



Urolithiasis

5th year medical students' curriculum
Section of urology
Department of Special Surgery
Faculty of Medicine
Mut'ah University

Dr. Fadi Sawaqed
Assistant Professor of Urology
Functional & Neuro-Urology

Urinary calculi are the third most common affliction of the urinary tract, exceeded only by urinary tract infections and pathologic conditions of the prostate.

Nephrolithiasis has a high worldwide prevalence with rates which range from 7 to 13% in North America, 5 to 9% in Europe, and 1 to 5% in Asia according to recent reports nephrolithiasis has been considered to be a male-predominant disease, a reanalysis over the time period 2007–2012 showed no difference in stone prevalence between men and women under 50 years of age.

Nephrolithiasis have been linked to systemic conditions such as obesity, diabetes, and metabolic syndrome. Weather related variables such as increasing ambient temperature and sunlight exposure constitute risk factors for nephrolithiasis as well

| Risk factors for urolithiasis from patient history | |
|--|--|
| Medical history | Primary hyperparathyroidism |
| | Renal Tubular Acidosis (RTA) Type 1 |
| | Gout |
| | Metabolic syndrome/diabetes mellitus Type 2 |
| | Obesity |
| | Inflammatory bowel disease |
| | Chronic diarrhea/malabsorptive gastrointestinal disorder |
| | Osteoporosis |
| | Spina Bifida or Other Neurologic Disorder |
| | Personal or family history of nephrolithiasis |
| | Recurrent urinary tract infections |
| | Surgical history |
| Gastrointestinal reconstruction | |
| Urinary diversion | |
| Prior urologic surgery | |
| Dietary history | Low fluid intake |
| | High salt intake |
| | High animal protein intake |
| | Low fruit and vegetable intake |
| | Very high or very low calcium intake |
| | High oxalate intake |
| | Special Diets (i.e. Low Carbohydrate/High Protein) |



Stone formation requires supersaturated urine. Supersaturation depends on urinary pH, ionic strength, solute concentration, and complexation.

The role of solute concentrations is clear: The greater the concentration of two ions, the more likely they are to precipitate.

As ion concentrations increase, their activity product reaches a specific point termed the **solubility product (K_{sp})**. Concentrations above this point are metastable and are capable of initiating crystal growth and heterogeneous nucleation. As solutions become more concentrated, the activity product eventually reaches the formation product (K_{fp}). Supersaturation levels beyond this point are unstable, and spontaneous homogeneous nucleation may occur. Complexation influences the availability of specific ions. For instance, sodium complexes with oxalate and decreases its free ionic form, while sulfates can complex with calcium. Crystal formation is modified by a variety of other substances found in the urinary tract, including magnesium, citrate, pyrophosphate, and a variety of trace metals. These inhibitors may act at the active crystal growth sites or as inhibitors in solution (as with citrate).

Crystal Component

Multiple steps are involved in crystal formation, including nucleation, growth, and aggregation. Nucleation initiates the stone process and may be induced by a variety of substances, including proteinaceous matrix, crystals, foreign bodies, and other particulate tissues.

Matrix Component

The amount of the noncrystalline, matrix component of urinary stones varies with stone type, commonly ranging from 2% to 10% by weight. It is composed predominantly of protein, with small amounts of hexose and hexosamine.

Stone Types

Stones may be classified according to composition, X-ray appearance, size, and shape.

Stone classification is traditionally divided into two groups: calcium based and non-calcium based stones

| Stone type | | Frequency (%) |
|-------------------|-------------------------------|---------------|
| Calcium (80%) | Calcium oxalate monohydrate | 35–55 |
| | Calcium oxalate dihydrate | 20–30 |
| | Calcium phosphate | 10–15 |
| Non-calcium (20%) | Struvite | 5–10 |
| | Uric acid | 5–10 |
| | Cystine | 1–2 |
| | Urate (Ammonium acid, Sodium) | <1 |
| | Xanthine | <1 |
| | Drug-induced | <1 |



Radiodensity on X-ray

Three broad categories of stones are described, based on their X-ray appearance. This gives some indication of the likely stone composition and helps, to some extent, to determine treatment options. However, in only 40% of cases is the stone composition correctly identified from visual estimation of the radiodensity on plain X-ray.

Radio-opaque

Opacity implies the presence of substantial amounts of calcium within the stone. Calcium phosphate stones are the most radio-dense stones, being almost as dense as bone. Calcium oxalate stones are slightly less radio-dense.

