary calcium excretion rates above **150 mg/day (3.75 mmol/day)**.

Mechanisms Hypercalciuria

- **Bone resorption** as a sole cause of hypercalciuria can occur with hyperparathyroidism, and cancer.

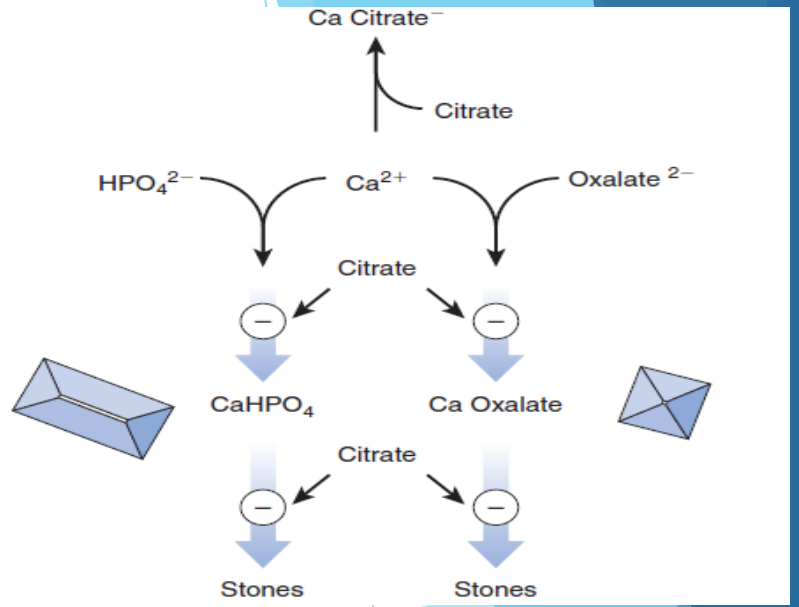
- **Dietary factors** can also contribute to hypercalciuria:
  - **High sodium intake** results in decreased proximal tubular calcium reabsorption.
  - **High animal protein intake** can enhance urinary calcium excretion as well, perhaps through the acid loading that it provokes.
  - **Excess simple sugar intake** has also beenb associated with hypercalciuria via unclear mechanisms.

Mechanisms Hypercalciuria

- **idiopathic hypercalciuria** there are varying degrees of excessive dietary calcium absorption and bone resorption at play as well as variable defects in renal tubular calcium conservation.This **syndrome is associated with loss of bone mineral and osteoporosise**

- **Increased gut absorption** as the sole mechanism for hypercalciuria is uncommon but can be seen with excessive **exogenous vitamin D supplementation, or diseases of calcitriol excess such as sarcoidosis**

Hypocitraturia



Mechanisms. ▶

- **Citrate is an endogenous inhibitor of calcium stone for**

- **Citrate complexes with calcium to create a soluble salt—limiting the binding of calcium with oxalate or phosphate—and directly inhibits crystal aggregation.**

- **Hypocitraturia, defined as citrate excretion of <320 mg/day, is encountered in 20%-60% of cases of calcium nephrolithiasis.**

Am J Kidney Dis. 2016;68(6):973-985

Hypocitraturia

- **The major determinant of urinary citrate excretion is acid-base balance. Metabolic acidosis increases proximal tubule citrate reabsorption and metabolism, leading to decreased urinary excretion.**

- **Clinical conditions associated with hypocitraturia include:**
  - **CKD**
  - **chronic diarrhea**
  - **RTA (genetic or drug-induced)**
  - **high dietary animal protein intake**
  - **potassium depletion.**

Hypocitraturia

Table 38.2 Clinical Conditions Associated With Hypocitraturia

Low Extracellular Fluid pH	Normal or High Extracellular Fluid pH
Overproduction acidosis • Chronic diarrhea • Exercise-induced lactic acidosis	Potassium deficiency
Underexcretion acidosis • Congenital or acquired distal RTA • Acetazolamide, topiramate	Angiotensin II–related • ACE inhibitors • Salt excess Excess dietary protein

ACE, Angiotensin-converting enzyme; *RTA*, renal tubular acidosis.

