

# CORE CURRICULUM IN NEPHROLOGY

## Nephrolithiasis

Alan G. Wasserstein, MD

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### EPIDEMIOLOGY AND NATURAL HISTORY

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#### 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)

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### CLINICAL FEATURES

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#### Renal Colic

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

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- Absence of peritoneal signs
- Hematuria (90%)
- Outcome:
  - 90% of stones pass spontaneously
  - Stones >5 mm less likely to pass

#### 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, stag-horn 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

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### MECHANISMS OF STONE FORMATION

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#### 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

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### CALCIUM NEPHROLITHIASIS

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#### 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-SO<sub>4</sub> 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

- Early onset renal failure or recurrent nephrolithiasis without renal failure
- Systemic oxalosis
- Treatment: pyridoxine, neutral phosphate, liver transplant

### **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, hypercalciuria, 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 (eg, 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 (hypercalciuria)
  - Low-oxalate diet (oxaluria)
  - Low-purine diet (hyperuricosuria)

#### *Drugs of choice*

- Thiazide diuretic (reduces urine calcium excretion):
  - Indications: hypercalciuria, 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 normocitraturic 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

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## URIC ACID STONE FORMATION

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### 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 ammoniogenesis or to chronic diarrheal disease:
  - Impaired ammoniogenesis 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

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**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

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**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

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## UROLOGICAL ASPECTS OF MANAGEMENT

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### 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)

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