Relatively radiolucent on plain X-ray

Cystine stones are relatively radio-dense because they contain Sulphur. Magnesium ammonium phosphate (struvite) stones are less radio-dense than calcium-containing stones.

Completely radiolucent on plain X-ray

Uric acid, triamterene, xanthine, indinavir (cannot be seen even on CTU, hence if suspected, confirm by IVU).

Calcium Oxalate Stones

Metabolic defects which have been associated with calcium oxalate stone formation include hypercalciuria (absorptive and renal), hypocitraturia, hyperuricosuria, hyperoxaluria, gouty diathesis (low urine pH), and low urine volume.

Calcium Phosphate Stones

Calcium phosphate stone formation, in contrast to calcium oxalate, is more likely to be associated with a specific metabolic disorder such as distal renal tubular acidosis (RTA 1) or primary hyperparathyroidism

Uric Acid

At a urine pH of less than 5.35, uric acid exists predominantly in its free form which has exceedingly poor solubility in urine and therefore crystallizes to form uric acid stones. Low urine volume and only occasionally hyperuricosuria can contribute to the development of uric acid stones, but these factors play a secondary role to low urine pH

Other medical conditions which may cause hyperuricosuria include gout, certain myeloproliferative and hematologic disorders with rapid cell turnover, and rarely hereditary

errors in purine metabolism or urate transport.



Infectious Urolithiasis

Infectious stones are composed of magnesium ammonium phosphate, more commonly referred to as struvite, which may be present purely or in mixed composition with other stone types, often carbonate apatite and hydroxyapatite

These calculi occur secondary to urinary tract infection by urease-splitting bacteria. Common uropathogenic organisms associated with urease production include *Proteus*, *Klebsiella*, *Providencia*, *Morganella*, *Corynebacterium*, and *Ureaplasma* species.

Bacterial urease catalyzes the conversion of urea to ammonia and carbon dioxide, which promotes the formation of alkaline urine (pH > 7.2) and creates a milieu conducive to the formation of struvite or mixed struvite stone

Cystine Urolithiasis

Cystinuria is a hereditary condition, usually with an autosomal recessive inheritance pattern, which is characterized by defective resorption of the dibasic amino acids cystine, ornithine, lysine, and arginine within the proximal renal tubule

Xanthine—Xanthine stones are secondary to a congenital deficiency of xanthine dehydrogenase. This enzyme normally catalyzes the oxidation of hypoxanthine to xanthine and of xanthine to uric acid. It is of interest that allopurinol, used to treat hyperuricosuric calcium nephrolithiasis and uric acid lithiasis, produces iatrogenic xanthinuria. Blood and urine levels of uric acid are lowered, and hypoxanthine and xanthine levels are increased; however, there are no case reports of xanthine stone formation resulting from allopurinol treatment.

Medication-Induced Stones

| Stone-inducing medications | | |
|----------------------------|--------------------------|---|
| Medications | Direct stone promotion | |
| | | Indinivir (and other antiretroviral protease inhibitors) |
| | | Ciprofloxacin |
| | | Triamterene |
| | | Silicates |
| | | Guafenesin/Ephedrine |
| | | Sulfa Medications |
| | Indirect stone promotion | Carbonic anhydrase inhibitors (Acetazolamide, Topiramate, Zonisamide) |
| | | Long term loop diuretics |
| | | Chronic corticosteroid use |
| | | Vitamin D and Calcium Supplements |
| | | Vitamin C Supplements |
| | | Chemotherapy |



Symptoms and Signs at Presentation

A. Pain

Upper tract urinary stones frequently cause pain when passing down the ureter. The character of the pain depends on the location. Calculi small enough to venture down the ureter usually have difficulty passing through the ureteropelvic junction, or entering the bladder at the ureterovesical junction

Renal colic and noncolicky renal pain are the two types of pain originating from the kidney. Renal colic usually is caused by stretching of the collecting system or ureter, whereas noncolicky renal pain is caused by distention of the renal capsule. These symptoms may overlap, making a clinical differentiation difficult or impossible. Urinary obstruction is the main mechanism responsible for renal colic.

Renal colic does not always wax and wane or come in waves like intestinal or biliary colic but may be relatively constant. Renal colic implies an intraluminal origin. Patients with renal calculi have pain primarily due to urinary obstruction.

Local mechanisms such as inflammation, edema, hyperperistalsis, and mucosal irritation may contribute to the perception of pain in patients with renal calculi. In the ureter, however, local pain is referred to the distribution of the ilioinguinal nerve and the genital branch of the genitofemoral nerve, whereas pain from obstruction is referred to the same areas as for collecting system calculi (flank and costovertebral angle), thereby allowing discrimination.