Hypocitraturia: Pathophysiology and Medical Management

Jack M. Zuckerman, BS, Dean G. Assimos, MD

Department of Urology, Wake Forest University School of Medicine, Winston-Salem, NC

Low urinary citrate excretion is a known risk factor for the development of kidney stones. Citrate inhibits stone formation by complexing with calcium in the urine, inhibiting spontaneous nucleation, and preventing growth and agglomeration of crystals. Hypocitraturia is a common metabolic abnormality found in 20% to 60% of stone formers. It is most commonly idiopathic in origin but may be caused by distal renal tubular acidosis, hypokalemia, bowel dysfunction, and a high-protein, low-alkali diet. Genetic factors, medications, and other comorbid disorders also play a role. Hypocitraturia should be managed through a combination of dietary modifications, oral alkali, and possibly lemonade or other citrus juice–based therapy. This review concerns the pathophysiology of hypocitraturia and the management of stone formers afflicted with this abnormality.

[Rev Urol. *2009;11(3):134-144 doi:10.3909/riu0424*]

Etiologies of Hypocitraturia

- **Acid–base balance**
  - Renal tubular acidosis
  - Other systemic acidosis
  - Diarrhea/malabsorption
  - Exercise
- **Hypokalemia**
- **Diet**
  - Dietary animal protein
  - High sodium intake
  - Ketosis promoting diets
  - Low fruit/vegetable intake
  - Starvation
- **Medications**
  - ACE inhibitors
  - Acetazolamide
  - Amiloride
  - Calcitonin
  - Calcium
  - Ethacrynic acid
  - Lithium
  - Topiramate
  - Vitamin D
- **Genetic influence**
  - VDR polymorphisms
  - NaDC–1 gene polymorphisms
- **Other associated disorders**
  - Renal insufficiency
  - Hyperaldosteronism
  - Type I glycogen storage disease
- **Hypocalciuria, hypomagnesuria**
- **Precursor compounds**
- **Metabolic inhibitors**

ACE, angiotensin–converting enzyme; VDR, vitamin D receptor

Hyperoxaluria

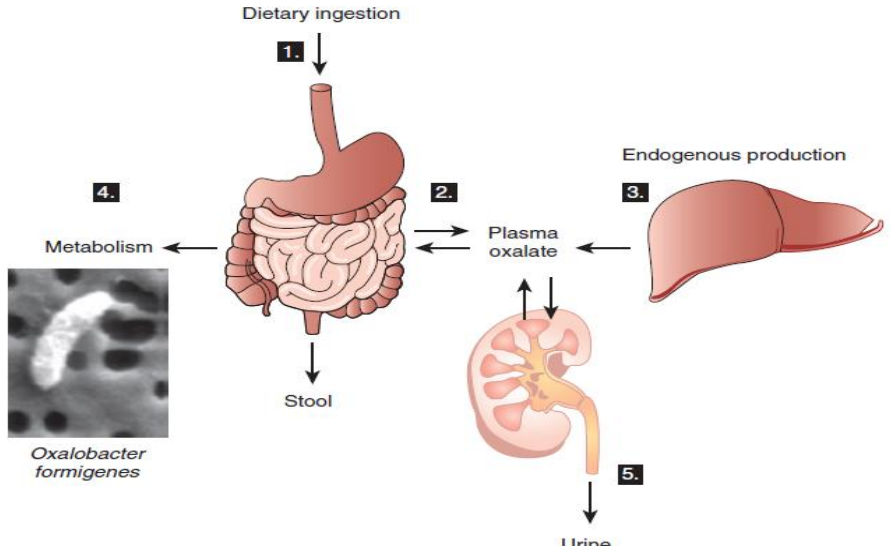
Mechanisms:

- **Hyperoxaluria, seen in 10%-50% of calcium stone-formers, increases calcium oxalate supersaturation to promote stone formation.**

- **Normal urinary oxalate excretion is < 40 mg/day .**

- **The mechanisms of hyperoxaluria include :**

- **overproduction**
- **excessive intestinal oxalate absorption**.



Am J Kidney Dis. 2016;68(6):973-985

Hyperoxaluria

- The **primary hyperoxalurias** are autosomal recessive disorders of overproduction arising from the shunting of **glyoxylate to oxalate**.

