Nephrolithiasis: Pathophysiology, Diagnosis, and Medical Management

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Nephrolithiasis: Pathophysiology, Diagnosis, and Medical Management

Learning Objectives

By the end of this session, students will be able to: - Identify stone types based on composition and clinical presentation - Understand pathophysiology of stone formation (supersaturation, inhibitors, promoters) - Diagnose nephrolithiasis using clinical history, imaging, and urinalysis - Manage acute stone episodes and provide appropriate analgesia - Apply medical therapy tailored to stone type and metabolic abnormalities - Implement dietary modifications and prevention strategies - Interpret 24-hour urine studies and guide metabolic stone evaluation - Recognize indications for surgical intervention (ESWL, ureteroscopy, PCNL)

I. Stone Types and Composition

Epidemiology and Prevalence

- **Lifetime prevalence:** 12% of men, 5% of women
- **Peak incidence:** 4th–5th decade; higher in males 3:1
- **Recurrence rate:** 50% within 5–10 years if untreated; 10–15% with prevention

Stone Type Distribution in USA

Stone Type	Frequency	Radiopacity	pH Range	Peak Age
Calcium oxalate monohydrate	35%	Very radiopaque	Acidic (5.0–6.5)	40s–50s
Calcium oxalate dihydrate	25%	Very radiopaque	Acidic (5.0–6.5)	40s–50s
Calcium phosphate (apatite)	10–15%	Radiopaque	Alkaline (>7.0)	40s–50s

Stone Type	Frequency	Radiopacity	pH Range	Peak Age
Struvite (magnesium ammonium phosphate)	10–15%	Radiopaque	Alkaline (>7.0)	Females, post-infection
Uric acid	5–10%	Radiolucent	Acidic (<5.5)	50s–60s
Cystine	1–2%	Radiopaque	Acidic–neutral (5.5–7.5)	Early adulthood (genetic)
Other (xanthine, ammonium urate)	<1%	Radiolucent–lucent	Variable	Rare

Calcium Oxalate Stones (60% of all stones)

Subtypes: - **Monohydrate (COM):** Dumbbell-shaped, harder, more aggressive clinically - **Dihydrate (COD):** Envelope-shaped, less damaging, often asymptomatic

Associated conditions: - Hypercalciuria (high urine calcium >250 mg/day) - Hyperoxaluria (high urine oxalate >40 mg/day) - Hypocitraturia (low urine citrate <320 mg/day) - Dehydration and low urine volume - Obesity - High animal protein diet (☐ uric acid and oxalate)

Calcium Phosphate Stones (10–15%)

Subtypes: - **Apatite (most common):** Whitish, forms in alkaline urine - **Brushite (calcium hydrogen phosphate):** Rare, more soluble

Associated conditions: - **Primary hyperparathyroidism** (most important association—check PTH and serum Ca) - Renal tubular acidosis (Type 1, distal RTA) — alkaline urine + hypocitraturia - Medullary sponge kidney (ductal dilatation) - Sarcoidosis and granulomatous diseases (☐ calcitriol production) - Hyperthyroidism - Vitamin D intoxication

Clinical pearl: Any patient with calcium phosphate stones should be screened for primary hyperparathyroidism and RTA.

Struvite Stones (Infection Stones, 10–15%)

Composition: Magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4 \cdot 6H_2O$)

Pathophysiology: - Caused by **urease-producing bacteria:** *Proteus mirabilis* (most common), *Klebsiella*, *Morganella*, *Pseudomonas* - Bacteria produce urease enzyme ☐ breaks down urea ☐ ☐ ammonia ☐ ☐ pH (>7.5–8.0) - Alkaline urine precipitates magnesium ammonium phosphate - Forms rapidly, often as “staghorn calculi” filling entire renal pelvis/calyces

Demographics: - More common in **women** (UTI frequency + catheterization) - Associated with chronic indwelling catheters, neurogenic bladder, frequent UTIs

Clinical significance: - Highly symptomatic; large size at diagnosis - Recurrent infections common - High surgical morbidity if nephrectomy needed

Treatment: Require antibiotics + stone removal (often surgical); medical management alone insufficient