Ureteropelvic stone: Severe costovertebral angle pain from capsular and pelvic distention; acute renal and urethral pain from hyperperistalsis of smooth muscle of calyces, pelvis, and ureter, with pain radiating along the course of the ureter (and into the testicle, since the nerve supply to the kidney and testis is the same). The testis is hypersensitive.

Midureteral stone: Same as described earlier but with more pain in the lower abdominal quadrant.

Low ureteral stone: Same as described earlier, with pain radiating into bladder, vulva, or scrotum. The scrotal wall is hyperesthetic. Testicular sensitivity is absent. When the stone approaches the bladder, urgency and frequency with burning on urination develop as a result of inflammation of the bladder wall around the ureteral orifice.

Most urinary stones present with the acute onset of pain due to acute obstruction and distention of the upper urinary tract. The severity and location of the pain can vary from patient to patient relative to stone size, stone location, degree of obstruction, acuity of obstruction, and variation in individual anatomy (eg, intrarenal vs extrarenal pelvis). The stone burden does not correlate with the severity of the symptoms. Small ureteral stones frequently present with severe pain, whereas large staghorn configured calculi may present with a dull ache or flank discomfort.

The pain frequently is abrupt in onset and severe and may awaken a patient from sleep. The severity of the pain is worsened by the unexpected nature of its onset. Patients



frequently move constantly into unusual positions while attempting to relieve the pain. This movement contrasts with the lack of movement of someone with peritoneal signs; such a patient lies in a stationary position.

B. Hematuria

A complete urinalysis helps confirm the diagnosis of a urinary stone by assessing for hematuria and crystalluria and documenting urinary pH. Patients frequently admit to intermittent gross hematuria or occasional tea-colored urine (old blood). Most patients will have at least microhematuria. Rarely (in 10–15% of cases), complete ureteral obstruction presents without microhematuria.

C. Infection

Magnesium ammonium phosphate (struvite) stones are synonymous with infection stones. They are commonly associated with *Proteus*, *Pseudomonas*, *Providencia*, *Klebsiella*, and *Staphylococcus* infections. They are rarely, if ever, associated with *E. coli* infections. Calcium phosphate stones are the second variety of stones associated with infections. Calcium phosphate stones with a urine pH of <6.4 are frequently referred to as **brushite stones**, whereas infectious apatite stones have a urinary pH of >6.4.

All stones, however, may be associated with infections secondary to obstruction and stasis proximal to the offending calculus. Culture-directed antibiotics should be administered before elective intervention.

D. Associated Fever

The association of urinary stones with fever is a relative medical emergency. Signs of clinical sepsis are variable and include fever, tachycardia, hypotension, and cutaneous vasodilation. Costovertebral angle tenderness may be marked with acute upper tract obstruction

E. Nausea and Vomiting

Upper tract obstruction is frequently associated with nausea and vomiting. Intravenous fluids are required to restore a euvolemic state. Intravenous fluids should not be used to force a diuresis while attempting to push a ureteral stone down the ureter. Effective ureteral peristalsis requires coaptation of the ureteral walls and is most effective in a euvolemic state.

Evaluation

A. Differential Diagnosis

Urinary stones can mimic other retroperitoneal and peritoneal pathologic states. A full differential diagnosis of the acute abdomen should be made, including acute appendicitis; ectopic and unrecognized pregnancies; ovarian pathologic conditions including twisted



ovarian cysts, testicular torsion, diverticular disease, bowel obstruction, and biliary stones with and without obstruction; peptic ulcer disease; acute renal artery embolism; and abdominal aortic aneurysm—to mention only a few. Peritoneal signs should be sought during physical examination.

B. History

A proper evaluation requires a thorough medical history. The nature of the pain should be evaluated, including its onset; character; potential radiation; activities that exacerbate or ease the pain; associated nausea, vomiting, or gross hematuria; and a history of similar pain. Patients with previous stones frequently have had similar types of pain in the past, but not always.

C. Risk Factors

1. Crystalluria—Crystalluria is a risk factor for stones. Stone formers, especially those with calcium oxalate stones, frequently excrete more calcium oxalate crystals, and those crystals are larger than normal ($>12\ \mu\text{m}$). The rate of stone formation is proportional to the percentage of large crystals and crystal aggregates.