- **Type 1 primary hyperoxaluria**, caused by a defect in alanine glyoxylate aminotransferase, often presents in childhood with **nephrolithiasis, nephrocalcinosis, and kidney failure. Cardiac and vascular oxalate deposition occur as the development of kidney failure impairs oxalate elimination.**

- **Type 2 and type 3 primary hyperoxalurias** are less prevalent and follow a milder course

  - **24-hour urine oxalate of >80 mg/day without an alternate explanation should prompt further evaluation by genetic testing**.

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Hyperoxaluria

- **Ingestion of oxalate precursors such as high-dose vitamin C.**

- **A unique form of "enteric hyperoxaluria" can occur in patients with fat malabsorption: fatty acids bind to calcium in the intestinal lumen, displacing oxalate and enhancing its bioavailability. Common clinical scenarios include :**
  - **pancreatic exocrine insufficiency**
  - **inflammatory bowel diseases**
  - **bariatric surgeries**

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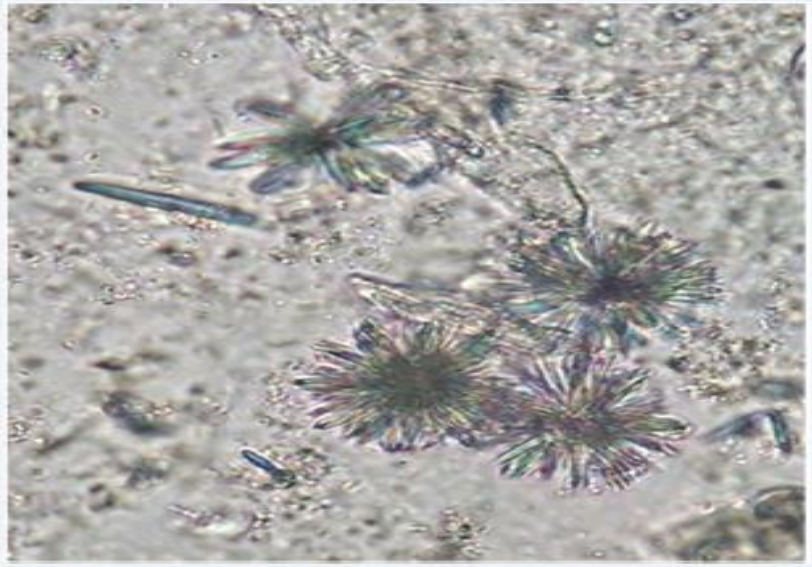
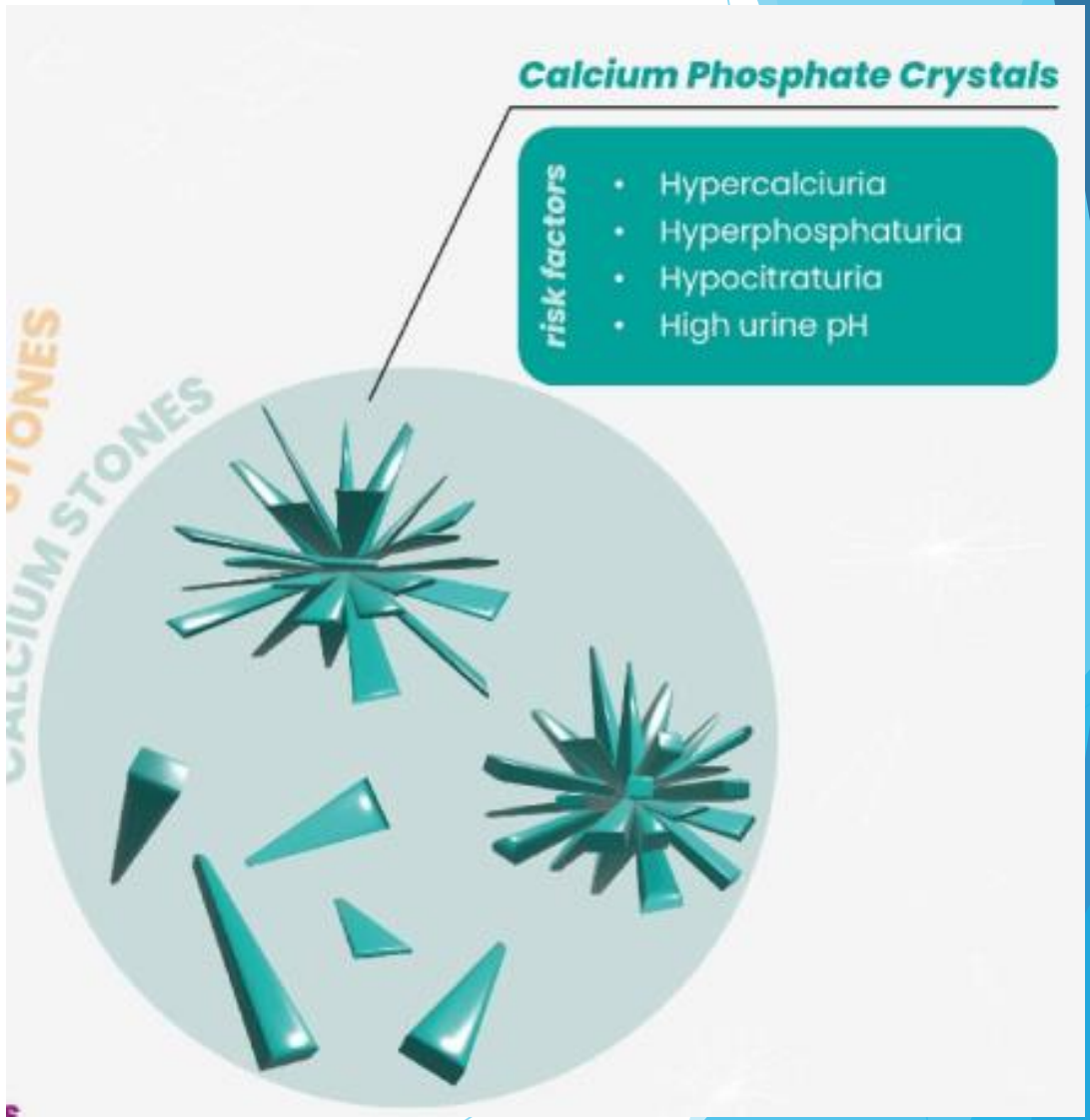
Calcium phosphat