Uric Acid Stones (5–10%)

Pathophysiology: - Uric acid poorly soluble in acidic urine (pKa 5.75) - Acidic urine (pH <5.5) favors crystallization - Most uric acid stones are **radiolucent** (not visible on plain X-ray)

Risk factors: - Gout (30% of gout patients get uric acid stones) - High purine diet (red meat, organ meats, shellfish, high-fructose drinks) - Dehydration - Diarrhea (☐ urinary pH from bicarbonate loss) - Malignancy with high cell turnover (leukemia, lymphoma) ☐ ☐ uric acid - Uricosuric diuretics (thiazides)

Unique feature: Uric acid stones are radiolucent but can appear as filling defects on CT or ultrasound.

Cystine Stones (1–2%, Genetic)

Pathophysiology: - Genetic disorder: **Cystinuria** — autosomal recessive - Defect in dibasic amino acid transporter (SLC3A1 or SLC7A9 genes) - ☐ Renal reabsorption of cystine, lysine, arginine, ornithine - Cystine poorly soluble; crystallizes at physiologic pH (6.5–7.0) - **Requires urine cystine >400 mg/day to form stones**

Diagnosis: - Elevated 24-hour urine cystine (>250 mg = abnormal) - Positive cyanide-nitroprusside test (qualitative urine cystine) - Genetic testing if confirmed - Family screening important (10–20% of siblings affected)

Clinical presentation: - **Early age of onset** (teens–30s) — red flag for cystinuria - Multiple recurrent stones - Large staghorn calculi common - Family history of stones in young patients

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II. Pathophysiology of Stone Formation

The Three-Component Model of Lithogenesis

1. Supersaturation Stone formation requires urine to become **supersaturated** with stone-forming substances.

Mechanism: - Solubility product (Ksp) is exceeded when [ion concentration] > Ksp - Example: For calcium oxalate, [Ca^{2}☐] × [Ox^{2}☐] > Ksp - Urine pH, temperature, ionic strength, and presence of inhibitors/promoters all affect solubility

Promoters of Supersaturation: - High sodium intake (☐ urinary Na ☐ ☐ Ca reabsorption inhibition ☐ ☐ urine Ca) - High animal protein (☐ uric acid, oxalate, acid load) - Dehydration (low urine volume concentrates solutes) - High fructose intake (☐ oxalate, ☐ uric acid) - Excessive ascorbic acid supplementation (☐ oxalate)

Inhibitors of Supersaturation (Protective): - **Citrate:** Forms soluble complexes with Ca^{2}☐; key inhibitor; excreted in urine - **Magnesium:** Forms soluble complex with oxalate - **Pyrophosphate:** Inhibits nucleation and crystal growth - **Proteins:** Nephrocalcin, Tamm-Horsfall protein inhibit crystallization - **High urine volume:** Dilutes solutes, ☐ saturation

2. Crystal Nucleation and Growth Once supersaturation occurs, crystals form and grow.

Nucleation (Initial crystal formation): - Heterogeneous nucleation: Crystals form on existing matrix (Tamm-Horsfall protein, cellular debris) - Homogeneous nucleation: Spontaneous crystal formation in supersaturated urine (rare)

Growth factors: - Prolonged stasis of urine (low flow, obstruction) - Presence of biofilm or cellular matrix - Inadequate inhibitor concentration

3. Aggregation and Stone Maturation Crystals clump together forming clinically significant stones.

Factors promoting aggregation: - Low urine volume - Prolonged urine contact time in renal pelvis/calyces - Presence of organic matrix (bacterial biofilm, cellular material) - Imbalance of inhibitors and promoters

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III. Clinical Presentation and Diagnosis

Classic Presentation: Renal Colic

Symptoms: - **Sudden-onset severe flank pain** (8–10/10 severity) - Pain radiates from flank to groin (testis/labia in women) - Associated nausea and vomiting (visceral pain ☐ vagal stimulation) - Hematuria (gross or microscopic) - Dysuria if stone in distal ureter near bladder - Frequency and urgency if stone low in ureter - Patient often **restless** (unlike peritonitis where still)

