Renal Stone Disease

(Nephrolithiasis)

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Epidemiology

- Urinary calculi are the third most common affliction of the urinary tract, exceeded only by urinary tract infections and pathologic conditions of the prostate.
- Gender : Men are affected 1.2 times more frequently than women.
- Age : No age is exempted but stone occurrence is relatively uncommon before 20 year of age, the peak incidence in the fourth to sixth decades of life (50% of patients present between 30-50 years of age)
- Stone recurrence rates can be as high as 50% within 5 years.

Pathogenesis

- *The most important determinant of Renal stones (is an increased urinary concentration of the stones 'constituents ,such that it exceeds their solubility (supersaturation).*
- *A low urine volume* in some metabolically normal patients may also favor supersaturation.
- Solubility is affected by
  1. Urine pH
  2. Volume
  3. Total excretion
- Stone formation is enhanced by a deficiency in inhibitors of crystal.
  1. Citrate.
  2. Pyrophosphate.
  3. Glycosaminoglycans.
  4. Osteopontin
  5. *Nephrocalcin (Glycoprotein).*

GENETICS

1. **Idiopathic hypercalciuria** (Polygenic,Calcium salt stones).
2. **Primary hyperoxaluria** (Autosomal recessive,Nephrocalcinosis, Risk of end-stage renal disease
3. **Distal renal tubular acidosis (RTA)**
   - ✓ Autosomal recessive or dominant
   - ✓ Calcium phosphate
   - ✓ Nephrocalcinosis
   - ✓ Risk of end-stage renal disease
4. **Cystinuria**
   - ✓ Autosomal recessive associated with a defect on chromosome 2.
   - ✓ Cystine stones
   - ✓ Risk of end-stage renal disease.

ENVIRONMENTAL

1. **Dietary factors**
   - Normal dietary calcium intake is associated with a reduced risk of calcium stones secondary to binding of intestinal oxalate.
   - Increased calcium supplementation increases the risk of calcium stones.
   - Increased dietary sodium intake is associated with an increased risk of calcium and sodium urinary excretion, which leads to increased calcium stones.
   - Increased dietary animal protein intake led to increased uric acid and calcium stones.
   - Increased water intake is associated with a reduced risk of all types of kidney stones.
2. **Obesity :** Obesity and weight gain are associated with an increased risk of developing kidney stones.
3. **Diabetes**
   - Diabetes is a risk factor for the development of kidney stones.
   - Insulin resistance may lead to altered acidification of the urine and increased urinary calcium excretion.

4. **Geographical factors**: Stone incidence peaks in highest annual temperature.
5. **Inadequate urinary drainage** & urinary stasis, functional & anatomical abnormalities of the urinary tract.
6. **prolonged immobilization.**

Composition of Renal Stones

Stones Composition	percentage
Calcium oxalate (dihydrate and monohydrate).	60%.
Calcium phosphate.	20%.
Mixed calcium oxalate and calcium phosphate	10- 30%.
Uric acid	7%.
Magnesium ammonium phosphate (struvite)	7%.
Cystine	1%.
Miscellaneous: xanthine, silicates, and drug metabolites, such as indinavir (radiolucent on x-ray and CT scan).	< 1%

PATHOPHYSIOLOGY OF STONE FORMATION

1. **Calcium oxalate**

- Approximately 70% to 80% of incident stones are calcium oxalate.
- Calcium oxalate stones preferentially develop in acidic urine (pH < 6).
- Development depends on supersaturation of both calcium and oxalate within the urine.

A. Idiopathic hypercalciuria

- Identified in 30-60% of calcium oxalate stone formers.
- The upper limit of normal for urinary calcium excretion is 250 mg/day for women and 300 mg/day for men.
- Need to exclude hypercalcemia, vitamin D excess, hyperthyroidism, sarcoidosis, and neoplasm.
- Diagnosed via exclusion in patients with a normal serum calcium but elevated urinary calcium on a random diet. ‘

B. Absorptive hypercalciuria

- Increased jejunal absorption of calcium possibly caused by elevated calcitriol (1,25 dihydroxy vitamin D 3) levels and increased vitamin D receptor expression.
- Increased calcium absorption leads to a higher filtered load of calcium delivered to the renal tubule.
- Normal serum calcium .