Box 2. Characteristic Crystalluria, Predisposing Factors, and Chronic Management Principles for Calcium Phosphate Nephrolithiasis

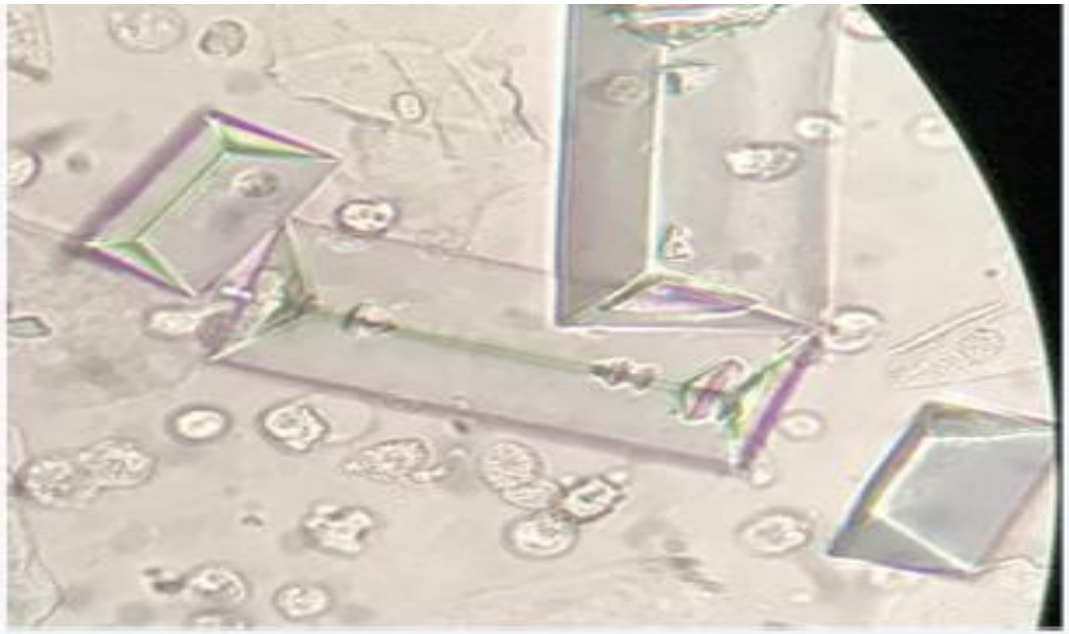


Predisposing Factors

- Higher urine pH
  - Secretory defect distal RTA (genetic or acquired, as occurs in Sjögren's syndrome)
  - "Incomplete" RTA
  - Carbonic anhydrase inhibitors (eg, acetazolamide, topiramate, or zonisamide)
  - Excess alkali administration, including potassium citrate
- Low urine volume[a]
- Hypocitraturia[a]
- Hypercalciuria[a]
- Medullary sponge kidney