Timeline: - Pain can last minutes to hours - Episodes separated by pain-free intervals (stone movement) - Mild variants may present as chronic flank ache (asymptomatic/indolent stones)

Atypical Presentations

- **Silent stones:** Found incidentally on imaging for other reasons (10–15%)
- **Chronic pyelonephritis:** Recurrent infection if stone obstructing
- **Acute kidney injury:** Large stone with complete obstruction to solitary kidney
- **Fever:** If infected obstructed system (pyonephrosis) — **surgical emergency**

Physical Examination Findings

- **Costovertebral angle (CVA) tenderness** — non-specific; also present in pyelonephritis
- **Hematuria** — microscopic in 85%, gross in 10%
- Vital signs may show tachycardia, mild hypertension from pain
- **Abdomen:** Non-specific; may have abdominal guarding if severe pain
- **No fever** (unless infected; fever = pyonephrosis until proven otherwise)

Diagnostic Imaging

Non-Contrast CT Scan (CT KUB) — GOLD STANDARD

- **Sensitivity:** 97–99%
- **Specificity:** 96–98%

- **Advantages:**
  - No contrast needed (better in renal failure)
  - Detects all stone types (including radiolucent uric acid/cystine stones)
  - Shows stone size, location, degree of obstruction
  - Identifies complications (perinephric stranding, abscess)
  - Alternate diagnosis if not stone (AAA, MI, etc.)
- **Disadvantages:**
  - Radiation exposure (~100 mSv)
  - Cost
  - Not ideal for monitoring asymptomatic stones or pregnancy

Ultrasound

- **Sensitivity:** 90–95% for stones >4 mm
- **Specificity:** 98–99%
- **Advantages:**
  - No radiation
  - Real-time, portable
  - Good for pregnancy
  - Detects hydronephrosis (obstruction)
  - Can assess for AAA if presented
- **Disadvantages:**
  - Operator-dependent
  - Misses distal ureteral stones
  - Limited in obese patients

Plain Abdominal X-Ray (KUB)

- **Sensitivity:** 50–80% (only radiopaque stones visible)
- **Not useful for diagnosis** (misses 20–50% of stones)
- **Use:** Follow-up imaging in known stone-formers; assess stone progression

Intravenous Pyelography (IVP)

- Largely **replaced by CT**
- Still used in some settings where CT unavailable
- Requires contrast; risk in renal insufficiency

Laboratory Findings

Urinalysis: - **Hematuria:** Present in 85% (microscopic), 10% (gross) - **Crystals:** May see oxalate, uric acid, or cystine crystals (not diagnostic) - **Pyuria:** Present if concurrent infection - **Proteinuria:** Usually absent unless concomitant kidney disease - **Glucose, ketones:** Absent (helps rule out DKA)

Serum Studies (initial workup): - **Creatinine:** Assess renal function; baseline for contrast toxicity risk - **Calcium, phosphate:** Screen for hyperparathyroidism - **Uric acid:** Elevated in gout, malignancy; risk for uric acid stones - **Magnesium:** Low magnesium associated with CaOx stones - **BUN:** Assess hydration

Urine Culture: - Obtain if fever, pyuria, or recurrent UTIs (rule out infection stone) - Essential before instrumentation if febrile

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IV. Medical Management by Stone Type

Acute Stone Episode Management

Pain Control (First Priority):

Agent	Dose	Route	Onset	Notes
NSAIDs	Indomethacin 50 mg q6h or Ketorolac 30–60 mg	PO/IV/IM	30–60 min	Preferred; inhibits prostaglandins; reduces pain + ureteral spasm
Opioids	Morphine 4–10 mg q4–6h; Hydromorphone 2–4 mg	IV/IM/PO	15–30 min	Backup if NSAID contraindicated; risk of constipation
Acetaminophen	650–1000 mg q6h	PO	30–60 min	Weaker; adjunct to NSAIDs
Antispasmodics	Dicyclomine 10–20 mg q4–6h	PO	1–2 hours	Reduces ureteral spasm; adjunct
Antiemetics	Ondansetron 4–8 mg q8h or metoclopramide 10 mg	IV/PO	15–30 min	Essential for nausea from visceral pain

