CORE CURRICULUM IN NEPHROLOGY

Nephrolithiasis

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EPIDEMIOLOGY AND NATURAL HISTORY

Incidence
- 12% lifetime incidence
- Sex: male predominance
- Race: relatively rare in African Americans
- Geographic: “stone belts,” developed countries

Associated Features and Risk Factors
- Obesity and hypertension
- Diet:
  - High animal protein intake
  - Low fluid intake
  - Low calcium intake
  - High salt intake
- Hot climate or occupation
- Family history
- Medications

Recurrence
- Up to 50% at 5 years, 80% lifetime (untreated)

CLINICAL FEATURES

Renal Colic
- Characteristic pain, severity, radiation
- Gastrointestinal:
  - Nausea, vomiting, ileus

Radiological Assessment
- Relative diagnostic sensitivity of different modalities:
  - Computed tomography, near 100%
  - Abdominal plain film, 60% to 65%
  - Ultrasound, 10% to 25%
- Specific applications:
  - Computed tomography in acute renal colic
  - Renal ultrasound in pregnancy
  - Abdominal plain film to determine if stone is radiopaque and thus likely not uric acid

Staghorn Stones
- Definition: extend from one calyx to another
- Struvite, cystine, uric acid
- Associated with urinary tract infection, renal failure, not stone passage

Medullary Nephrocalcinosis
- Definition: calcification of renal parenchyma
- Causes:
  - Primary hyperparathyroidism
  - Distal renal tubular acidosis (RTA)
  - Medullary sponge kidney
  - Milk alkali syndrome
  - Idiopathic hypercalciuria
  - Dent’s disease, and other genetic hypercalciurias
- Associations with alkaline urine, renal failure, carbonate apatite stones

Medullary Sponge Kidney
- Clinical features:
  - Female predominance
  - Nephrolithiasis
  - Urinary tract infection
Pathogenesis:
- Congenital collecting duct dilatation
- Urinary stasis
- Diagnosis: characteristic brush appearance of papillae on intravenous urography
- Associated with nephrocalcinosis, hypercalciuria, primary hyperparathyroidism, and distal RTA, not progressive renal failure

Renal Failure
- Unusual except with nephrocalcinosis, staghorn stones, or repeated infection associated with stones
- Modest, usually nonprogressive renal injury due to recurrent stone passage
- Ureteral stricture due to stone passage or iatrogenic

Osteopenia
- Association with high bone turnover and hypercalciuria
- Mechanisms of osteopenia:
  - Hypercalciuria and low dietary calcium intake
  - Cytokine-induced bone resorption
  - Hyperparathyroidism

Urinary Tract Infection
- Stones of any type can provide nidus for secondary infection
- Urease-positive infection can promote struvite stone formation
- Infection with obstruction (eg, fever with obstructing stone) is a urological emergency
- In sepsis with ureteral obstruction and hemodynamic instability, percutaneous nephrostomy is treatment of choice

MECHANISMS OF STONE FORMATION

Saturation and Crystallization
- Concept of saturation (minimum activity product to support crystallization):
  - Urine supersaturated with respect to calcium oxalate in most healthy (non–stone-forming) individuals
- Concept of formation product (activity product that forces crystallization):
  - Dependence on balance of promoters and inhibitors
  - Concept of metastability (activity product between saturation and formation product)

Modes of Stone Growth
- Nucleation: process by which free ions in solution associate into microscopic particles
- Aggregation: agglomeration of large particles
- Crystal growth: movement of ions out of solution onto the growing crystal

Sites of Stone Growth
- Randall’s plaques: calcium phosphate deposits on external surface of papillae (nidus and anchor of calcium oxalate stones)
- Calcium oxalate receptors in collecting duct epithelium

Promoters and Inhibitors

Promoters
- Reduce formation product
- Uric acid: nidus for calcium oxalate nucleation
- Alkaline urine pH: favors calcium phosphate crystallization (RTA, primary hyperparathyroidism, milk alkali syndrome, carbonic anhydrase inhibitors)
- Acid urine pH: favors uric acid precipitation and cystine precipitation