Struvite Stones (Magnesium Ammonium Phosphate or Triple Phosphate)



Predisposing Factors

- Urinary tract infection with urease expressing bacteria resulting in urinary alkalinization and excess ammonium production
- Low urine volume[a]

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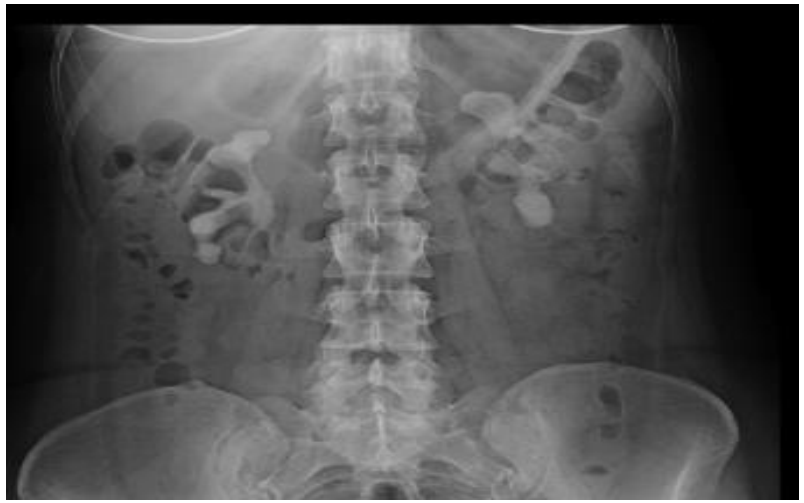
Struvite Stones (Magnesium AmmoniumPhosphate or Triple Phosphate)

- **Struvite stones or triple phosphate stones comprise about 1% of all stones.**
- **Composed of magnesium ammonium phosphate and calcium carbonate-apatite, these rapidly growing stones can fill the entire renal pelvis.**

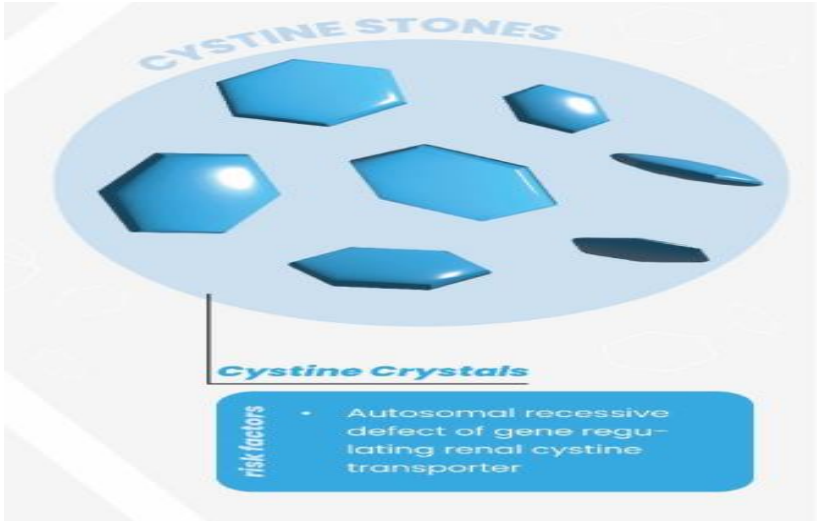
- **These result from chronic urinary tract infection by urease-producing organisms such as Proteus. Urea isn converted into ammonium and bicarbonate, increasing the urine pH and thus lowering the solubility of triple phosphate.**