C. Renal hypercalciuria

- Impaired proximal tubular reabsorption of calcium leads to renal calcium wasting.
- Normal serum calcium; hypercalciuria persists despite a calcium restricted diet.

D. Resorptive hypercalciuria

- Primary hyperparathyroidism is the underlying mechanism.
- Increased PTH levels cause bone resorption and intestinal calcium absorption, which leads to elevated serum calcium that exceeds the resorptive capacity of the renal tubule.
- Normal to slightly elevated serum calcium

E. Hypercalcemic hypercalciuria

- Primary hyperparathyroidism, hyperthyroidism, sarcoidosis, vitamin D excess, milk alkali syndrome, immobilization, and malignancy .

F. Hyperoxaluria

- Dietary hyperoxaluria is related to increased consumption of oxalate-rich foods, and/or a low-calcium diet, which by reducing the availability of intestinal calcium to complex to oxalate, allows an increased rate of free oxalate absorption by the gut.
- Enteric hyperoxaluria can be caused by small bowel disease or loss, or diarrhea, all of which reduce small bowel fat absorption, leading to an increase in fat complexing with calcium, and thereby facilitating free oxalate absorption by the colon.
- Primary hyperoxaluria is a genetic disorder in one of two genes, which results in increased production or urinary excretion of oxalate.

2. Hypocitraturia

- Acts as an inhibitor of stone formation by complexing with calcium.
- Citrate is regulated by tubular reabsorption, and reabsorption varies with urinary pH. In acidic conditions, tubular reabsorption is enhanced, which lowers urinary citrate levels.
- Diseases that cause acidosis, such as chronic diarrhea or distal RTA, cause lower urinary citrate levels. Thiazide therapy can also reduce citrate levels via potassium depletion.
- In many patients with hypocitraturia, no etiology is identified, and these patients are classified as having idiopathic hypocitraturia.

3. Hyperuricosuria/uric acid stones

- Approximately 7% of incident stones are uric acid.
- The upper limit of normal is greater than 750 mg/d for women and 800 mg/d for men.
- Uric acid is a promoter for calcium oxalate stone formation by serving as a nucleus for crystal generation and also by reducing the solubility of calcium oxalate.
- A low urinary pH is critical for uric acid stone formation. At a urinary pH less than 5.5, uric acid exists in its insoluble undissociated form, which facilitates uric acid stone formation. As the urinary pH increases, the dissociated monosodium urate crystals are predominant and serve as a nucleus for calcium-containing stone formation.
- Increased uric acid production is common in patients with a high dietary intake of animal protein, in myeloproliferative disorders, and in gout. However, uric acid stone formation is also common in patients with diabetes and the metabolic syndrome presumably caused by insulin resistance, which impairs renal ammonia excretion necessary for urinary alkalization.

4. Cystinuria

- In both men and women, urinary cystine excretion exceeds 350 mg/ d.
- Caused by autosomal recessive disorder involving chromosome 2.
- The dibasic amino acid transporter, which is located within the tubular epithelium, facilitates reabsorption of dibasic amino acids, such as cystine, ornithine, lysine, and arginine, (COLA). A defect in this enzyme leads to de-creased cystine reabsorption and increased urinary excretion of cystine.
- Cystine solubility rises with increasing pH and urinary volume.
- Positive urine cyanide-nitroprusside colorimetric reaction is a qualitative screen.

5. Calcium phosphate stones

- Calcium phosphate stones preferentially develop in alkaline urine (pH greater than 7.5).
- Calcium phosphate stones can be present as either apatite or brushite (calcium phosphate monohydrate).
- Over alkalinization with potassium citrate for hypercalciuria can sometimes lead to calcium phosphate stones.

6. Struvite stones/triple phosphate/infection stones

- Approximately 5% of incident stones are struvite.
- Struvite stones are composed of magnesium ammonium phosphate and calcium phosphate. They may also contain a nidus of another stone composition.
- Often grow to encompass large areas in the collection system or staghorn calculi.
- Urinary tract infections (UTIs) with urease splitting organisms, which include Proteus spp., Klebsiella spp., Staphylococcus aureus, Pseudomonas spp. are required to split urea into ammonia, bicarbonate, and carbonate.
- A urinary pH greater than 7.2 is required for struvite stone formation.
- Conditions that predispose to urinary tract infections increase the likelihood of struvite stone formation. Struvite stones are common in patients with spinal cord injuries and neurogenic bladders.