Inhibitors
- Alkaline urine pH (inhibits cystine and uric acid stone formation)
- Citrate
- Pyrophosphate
- Magnesium
- Proteins: Tamm-Horsfall protein, nephrocalcin, uropontin, glycosaminoglycans

Urine Chemical Risk Factors for Calcium Stone Formation
- Increased crystalloid concentration:
  - Low urine volume
  - Hypercalciuria
  - Hyperoxaluria
- Increased promoter concentration:
  - Hyperuricosuria
- Alkaline urine pH
- Reduced inhibitor concentration
- Hypocitraturia

**ADDITIONAL READING**


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**CALCIUM NEPHROLITHIASIS**

**Clinical Features**

- 75% to 90% of kidney stones
- Composition: calcium oxalate
  - Monohydrate or dihydrate: correlation with duration of stone formation, resistance to shock-wave lithotripsy
  - Typical calcium phosphate core
- Predominant calcium phosphate (apatite or brushite) stones: uncommon; Associations with primary hyperparathyroidism and RTA
- Radiological appearance
- Characteristic calcium oxalate crystals (envelope)
- Typical stone passage rather than staghorn formation

**Urinary Risk Factors for Nephrolithiasis**

**Low urine volume**

- Sharply increased risk when urine volume <1 L/d
- Causes of low urine volume:
  - Habitual or sociocultural low fluid intake
  - Hot climate or occupation
  - Gastrointestinal losses
  - Urinary frequency (aversion to fluid intake)
- Wine, beer, coffee, and tea may have additional benefit

**Hypercalciuria**

- Definitions:
  - Men, >300 mg/d
  - Women, >250 mg/d
  - Children, >4 mg/kg/d
- Incidence: about 50% of calcium stone formers
- Causes:
  - Primary hyperparathyroidism (5%), sarcoidosis, distal RTA, vitamin D intoxication, hyperthyroidism
  - Rare genetic disorders: Dent’s disease, autosomal dominant hypocalcemia
  - Idiopathic (95%)
  - Primary hyperparathyroidism:
    - Hypercalcemia, sometimes subtle and variable
    - Epidemiology: middle-aged or older women
    - Pathogenesis: Increased 1,25 vitamin D synthesis due to parathyroid hormone (PTH)
    - Diagnosis: Hypercalcemia with high or inappropriately normal immunoreactive PTH
    - Treatment: parathyroidectomy
  - Idiopathic hypercalciuria:
    - Epidemiology:
      - Young and middle-aged men
      - May be inherited (possibly autosomal dominant) in a significant proportion
    - Associated features:
      - Affluence
      - Obesity
      - Hypertension
      - Osteopenia
      - Medullary sponge kidney
      - Nephrocalcinosis
    - Pathogenesis: multiple mechanisms:
      - Intestinal calcium hyperabsorption
      - Often increased bone resorption and/or renal leak of calcium
      - Increased circulating 1,25 vitamin D and/or vitamin D receptors
      - Phosphate depletion
      - Cytokine-mediated bone resorption: abnormality of arachidonic acid metabolism
      - Excess dietary sodium: inhibits proximal sodium and calcium absorption
      - Excess dietary protein, mediated by acid load, poorly absorbed Ca-SO4 complexes, insulin, and glucagon
      - Possible role of genetic polymorphisms: calcium receptor, CLC-5 chloride channels, proximal tubular sodium phosphate transporter (NPT2a)
    - Defined genetic disorders of tubular calcium reabsorption (rare):
      - Dent’s disease (chloride channel CLC-5): hypercalciuria, nephrocalcinosis, low-molecular-weight proteinuria
Autosomal dominant hypocalcemia (activating mutation of calcium sensing receptor)