Fluid Management: - **Hydration:** Aggressive IV or PO hydration (target urine output 1–2 L/day) - Dilutes urine, promotes stone passage - Avoid over-hydration (risk of pulmonary edema)

Expulsive Therapy (Passage of Small Stones): - **Alpha-blockers:** Tamsulosin 0.4 mg daily - Relaxes ureteral smooth muscle - Effective for distal ureteral stones <6 mm - NNT = 6 to prevent one stone passage procedure - Side effect: Orthostatic hypotension - **Calcium channel blockers:** Nifedipine XL 30 mg daily - Similar efficacy to alpha-blockers - Better tolerated in some patients

Monitoring: - Pain control; expect improvement within 24–48 hours - Urine output and hydration status - Renal function (creatinine) - Follow-up imaging in 2–4 weeks to confirm passage

Medical Management by Stone Type

Calcium Oxalate Stones **Management goals:** - ☐ Urine calcium (hypercalciuria) - ☐ Urine oxalate (hyperoxaluria) - ☐ Urine citrate (hypocitraturia) - ☐ Urine volume (dilute urine)

Dietary modifications (First-line): 1. **Fluid intake:** 2–3 L/day urine output (split across waking hours) 2. **Sodium restriction:** <2.3 g/day (high Na ☐ ☐ urine Ca) 3. **Protein restriction:** 0.8–1.0 g/kg/day (high protein ☐ ☐ uric acid, oxalate) 4. **Calcium intake: DO NOT restrict** (paradoxically worsens stones); maintain 800–1000 mg/day - Low Ca diet ☐ ☐ intestinal oxalate absorption ☐ ☐ urine oxalate 5. **Oxalate restriction:** Avoid high-oxalate foods (spinach, rhubarb, nuts, chocolate, tea, colas) 6. **Magnesium:** Increase intake (Mg forms soluble complex with oxalate)

Pharmacologic therapy (if dietary modification insufficient after 3–6 months):

Drug	Dose	Mechanism	Use Case
Thiazide diuretic (HCTZ)	25 mg daily	☐ urine Ca	Hypercalciuria (urine Ca >250 mg/day)
Potassium citrate	20 mEq BID–TID	☐ urine citrate; alkalinize urine	Hypocitraturia (<320 mg/day) + CaOx
Allopurinol	100–300 mg daily	☐ uric acid production	If uric acid >800 mg/day (☐ CaOx)
Vitamin B6 (pyridoxine)	25–100 mg daily	☐ oxalate synthesis	Hyperoxaluria or genetic predisposition
Magnesium glycinate	400–500 mg daily	☐ urine Mg	Hypomagnesemia or hypomagnesuria

Specific Workup: - 24-hour urine: Calcium, oxalate, citrate, magnesium, volume, uric acid - Serum: Calcium, phosphate, PTH (rule out hyperparathyroidism) - Urine pH: If <5.5, more likely CaOx; may add potassium citrate

Calcium Phosphate Stones Management goals: - ☐ Urine phosphate and calcium - ☐ Urine pH (acidify urine) - Screen for and treat underlying cause (hyperparathyroidism, RTA, sarcoidosis)

Workup (ESSENTIAL): - Serum: **PTH and serum calcium** (hyperparathyroidism in 50% of apatite stones) - Serum and urine electrolytes, bicarbonate - 24-hour urine: Calcium, phosphate, citrate, pH - **Screen for RTA:** Urine anion gap (GAP = [Na+K-Cl]; <0 suggests dRTA), urine pH >5.5 in setting of acidemia

Treatment of hyperparathyroidism: - Surgical parathyroidectomy if symptomatic (elevated Ca, osteoporosis) — cures stone formation - Medical management alone (thiazide, cinacalcet) less effective for stone prevention

Medical therapy if no parathyroidism: 1. **Acetazolamide:** 250 mg daily - Carbonic anhydrase inhibitor - ☐ Urine pH (acidifies urine) - ☐ Citrate (risk: may ☐ CaOx stones) - Use cautiously; monitor stone type 2. **Potassium citrate:** AVOID (alkalinizes urine; worsens apatite stones) 3. **Thiazide + Amiloride:** - Thiazide ☐ urine Ca - Amiloride prevents hypokalemia from thiazide 4. **Fluid + dietary sodium/protein reduction:** As per CaOx

Struvite (Infection) Stones Key principle: Medical therapy alone CANNOT dissolve struvite stones. Surgery required.