Clinical Manifestations of Nephrolithiasis

- Asymptomatic kidney stones are found in 10% of screening populations undergoing a CT scan for unrelated reasons.
- Pain is the most common presenting symptom in most patients. Renal colic and non-colicky renal pain are the 2 types of pain originating from the kidney. *Fixed Renal Pain I*s located posteriorly in the renal angle, anteriorly in the hypochondrium or in both.

Evaluation of Patients with Nephrolithiasis

1.General considerations

A. All patients in the acute phase of renal colic should have.

⇒ a history and physical.

⇒ urinalysis, a urine culture if urinalysis demonstrates bacteriuria or nitrites, and

⇒ a serum creatinine.

⇒ complete blood count If the patient presents with fever.

⇒ Basic evaluation with a medical history including family history, dietary history, and medications; ultrasound, calcium, and uric acid, stone analysis.

B. Patients at high risk include.

1. Family history of nephrolithiasis.
2. recurrent stone formation.
3. large stone burden.
4. residual stone fragments after therapy.
5. solitary kidney.
6. metabolic, or genetic abnormalities known to predispose to stone formation, stones other than calcium oxalate.
7. children given a higher rate of an underlying metabolic, anatomic, and/or functional voiding abnormality.

⇒ These patients they should undergo the basic evaluation, plus two 24-hour urine collections, at least 4 weeks following the acute stone episode. Further therapy will be guided by the stone analysis and 24-hour urine collections.

2. Medical history

a. General medical history is mandatory in all stone formers.
b. Past medical history with a specific focus on diseases known to contribute to stone formation, including inflammatory bowel disease, previous bowel resection, or gastric bypass, hyperparathyroidism, hyperthyroidism, RTA, and gout.
c. Family history is of particular importance because a positive family history is a risk factor for incident stone formation and recurrence.
d. Review medications for drugs known to increase stone formation, such as acetazolamide, ascorbic acid, corticosteroids, calcium-containing drug, triamterene, acyclovir, and indinavir.
e. Dietary history can also be relevant, especially in those with high- or low-calcium diets, diets high in animal protein, and diets with significant sodium intake.

Physical exam : May provide clues to underlying systemic diseases.

Laboratory evaluation

1. **Urinalysis**
   - Calcium oxalate stones preferentially form in a relatively acidic pH (less than 6.0), whereas calcium phosphate stones preferentially form in a relatively alkaline pH (greater than 7.5). A low pH (less than 5.5) is mandatory for uric acid stone formation. A high pH (greater than 7.2) is critical for struvite stone formation. A pH constantly greater than 5.8 may suggest an RTA.
   - Microscopy may reveal red blood cells, white blood cells (WBCs), and bacteria.
   - Crystalluria can define stone type: Hexagonal crystals are cystine, coffin lid crystals are calcium phosphate, and rhomboidal crystals are uric acid.
2. **Urine culture** is mandatory if microscopy reveals bacteriuria, if struvite stones are suspected, or if symptoms or signs of infection are present.

3. **Electrolytes**
   - **Calcium** (ionized or calcium with albumin): Elevated calcium may suggest hyperparathyroidism, and a parathyroid hormone (PTH) blood test should be done.
   - **Uric Acid:** Elevated uric acid is common in gout and, in conjunction with a radiolucent stone, is suggestive of uric acid nephrolithiasis.
4. **A complete blood count (CBC)** may show mild peripheral leukocytosis. WBC counts higher than 15,000/mm 3 may suggest an active infection.
5. **24-Hour urine collection:** Collection is done to determine total urine volume, pH, creatinine, calcium, oxalate, uric acid, citrate, magnesium, sodium, potassium, phosphorus, sulfate, urea, and ammonia.
6. **Stone analysis:** Performed with infrared spectroscopy. It provides information about the underlying metabolic, genetic, or dietary abnormality.