**Hyperoxaluria**
- Incidence: 10% to 60% of stone formers (difficulties of definition and of oxalate assay)
- May be more lithogenic than calcium (calcium present in molar excess)
- **Metabolism:**
  - Intestinal absorption accounts for >50% of urinary oxalate, varies over 4-fold range with dietary oxalate content
  - Dietary sources: spinach, rhubarb, meat, soy products; variable bioavailability, absence of reliable data on oxalate content of foods
  - Oxalate absorption mainly in colon; role of dietary calcium to bind oxalate in intestinal lumen and reduce absorption
  - Remainder derived from endogenous production (metabolism of glyoxylate and ascorbic acid)
  - Glomerular filtration, tubular absorption, sometimes secretion (during oxalate excess)
- **Pathogenesis:**
  - Increased intestinal absorption:
    - High-oxalate diet
    - Low-calcium diet
    - Enteric oxaluria (inflammatory bowel disease, intestinal bypass): mechanisms:
      - Calcium bound in “soaps”
      - Increased colonic permeability
      - Deficiency of oxalate-metabolizing intestinal bacteria (*Oxalobacter formigenes*)
  - Treatment: oral calcium supplements, low-oxalate diet, cholestyramine; reversal of intestinal bypass
- Increased production:
  - Primary hyperoxaluria
  - Pyridoxine deficiency
  - Vitamin C (unclear significance)
- **Primary hyperoxaluria (PH):**
  - PH type I: due to mistargeting of alanine-glyoxylate aminotransferase in hepatic mitochondria

**Hypocitraturia**
- Incidence: 10% to 40% of calcium stone formers
- **Causes:**
  - Tubular reabsorption stimulated by intracellular acidosis
  - Mechanisms:
    - Acidosis: renal insufficiency, chronic diarrheal states, high-protein diet, RTA
    - Intracellular acidosis: potassium depletion
    - Urinary tract infection: bacterial metabolism of citrate
    - Idiopathic
- **RTA type I (distal):**
  - Profound hypocitraturia, hypercalciumia, alkaline urine pH
  - Carbonate apatite stones and nephrocalcinosis
  - **Etiology:**
    - Several defined genetic defects, one associated with deafness
    - Systemic lupus, Sjögren’s syndrome
    - Idiopathic
  - **Treatment**
    - Alkali (bicarbonate or citrate); potassium preferred to sodium
    - Neutralize daily acid load (1-2 mEq/kg/d); higher alkali requirement in RTA

**Hyperuricosuria**
- Uric acid provides crystal lattice for calcium oxalate nucleation
- Usually due to dietary purine excess
- **Treatment**: allopurinol

**Metabolic Evaluation of Calcium Nephrolithiasis**
- **Indications:**
  - Limited evaluation of single stone former
  - Metabolic versus anatomic activity
- **Timing:** 2 to 3 months after acute stone episode
- Single versus multiple urine collections
Diet: free (self selected) versus defined (e.g., low calcium or low salt)

Serum studies: metabolic panel, calcium, phosphate, magnesium, PTH, vitamin D metabolites

24-hour urine studies: calcium, oxalate, citrate, uric acid, sodium, urea nitrogen or ammonia, volume

Prior acidification to avoid loss of calcium oxalate to precipitation

Sodium and urea nitrogen or ammonia to assess salt and protein intake

Role of saturation measurements

Prevention of Calcium Nephrolithiasis

Systematic high fluid intake

Proven efficacy in single stone formers:
- Goal: urine output of at least 2 L daily
- Benefit of specific beverages (wine, beer, coffee, tea, lemonade)
- Risk of certain beverages (grapefruit juice, possibly dark colas)

Diet

Moderate calcium intake:
- Risks of calcium restriction: increased stone formation, osteopenia
- Salt and protein restriction (hypercalcuria)
- Low-oxalate diet (oxaluria)
- Low-purine diet (hyperuricosuria)

Drugs of choice

Thiazide diuretic (reduces urine calcium excretion):
- Indications: hypercalcuria, hypertension, osteopenia; benefit also in normocalciuric stone formers
- Mechanisms: increased renal tubular calcium absorption in proximal tubule (volume depletion) and early distal convoluted tubule (sodium chloride cotransporter [NCCT])
- Concomitant salt restriction
- Adverse effect: hypocitraturia (potassium depletion)
- Potassium citrate:
- Benefit in normocalciuric or normocitruric stone formers as well as hypocitraturia
- Potassium supplement of choice during thiazide treatment or in mixed calcium–uric acid nephrolithia
- Neutral phosphate: theoretical benefit in patients with activation of 1,25 dihydroxyvitamin D pathway (not proven in clinical trials)
- Allopurinol: hyperuricosuric normocalciuric calcium stone formers
- Magnesium: theoretical benefit, not proven in clinical trials