Medical management (supportive only): 1. **Antibiotics:** Culture-guided; prolonged suppression (months) may slow growth - Urine culture essential before any intervention - Target gram-negative urease producers (*Proteus*, *Klebsiella*) - Prophylactic antibiotics if recurrent UTIs 2. **Urine acidification:** Lower urine pH (urease more active at pH >7) - Acetazolamide 250 mg BID or Potassium acid phosphate - Less effective alone 3. **Urease inhibitors:** - **Acetohydroxamic acid (AHA):** 250 mg TID–QID - Inhibits bacterial urease - Modest effect; significant side effects (tremor, hemolytic anemia) - Rarely used now; surgery preferred

Surgical management (definitive): - **Percutaneous nephrolithotomy (PCNL):** For large staghorn calculi - **Partial nephrectomy:** If renal function already compromised and stone burden large - **Complete nephrectomy:** If recurrent infections, non-functioning kidney, patient unable to tolerate repeat surgery

Prevention of recurrence: - Treat underlying UTI/neurogenic bladder aggressively - Consider prophylactic antibiotics if recurrent infections - Regular imaging to monitor for recurrence

Uric Acid Stones **Management goals:** - ☐ Urine pH (>5.5–6.0 dissolves uric acid) - ☐ Uric acid production/excretion - ☐ Urine volume

Unique feature: Uric acid stones can partially or completely dissolve with medical therapy (unlike CaOx/struvite).

Dietary modifications: 1. **Fluid intake:** 2–3 L/day (more than CaOx because stones can dissolve) 2. **Purine restriction:** Low-purine diet (limit red meat, organ meats, shellfish, anchovies) 3. **Avoid fructose:** High-fructose drinks ☐ uric acid 4. **Alkali supplementation:** Potassium citrate or sodium bicarbonate to target urine pH >6.0

Pharmacologic therapy:

Drug	Dose	Mechanism	Notes
Potassium citrate	20 mEq BID–TID	Alkalinize urine	First-line; target pH 6.0–6.5
Sodium bicarbonate	500–1000 mg TID	Alkalinize urine	Alternative if K+ restricted
Allopurinol	100–300 mg daily	☐ xanthine oxidase; ☐ uric acid	If uric acid >800 mg/day or gout
Febuxostat	40–80 mg daily	Xanthine oxidase inhibitor	Alternative to allopurinol; less renal dosing
Rasburicase	0.2 mg/kg IV	Uricase; converts uric acid ☐ allantoin	Acute tumor lysis syndrome only; very expensive

Monitoring: - 24-hour urine pH (target 6.0–6.5) - Serum uric acid (if on allopurinol; target <6 mg/dL) - Repeat imaging at 6–12 weeks to assess stone dissolution

Cystine Stones **Management goals:** - ☐ Urine volume (massive; target 3–4 L/day or higher) - ☐ Urine pH (>7.0 increases cystine solubility) - ☐ Urine cystine concentration (<250 mg/day)

Dietary modifications: 1. **Fluid intake: 3–4 L/day minimum** (most important intervention) - Split intake: 1 L before bed + nocturia to maintain high nighttime urine volume - This alone may prevent stone formation 2. **Sodium restriction:** <2.3 g/day (☐ Na ☐ ☐ cystine reabsorption) 3. **Protein restriction:** 0.8–1.0 g/kg/day (reduces urine cystine) 4. **Potassium citrate:** Alkalinize urine to pH >7.0 (but careful not to precipitate calcium phosphate)

Pharmacologic therapy (if dietary changes insufficient):