Brenner. Section V — Disorders of Kidney Structure and F unction

Cystine stone

- Cystine stones are found in 1% to 2% of kidney stone patients, with a higher percentage among children .
- The first symptomatic cystine stone usually occurs between ages 2 to 40 years (median age of onset: girls, 12 years; boys, 15 years). The clinical presentation includes flank pain and hematuria.
- Urinalysis demonstrates pathognomonic hexagonal cystine crystals in one-quarter of patients



Am J Kidney Dis. 2016;68(6):973-985

Cystine stone

- **Cystine, the homodimer of the amino acid cysteine, is poorly soluble in urine at typical pH, forming cystine stones when in excess.**

- **Patients with cystinuria excrete > 250 mg/day of cystine (normal < 30 mg/day).**

❖ **Cystinuria should be suspected in any patient presenting with early onset, recurring kidney stones.**

Cystine stone

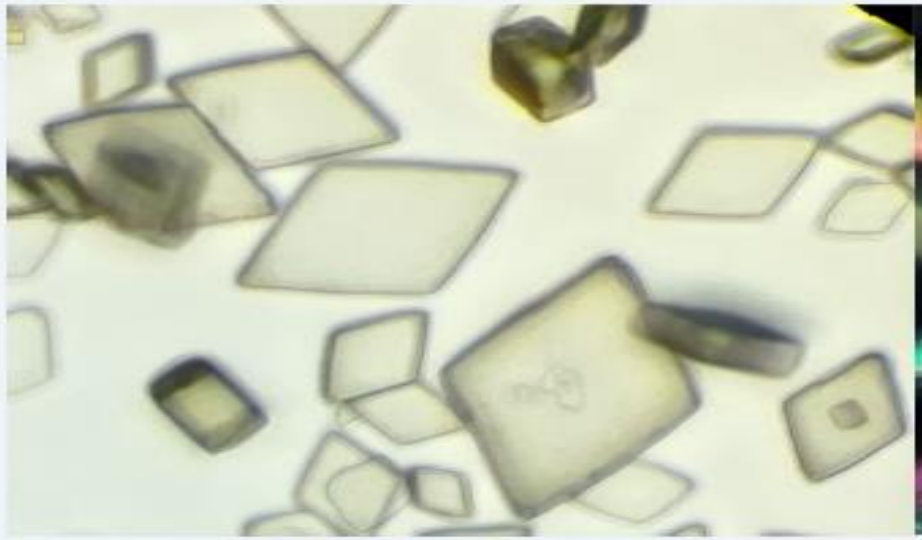
- The **cyanide-nitroprusside screen** of urine represents a qualitative screening test that detects urinary cystine concentrations . **75 mg/L**. However, specificity is limited because **false-positive** results can be obtained in patients with **Fanconi syndrome** or **ingesting ampicillin** medications.

❖ Patients with confirmed cystine stones, urinary cystine crystals, or a positive cyanide-nitroprusside test result

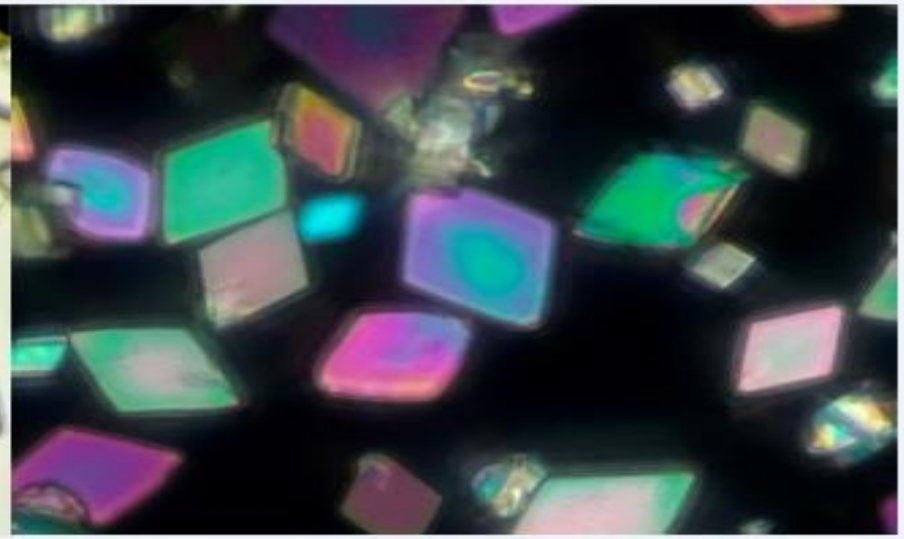
❖ should undergo **24-hour urine collection** to quantify cystine excretion.