Additional Reading


Uric Acid Stone Formation

Clinical Features

- Incidence: 10% of kidney stones
- Radiolucent on plain abdominal film (unless secondarily calcified)
- Crystalluria: rhomboid or football shaped
- Occasional staghorn stone formation
- Association with gout, chronic diarrheal disease or ileostomy, diabetes, and congenital disorders of purine metabolism (rare)
Pathogenesis

- Usually (80%) persistently acid urine due to impaired renal ammoniagenesis or to chronic diarrheal disease:
  - Impaired ammoniagenesis may be due to insulin resistance
  - Acid urine pH shifts uric acid:urate equilibrium toward uric acid, which is much less soluble
- Hyperuricosuria (20%), usually due to excessive dietary purine consumption, rarely to inherited metabolic disease (eg, Lesch-Nyhan)

Treatment

- Effect of alkali (pH 6 to 7) to decrease uric acid and increase urate concentration
- Stone dissolution (unless stone is secondarily calcified); may be attempted even with acute passage of ureteral stone
- Potassium forms of alkali preferred
- Dietary purine restriction or allopurinol for hyperuricosuria

ADDITIONAL READING

INFECTION STONES

Clinical Features

- Stone composition: magnesium ammonium phosphate (struvite) and carbonate apatite (“triple phosphate”)
- Chronic or recurrent urinary tract infection, anatomic abnormality of urinary tract (neurogenic bladder, indwelling prosthetic devices)
- Renal or perinephric abscess; renal insufficiency; staghorn stone formation, not stone passage
- Crystalluria: coffin-lid crystals

Pathogenesis

- Effect of bacterial urease on ammonia production and urine pH
- Urease-positive organisms: Proteus, Klebsiella, Pseudomonas, Staphylococcus saprophyticus, rarely (if ever) Escherichia coli

Treatment

- Antibiotics: difficulty of sterilizing urine; prolonged or indefinite course
- Urological treatment: often combined endourological and extracorporeal techniques
- Urease inhibitor: acetohydroxamic acid

CYSTINURIA

Clinical Features

- Incidence: 1% of stones
- Staghorn stones or stone passage with renal colic
- Hexagonal plate crystals
- Intermediate radiodensity

Pathogenesis

- Inherited tubular defect of amino acid reabsorption of cystine, ornithine, arginine and lysine
- Cystine solubility threshold: 250 mg/L

Treatment

- Hydrotherapy: very high fluid intake (3 to 4 L/d) with target urine cystine concentration below solubility threshold
- Alkali (potassium citrate) with goal urine pH 7.5 or above
- Tiopronin or penicillamine (second-line: captopril): drug-disulfide-cysteine moieties of higher solubility than cystine

ADDITIONAL READING

MISCELLANEOUS STONE TYPES

- Protein matrix stones: chronic infection (with struvite stones), end-stage renal disease
- Ammonium urate stones: laxative abuse
- Xanthine and 2,8 dihydroxyadenine stones: inherited metabolic errors
- Stones composed of drugs: indinavir, sulfadiazine, triamterene
UROLOGICAL ASPECTS OF MANAGEMENT

Acute Renal Colic From Ureteral Stone

- Conservative management:
  - analgesics (nonsteroidal anti-inflammatory drugs such as ketorolac, narcotics)
  - moderate hydration
  - minimize ureteral spasm
- Strain urine; observation up to 4 weeks
- Indications for urgent intervention (stent or nephrostomy):
  - intractable pain or vomiting
  - urinary infection with obstruction
  - anuria
  - acute renal failure
  - high-grade obstruction with solitary or transplant kidney
- Role of severity and duration of obstruction, likelihood of stone passage

Urological Procedures (Nonurgent Intervention)

- Shock-wave lithotripsy:

  - Indications:
    - Larger renal pelvic stones with high risk of obstruction
    - Small proximal ureteral stones
    - Distal ureteral stones

  - Risks
  - Influence of stone composition on fragmentation

- Ureteroscopy:

  - Indications:
    - Large proximal ureteral stones
    - Distal ureteral stones

  - Ureteral stenting in pregnancy (temporizing)

- Traditional (open) surgical management (rare)

ADDITIONAL READING