Drug	Dose	Mechanism	Notes
Potassium citrate	20 mEq BID–TID	☐ pH to 7.0–7.5	Mandatory; forms soluble calcium cystinate complex
D-Penicillamine	250–500 mg BID	Chelates cystine ☐ form soluble disulfide	Second-line; significant side effects (rash, taste, proteinuria)
Tiopronin	100–300 mg TID	Similar to penicillamine; fewer side effects	Preferred over penicillamine; still significant SE profile
Alpha-lipoic acid	300–600 mg daily	May reduce cystine; investigational	Limited evidence; some benefit reported

Monitoring: - 24-hour urine cystine (target <250 mg/day) - Urine pH (target 7.0–7.5) - Serum electrolytes (hypokalemia risk from citrate) - Renal function (monitor for proteinuria from chelators)

V. Dietary Modifications Summary

Universal Recommendations (All Stone Types)

Recommendation	Rationale
Increase fluid intake to 2–3 L/day urine output	☐ supersaturation; dilutes solutes
Restrict sodium to <2.3 g/day	☐ urine Ca; improves citrate retention
Moderate protein: 0.8–1.0 g/kg/day	☐ uric acid, oxalate, acid load
Maintain calcium intake: 800–1000 mg/day	☐ intestinal oxalate absorption
Increase magnesium intake	Forms soluble complexes with oxalate
Limit high-purine foods	☐ uric acid (if uric acid stones)
Avoid high-fructose drinks	☐ uric acid, oxalate

Stone-Specific Dietary Recommendations

Stone Type	Add	Avoid
CaOx	Magnesium, potassium citrate	Spinach, nuts, chocolate, tea
$CaPO_4$	Acid (citric), possibly magnesium	Dairy excess (unless CaOx risk)
Uric acid	Potassium citrate, water	Purines, fructose
Cystine	**Massive water intake** (3–4 L/day urine), potassium citrate	Sodium, high protein
Struvite	Water, acidifying diet	Alkaline foods

VI. Surgical Management Indications and Options

Indications for Intervention (Non-Medical Management)

Emergent: - Infected obstructed kidney (pyonephrosis) with sepsis □ ureteral stent/nephrostomy + antibiotics, then definitive treatment - Complete bilateral obstruction with AKI - Obstruction of solitary kidney with AKI

Urgent (within 1–2 weeks): - Persistent pain despite optimal medical therapy - Fever/infection - Complete obstruction with nausea/vomiting preventing hydration

Elective: - Stone >6 mm (less likely to pass spontaneously) - Distal ureteral stones (lower pass rate than proximal) - Multiple stones - Stones causing recurrent infection - Recurrent symptoms despite medical therapy

Surgical Options by Stone Location and Size

Shock Wave Lithotripsy (ESWL) **Mechanism:** Externally applied shock waves fragment stone via energy transmission through tissues.

Advantages: - Non-invasive, outpatient - Can treat multiple stones - No instrumentation of urinary tract

Disadvantages: - Lower success rate (70–80%) vs. ureteroscopy (>90%) - Requires stone visualization (need radiopaque stone or CT guidance) - Residual fragments common; may require second procedure - Contraindicated in pregnancy - Risk of renal injury (minor, usually)

Best use: Proximal ureteral stones 10–20 mm, or as first-line if patient desires non-invasive approach

Ureteroscopy (URS) **Mechanism:** Endoscopic visualization of ureter; stone fragmented (laser, pneumatic) or removed directly.

Advantages: - High success rate (>95% for stones <15 mm) - Can treat distal ureteral stones (where ESWL difficult) - Minimal residual fragments - Real-time visualization - Lower re-treatment rate than ESWL

Disadvantages: - Requires instrumentation (risk of ureteral perforation, stricture, infection) - Anesthesia required - Not ideal for very large stones (>20 mm) - Operative time longer than ESWL

Best use: Distal ureteral stones, recurrent stones, large stones unsuitable for ESWL, pregnancy

Percutaneous Nephrolithotomy (PCNL) **Mechanism:** Percutaneous puncture of kidney; nephroscope inserted; stone fragmented (ultrasonic, laser) or removed.