Imaging considerations

1. **A noncontrast CT scan** :is the recommended initial imaging modality for an acute stone episode. A noncontrast CT scan has a sensitivity of 98% and a specificity of 97% in detecting ureteral calculi.
2. **A renal bladder ultrasound**: is the recommended initial imaging modality in both children and pregnant patients in order to limit ionizing radiation. Ultrasonography has a median sensitivity of 61% and a specificity of 97%. If ultrasonography is equivocal, and the clinical suspicion is high for nephrolithiasis, then a low-dose noncontrast CT scan.
3. **Plain film of the kidneys, ureters, and bladder (KUB)** is also used. a KUB has a median sensitivity of 57% and a specificity of 76%. Pure uric acid, cystine, indinavir, and xanthine stones are radiolucent, and are not visible on KUB.
4. **A combination of ultrasonography and KUB** is recommended for monitoring patients with known radiopaque ureteral calculi on medical expulsion therapy because this limits costs and radiation exposure. Those with radiolucent stones will require a low dose noncontrast CT scan.
5. **Nuclear Scintigraphy.**

Management of Nephrolithiasis

A. ACUTE RENAL COLIC:

B. Medical expulsive therapy :

1. Alpha-blockers, such as tamsulosin, and calcium channel blockers (nifedipine) or steroids can facilitate stone passage via ureteral smooth muscle relaxation.
2. Medical expulsive therapy (MET) is acceptable in patients with ureteral calculi less than 10 mm who have:
   a. well- controlled pain
   b. no evidence of infection.
   c. adequate renal function.
   d. no other contraindications to the therapy.

C. MEDICAL THERAPY

1. All stone formers

1. High fluid intake of 2.5-3.0 L/day with urine volume greater than 2 L/ day
2. Normal calcium diet of 800-1200 mg/day, preferably not through supplements. Avoid excess calcium supplementation; however, calcium citrate is preferred if indicated.
3. Limit sodium to 4-5 g/day.
4. Limit animal protein to 0.8-1.0 g/kg/day.
5. Limit oxalate-rich foods.
6. Maintain a normal BMI and physical activity.
7. Targeted therapy depending on underlying metabolic ab- normality and/or 24-hour urine collection results.

2. Calcium oxalate stones

⇒ Dietary hyperoxaluria: Limit oxalate-rich foods.

⇒ Enteric hyperoxaluria: Limit oxalate-rich foods and calcium supplementation with greater than 500 mg/day.

⇒ Hypocitraturia: Potassium citrate both raises the urinary pH out of the stone-forming range and restores the normal urinary citrate concentration. Sodium bicarbonate may also be used, if unable to tolerate potassium supple-mentation.

⇒ Hypercalciuria: Thiazide diuretics, which inhibit a sodium- chloride co-transporter, therefore enhancing distal tubular sodium reabsorption via the sodium-calcium co-transporter to promote tubular calcium reabsorption. Thiazides de- crease urinary calcium by as much as 150 mg/day.

3. Calcium phosphate stones :

⇒ Primary hyperparathyroidism: Requires parathyroidectomy.

⇒ Distal RTA (Type I): Potassium citrate to restore the natural pH balance.

4. Struvite/infection stones :

⇒ Total stone removal because each fragment harbors urease- producing bacteria and serves as a nidus for further stone growth.

⇒ Appropriate antibiotic therapy to eradicate the urease-producing bacteria.

⇒ Restoration of normal pH with urinary acidification with L-methionine or inhibition of urease enzyme with acetohydroxamic acid

5. Uric acid stones:

⇒ Low animal protein diet.

⇒ Alkalinization of the urine with potassium citrate for stone dissolution is possible with a pH of 7 and for maintenance of a stone-free state with a pH of 6.2 to 6.8.

⇒ Hyperuricosuria (with or without hyperuricemia): Allopurinol at 100-300 mg/day, which inhibits xanthine oxidase to reduce uric acid production.

6. Cystine stones

1. Increase daily fluid intake to 3.5 to 4.0 L/day.
2. Specific therapy depends on 24-hour urine collection results.
3. Alkalinization of the urine with potassium citrate above a pH of 7.5 to improve solubility of cystine threefold .
4. D-penicillamine is a chelating agent that forms a disbound with cysteine to produce a more soluble compound, thereby preventing the formation of cysteine into the insoluble, stone forming, cystine.
5. Alpha-mercaptopropionyl-glycine (tiopronin) is the preferred alternative to D-penicillamine, as it has a better safety and efficacy profile. Alpha-mercaptopropionyl-glycine reduces the disulfide bond of cystine to form the more soluble cysteine, again reducing stone formation.
6. captopril is an angiotensin-converting enzyme inhibitor, which can reduce cystine, but its role in therapy is not yet well defined.