2. Socioeconomic factors—Renal stones are more common in affluent, industrialized countries. Immigrants from less industrialized nations gradually increase their stone incidence and eventually match that of the indigenous population. Use of soft water does not decrease the incidence of urinary stones.

3. Diet

Vegetarians may have a decreased incidence of urinary stones. High sodium intake is associated with increased urinary sodium, calcium, and pH and a decreased excretion of citrate; this increases the likelihood of calcium salt crystallization because the urinary saturation of monosodium urate and calcium phosphate (brushite) is increased. Fluid intake and urine output may affect urinary stone disease. The average daily urinary output in stone formers is 1.6 L.

4. Occupation—Occupation can have an impact on the incidence of urinary stones. Physicians and other white-collar workers have an increased incidence of stones compared with manual laborers. This finding may be related to differences in diet but also may be related to physical activity; physical activity may agitate urine and dislodge crystal aggregates. Individuals exposed to high temperatures may develop higher concentrations of solutes owing to dehydration, which may have an impact on the incidence of stones.

5. Climate—Individuals living in hot climates are prone to dehydration, which results in an increased incidence of urinary stones, especially uric acid calculi. Although heat may cause a higher fluid intake, sweat loss results in lowered voided volumes. Hot climates usually expose people to more ultraviolet light, increasing vitamin D₃ production. Increased calcium and oxalate excretion have been correlated with increased exposure time to sunlight.



6. Family history—A family history of urinary stones is associated with an increased incidence of renal calculi. A patient with stones is twice as likely as a stone-free cohort to have at least one first-degree relative with renal stones (30% vs 15%). Those with a family history of stones have an increased incidence of multiple and early recurrences.

Large studies of identical twins have found that >50% of stones have a significant genetic component. A significant association between urinary stones and cardiovascular disease has been confirmed in many studies.

7. Medications—A thorough history of medications taken may provide valuable insight into the cause of urinary calculi. The antihypertensive medication triamterene is found as a component of several medications, including Dyazide, and has been associated with urinary calculi with increasing frequency. Long-term use of antacids containing silica has been associated with the development of silicate stones. Carbonic anhydrase inhibitors may be associated with urinary stone disease (10–20% incidence). Protease inhibitors in immunocompromised patients are associated with radiolucent calculi

D. Physical Examination

The patient presenting with acute renal colic typically is in severe pain, often attempting to find relief in multiple, frequently bizarre, positions. This fact helps differentiate patients with this condition from those with peritonitis, who are afraid to move. Systemic components of renal colic may be obvious, with tachycardia, sweating, and nausea often prominent. Costovertebral angle tenderness may be apparent. An abdominal mass may be palpable in patients with longstanding obstructive urinary calculi and severe hydronephrosis.

Fever, hypotension, and cutaneous vasodilation may be apparent in patients with urosepsis.

Referred pain may be similar owing to common afferent neural pathways.

Testicular torsion referred to the ipsilateral side

Intestinal ileus may be associated with renal colic or other intraperitoneal or retroperitoneal processes.

Bladder palpation should be performed because urinary retention may present with pain similar to that due to renal colic.

Incarcerated inguinal hernias, epididymitis, orchitis, and female pelvic pathologic states may mimic urinary stone disease.

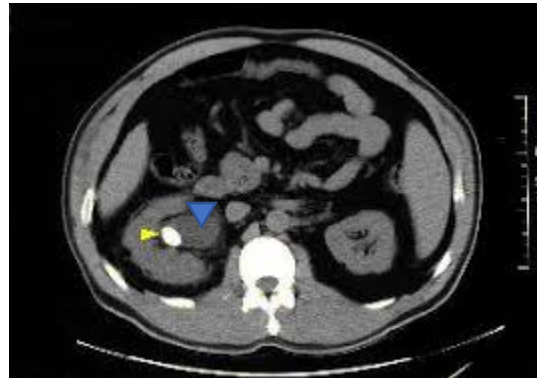
A rectal examination helps exclude other pathologic conditions.