Uric Acid Stones

Box 3. Characteristic Crystalluria, Predisposing Factors, and Chronic Management Principles for Uric Acid Nephrolithiasis



Standard lighting



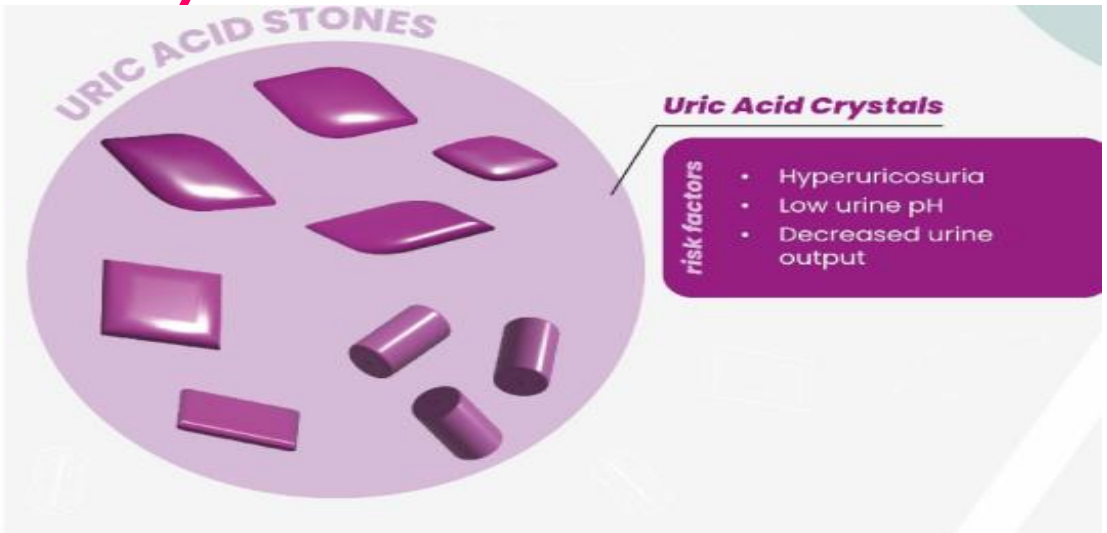
Light

Predisposing Factors

- Markedly acidic urine
  - Metabolic syndrome
  - High animal protein intake
  - Metabolic acidosis
  - Potassium excess
- Low urine volume[a]
- Polycystic kidney disease
- Hyperuricosuria
- Lesch-Nyhan disease/partial HGPRT deficiency
- Excess purine intake or high cell turnover
- Glycogen storage disease

Uric Acid Stones

- **factors in the pathogenesis of uric acid stones**:
- **low urine pH (<5.5)**
- **low urine volume**
- **hyperuricosuria (defined a uric acid excretion > 800 mg/d in men and > 750 mg/ day in women)**



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Uric Acid Stones

- **A diet high in animal protein** and **impaired renal ammoniagenesis** **are 2 common causes of acidic urine in uric acid stone-formers.**

- **Impaired ammoniagenesis** **has been described in patients with type 2 diabetes mellitus, obesity, and the metabolic syndrome.**

- **Gout almost doubles the risk of nephrolithiasis** **but not necessarily uric acid stones.**

- **Hyperuricosuria** **but may be seen in conditions with high cell turnover, such as myeloproliferative disorders, and genetic disorders**

Uric Acid Stones

Table 38.4 Causes and Mechanisms for Uric Acid Nephrolithiasis

Causative Factors	Low Urine Volume	Low Urinary pH	Hyperuricosuria
Acquired			
• Diarrhea	+	+	+
• Myeloproliferative			+
• High animal protein		+	+
• Uricosuric drugs			+
• Primary gout		+	+
• Metabolic syndrome		+	

Brenner. Section V — Disorders of Kidney Structure and F unction

Uric Acid Stones

- Certain uricosuric drugs have been shown to increase UA excretion, which may increase the risk of UA stone formation. such as :

- **high-dose salicylates**
- **Probenecid**
- **radiocontrast agents**
- **losartan**