SURGICAL THERAPY

A. Extracorporeal Shock wave lithotripsy (ESWL):

- Shock waves are high-energy focused-pressure waves that can travel in air or water. When passing through two different mediums of different acoustic impedance, energy is released, which results in the fragmentation of stones. Shock waves travel harmlessly through substances of the same acoustic density. Because water and body tissues have the same density, shock waves can travel safely through skin and internal tissues. The stone is a different acoustic density and, when the shock waves hit it, they shatter and pulverize it. Urinary stones are thus fragmented, facilitating in their spontaneous passage.
- Treatment success depends on stone size, location, composition, hardness, and body habitus. For renal stones, upper or middle polar stones are ideally treated with **E**SWL, whereas lower pole stones have a clearance rate as low as 35%.
- Ideally all stones less than 1 cm in any location in the kidney can be treated with **E**SWL.
- Contraindications of **E**SWL include
  - ✓ (**absolute**) pregnancy, bleeding diathesis, and obstruction below the level of the stone.
  - ✓ (**relative**) calcified arteries and/or aneurysms and cardiac pacemaker.
- Complications of **E**SWL include
  - ✓ skin bruising.
  - ✓ subscapular and perinephric hemorrhage.
  - ✓ Pancreatitis.
  - ✓ Urosepsis.
  - ✓ Stein Strasse (“street of stone,” which may accumulate in the ureter and cause obstruction).

B. Percutaneous nephrolithotomy (PCNL) :

- The technique is establishment of access at a lower pole calyx, dilation of the tract with a dilator under fluoroscopy, and stone removal with graspers or its fragmentation using electrohydraulic, ultrasonic, or laser lithotripsy. A nephrostomy tube or ureteral stent is left for drainage.
- Additional candidates for PCNL include cystine calculi, which are large volume and resistant to **E**SWL, and anatomic abnormalities, such as those with ureteropelvic junction (UPJ) obstruction, caliceal diverticula, obstructed infundibula, ureteral obstruction, malformed kidneys (e.g., horseshoe and pelvic), and obstructive or large adjacent renal cysts.
- Contraindications of PCNL include:
  - ✓ uncontrolled bleeding diathesis.
  - ✓ untreated urinary tract infection (UTI).
  - ✓ inability to obtain optimal access for PCNL because of obesity, splenomegaly, or interposition of colon.
- Complications of PCNL include:
  - ✓ Hemorrhage (5% to 12%).
  - ✓ Perforation.
  - ✓ Extravasation (5.4% to 26%).
  - ✓ Damage to adjacent organs (1%).
  - ✓ Ureteral obstruction (1.7% to 4.9%).
  - ✓ Infection/urosepsis (3%).

3. Retrograde intrarenal surgery (ureteroscopy [URS]):

- Instrumentation includes both rigid and flexible ureteroscopes. Rigid ureteroscopes are ideally suited for access to the distal ureter but can be utilized up to the proximal ureter. Flexible ureteroscopes are ideally suited for ureteral and intrarenal access.
- URS may be safely performed in patients with:
  1. morbid obesity
  2. pregnancy.
  3. bleeding diathesis.
- Complications include:
  1. failure to retrieve the stone.
  2. mucosal abrasions.
  3. false passages
  4. ureteral perforation.
  5. complete ureteral avulsion
  6. Infection/urosepsis
  7. ureteral stricture.

4. Open/laparoscopic/robotic surgery

- Since the introduction of minimally invasive techniques such as ESWL, URS, and PCNL, open surgery has been reduced to rates of 1% to 5%.
- Indications for open stone surgery include:
  1. complex stone burden.
  2. treatment failure with endoscopic techniques.
  3. anatomic abnormalities
  4. nonfunctioning kidney.
- Laparoscopic or robotic surgery can be used in place of open techniques, but because of the complexity and rarity of these procedures, they are generally referred to centers of excellence.

Thank You
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