E. Radiologic Investigations



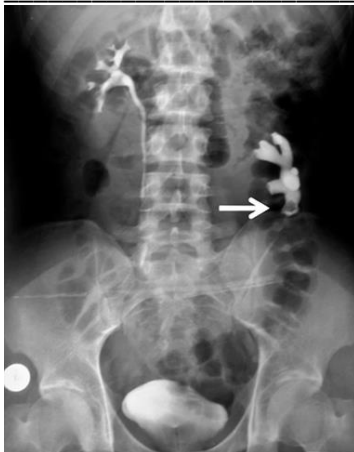
1. Computed tomography—Noncontrast spiral CT scans are now the imaging modality of choice in patients presenting with acute renal colic. It is rapid, and is operator-independent

Uric acid stones are visualized no differently from calcium oxalate stones. Matrix calculi have adequate amounts of calcium to be visualized easily by CT scan. Hounsfield unit measurement can help predict stone type and hardness. Hard calcium oxalate monohydrate stones, for example, frequently have a HU of >1000, whereas uric acid stones frequently have HU < 500



2. Intravenous pyelography—An IVP can simultaneously document nephrolithiasis and upper tract anatomy. It is rarely used today with the widespread availability of CT scanners and ultrasound machines. Extraosseous calcifications on radiographs may be erroneously assumed to be urinary tract calculi





3. The ultrasound examination should be directed by notation of suspicious areas seen on a KUB film; it is, however, operator-dependent. The distal ureter is easily visualized through the acoustic window of a full bladder. Ultrasound imaging by a trained emergency physician, or by a radiologist appears just as useful when compared to CT imaging for the acute diagnosis of urinary stones.





4. KUB films—A KUB film and renal ultrasound may be as effective as a CT scan in establishing a diagnosis.



Intervention

A. Conservative Observation

Most ureteral calculi pass and do not require intervention. Spontaneous passage depends on stone size, shape, location, and associated ureteral edema (which is likely to depend on the length of time that a stone has not progressed). Ureteral calculi 4–5 mm in size have a 40–50% chance of spontaneous passage.

Medical expulsive therapy (MET) helps facilitate spontaneous passage of ureteral stones. An α -blocker, nonsteroidal anti-inflammatory medications with or without low-dose steroids has been studied to optimize spontaneous ureteral stone passage;

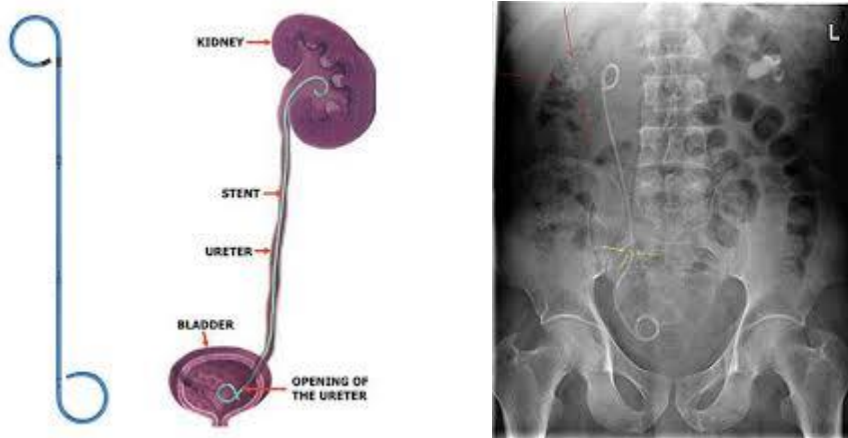
B. Dissolution Agents

Oral alkalinizing agents used for uric acid dissolution include sodium or potassium bicarbonate and potassium citrate.

Struvite stone dissolution requires acidification and may be achieved successfully with Suby's G solution and hemiacidrin (Renacidin).

C. Relief from Obstruction

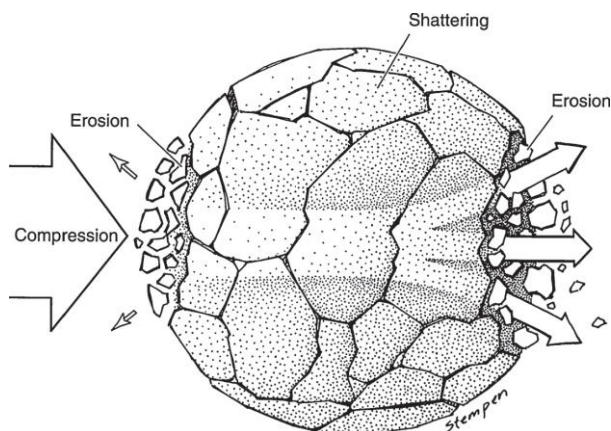
A patient with obstructive urinary calculi with fever and infected urine requires emergent drainage. Retrograde pyelography to define upper tract anatomy is logically followed by retrograde placement of a double-J ureteral stent. On occasion, such catheters are unable to bypass the offending calculus or may perforate the ureter. In such situations, one must be prepared to place a percutaneous nephrostomy tube.