Advantages: - Highest success rate (95–98%) for any stone - Can treat very large (>2 cm) and staghorn stones - Can obtain stone fragments for analysis - Best for complex stone burden

Disadvantages: - Invasive; requires percutaneous renal access - Highest bleeding risk (~15% transfusion in unselected patients) - Significant morbidity (fever, infection, sepsis 3–8%) - Highest cost - Requires anesthesia and skilled percutaneous access

Best use: Large (>2 cm) stones, staghorn calculi, PCNL failure, struvite stones, pediatric stones

Prone PCNL vs. Supine PCNL

- **Prone:** Traditional; easier anatomic access; risk of aspiration under anesthesia
- **Supine:** Newer; less risk of aspiration; may allow combined cystoscopy/ESWL; slightly limited access

Mini-PCNL or Ultra-Mini-PCNL

- Smaller bore access (20–24 Fr vs. 28–30 Fr for standard)
- Lower bleeding risk; higher re-treatment rate; emerging technique

Robotic-Assisted Pyelolithotomy

- Open surgical approach (planned intra-renal stone extraction)
- Rarely indicated; reserved for complex cases or failed endoscopic approach

Success Rates and Complications by Procedure

Procedure	Success Rate (Stone-Free)	Perforation Risk	Bleeding Risk	Infection Risk	Cost
ESWL	70–85%	Minimal	Minimal	Low	Low
URS	90–98%	1–2% (ureteral)	Minimal	Low–moderate	Moderate
PCNL	95–98%	1–3% (collecting system)	15% (transfusion)	3–8%	High

VII. 24-Hour Urine Interpretation and Metabolic Workup

When to Order 24-Hour Urine

Indications: 1. **First stone episode** in patient <50 years (higher risk of metabolic abnormality) 2. **Recurrent stones** (>1 stone in 5 years) 3. **Young age of onset** (<25 years) 4. **Unusual stone composition** (uric acid, cystine, struvite) 5. **Family history** of kidney stones 6. **CKD** with stone formation 7. **Pediatric patients** (nearly all should have metabolic workup)

Timing: Collect after acute stone episode resolves (3–4 weeks later); patient on normal diet/hydration.

Standard 24-Hour Urine Parameters

Standard panels measure: - **Volume:** Target >2 L/day; <1 L/day is risk for any stone - **Creatinine:** Verify adequate collection (normal 15–25 mg/kg; low = inadequate collection) - **Calcium:** Target <250 mg/day; >300 = hypercalciuria - **Oxalate:** Target <40 mg/day; >45 = hyperoxaluria - **Citrate:** Target >320 mg/day (>400 ideal); <320 = hypocitraturia (risk factor) - **Magnesium:** Target >100 mg/day; <100 = hypomagnesuria (risk factor) - **Phosphate:** Elevated in RTA, hyperparathyroidism - **Uric acid:** Target <800 mg/day; >800 = hyperuricosuria - **Sodium:** Assess dietary sodium; should reflect <2.3 g/day sodium diet - **Potassium:** Assess dietary intake - **pH:** Varies by stone type (acidic for CaOx/cystine; alkaline for apatite/struvite) - **Cystine:** If cystinuria suspected; target <250 mg/day (diagnostic if >400 mg/day with symptoms) - **Ammonia:** Elevated in RTA

Interpretation Patterns by Stone Type

Calcium Oxalate Stone Pattern

- ☐ Calcium (>250 mg/day)
- ☐ Oxalate (>40 mg/day)
- ☐ Citrate (<320 mg/day) — common finding
- ☐ Magnesium (<100 mg/day) — common finding
- ☐ Volume (<2 L/day) — nearly always present
- pH: Acidic (5.5–6.5)

Intervention: ☐ Volume, ☐ Na, ☐ protein, ☐ oxalate intake, ☐ Mg, consider potassium citrate and/or thiazide

Uric Acid Stone Pattern

- ☐ Uric acid (>800 mg/day, often >1000)
- ☐ pH (<5.5) — KEY finding
- ☐ Citrate (often <300 mg/day)
- ☐ Volume often present
- Normal Ca, P, Mg

Intervention: Alkalinize urine (potassium citrate), allopurinol if uric acid >900 mg/day, purine-restrict diet

Cystine Stone Pattern

- ☐ Cystine (>250 mg/day; diagnostic if >400)
- Positive cyanide-nitroprusside test on random urine
- ☐ Volume critical finding
- ☐ pH often <6.0
- Family history often positive