D. Extracorporeal Shockwave Lithotripsy

Extracorporeal SWL has revolutionized the treatment of urinary stones.

All shockwaves, despite their source, are capable of fragmenting stones when focused. Fragmentation is achieved by erosion and shattering



Patients with large renal pelvic calculi (1.5 cm) have a stone-free rate at 3 months approximating 75%, in comparison with those with a similar stone in a lower calyx, which approximates only 35%. Patients with small renal pelvic stones (<1.5 cm) have approximately a 90% stone-free rate in comparison with those with similar stones in a middle calyx (approximately 75%) or lower calyx (approximately 50%).

75% of patients with renal calculi treated with SWL become stone-free in 3 months. As stones increase in size, stone-free rates decrease, more so in the lower and middle calyces than in superior calyceal and renal pelvic locations

E. Ureteroscopic Stone Extraction

Ureteroscopic stone extraction is highly efficacious for lower ureteral calculi. The use of small-caliber ureteroscopes and the advent of balloon dilation or ureteral access sheaths have increased stone-free rates dramatically. Even relatively large-caliber endoscopes without balloon dilation are effective in lower ureteral stone retrieval



It is likely that disposable ureteroscopes will become more common to ensure a functional, clean, and available instrument. Stone-free rates approach 95–100% and are dependent on stone burden and location, length of time that the stone has been impacted, history of retroperitoneal surgery, and the experience of the operator.

A variety of lithotrites can be placed through an ureteroscope, including electrohydraulic, solid and hollow-core ultrasonic probes, a variety of laser systems, and pneumatic systems.

F. Percutaneous Nephrolithotomy

Percutaneous removal of renal and proximal ureteral calculi is the treatment of choice for large (>2.0 cm) calculi; those resistant to SWL; select lower pole calyceal stones with a narrow, long infundibulum and an acute infundibulopelvic angle; and instances with evidence of obstruction;

Percutaneous extraction of calculi requires patience and perseverance. Residual calculi can be retrieved with the aid of flexible endoscopes, additional percutaneous puncture access, follow-up irrigations, SWL, or additional percutaneous sessions.

G. Open-Stone Surgery

Open-stone surgery is the historic way to remove calculi, yet it is rarely used today.

Prevention

In general, 50% of patients experience recurrent urinary stones within 5 years without prophylactic intervention.

Appropriate education and preventive measures

Risk factors should be identified and modified

Fluid intake should result in about 1.5–2.0 L of urine/24 hours. Fluids should be encouraged during mealtime. In addition, liquids should be increased approximately 2 hours after meals

A. Metabolic Evaluation

A systematic metabolic evaluation should be instituted after a patient has recovered from urinary stone intervention or spontaneous stone passage. Stone analysis should be obtained to help direct the workup. An outpatient urine collection during typical activities and fluid intake helps unmask significant abnormalities. An initial 24-hour urine collection for calcium stone formers should include tests for calcium, uric acid, oxalate, citrate, phosphate, sulfate, sodium, volume, and pH.

Baseline serum levels for blood urea nitrogen, creatinine, calcium (with or without parathyroid hormone), phosphorous, and uric acid

B. Oral Medications

1. Alkalinizing pH agents—Potassium citrate



It is indicated in those with calcium oxalate calculi secondary to hypocitraturia (<450 mg/day), including those with renal tubular acidosis. Potassium citrate also may be used effectively to treat uric acid lithiasis and milder forms of hyperuricosuric calcium nephrolithiasis.

2. Gastrointestinal absorption inhibitor—Cellulose phosphate binds calcium in the gut and thereby inhibits calcium absorption and urinary excretion and is appropriate for patients with type 1 absorptive hypercalciuria

3. Phosphate supplementation—Renal phosphate leak is best treated by replacing phosphate.

4. Diuretics—Thiazides can correct the renal calcium leak associated with renal hypercalciuria.

5. Calcium supplementation—Enteric hyperoxaluric calcium nephrolithiasis is effectively treated with calcium supplements.

6. Uric acid-lowering medications—Allopurinol is used to treat hyperuricosuric calcium nephrolithiasis with or without hyperuricemia.

7. Urease inhibitor—Acetohydroxamic acid is an effective adjunctive treatment in those with chronic urea-splitting urinary tract infections associated with struvite stones

8. Prevention of cystine calculi—Conservative measures, including massive fluid intake and urinary alkalization, are frequently inadequate to control cystine stone formation. Penicillamine, Mercaptopropionylglycine (Thiola)

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