Intervention: Massive volume (3–4 L/day), sodium restriction, potassium citrate, consider D-penicillamine or tiopronin

Hyperparathyroidism Pattern (Apatite/Calcium Phosphate Stones)

- ☐☐ Calcium (often >300 mg/day)
- ☐ Phosphate
- ☐ Citrate
- Elevated serum PTH and serum calcium
- pH: Alkaline (>7.0)
- Note: May form apatite concurrently with CaOx

Intervention: Check serum PTH, consider parathyroidectomy if surgical candidate; thiazide if not surgical

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VIII. Prevention and Long-Term Management

Lifestyle Modifications for Stone Prevention

Tier 1 (Universal, for all patients): 1. Increase hydration (target 2–3 L/day urine output; split throughout day) 2. Reduce sodium (<2.3 g/day) 3. Moderate protein (0.8–1.0 g/kg) 4. Maintain calcium intake (800–1000 mg/day; don't restrict) 5. Increase vegetables and whole grains

Tier 2 (Based on stone type/metabolic abnormalities): 1. Restrict oxalate (if hyperoxaluria) 2. Restrict purines (if uric acid stones) 3. Increase magnesium (if hypomagnesuria or CaOx) 4. Alkali supplementation (if uric acid or cystine stones)

Tier 3 (Pharmacologic, if dietary modifications insufficient): - See Section IV (Medical Management) for specific agents

Monitoring Strategy

After first stone (no known risk factors): - Repeat imaging at 6–12 months - Annual follow-up

After recurrent stones or high-risk metabolic profile: - Repeat 24-hour urine at 6 weeks after implementing interventions - Adjust therapy based on results - Repeat annually if ongoing risk

High-risk patients (cystine, young age, multiple recurrences): - 24-hour urine every 6–12 months - Imaging every 6–12 months - More aggressive pharmacologic intervention

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Practice Questions

1. **A 45-year-old man with a history of one prior kidney stone presents with severe left flank pain radiating to the groin. Non-contrast CT shows a 5 mm stone in the left proximal ureter with mild hydronephrosis. No fever. Labs show normal creatinine and urinalysis shows microscopic hematuria. Urine culture is negative. What is the best initial management?**

   - A) Immediate ureteroscopy for stone removal
   - B) IV fluids, NSAIDs, antiemetics, and observation for stone passage
   - C) Shock wave lithotripsy
   - D) Empiric antibiotics

   Answer: B. A 5 mm proximal ureteral stone has a 50–70% chance of spontaneous passage with conservative management. First-line treatment is hydration, analgesia (NSAIDs preferred), and antiemetics. If pain is controlled and no fever/infection, observe. Add expulsive therapy (tamsulosin) if desired. Consider ureteroscopy if pain not controlled, fever develops, or stone fails to pass after 4–6 weeks. ESWL or URS would be reserved for larger stones (>6–8 mm) or failed passage.

2. **A 38-year-old woman has a 1 cm calcium oxalate kidney stone. 24-hour urine shows: Calcium 320 mg/day (normal), Oxalate 65 mg/day (elevated; normal <40), Citrate 250 mg/day (low; target >320), Volume 0.8 L/day (low), Magnesium 80 mg/day (low; target >100). Serum PTH and calcium are normal. Which intervention is MOST important?**

   - A) Start thiazide diuretic
   - B) Increase fluid intake to 2–3 L/day urine output
   - C) Start allopurinol
   - D) Restrict dietary calcium

   Answer: B. This patient's biggest risk factors are LOW VOLUME (0.8 L/day) and HYPEROXALURIA (65 mg/day). Increasing urine volume is the single most important intervention—it dilutes urine and reduces supersaturation. Volume expansion also improves citrate excretion and reduces urine calcium through renal hemodynamics. Secondary interventions would include: dietary oxalate restriction (for hyperoxaluria), increased magnesium intake, and potassium citrate (for hypocitraturia). Thiazide is not needed (calcium already normal); allopurinol is not indicated (uric acid normal).

3. **A 32-year-old man presents with his third kidney stone in 2 years. Basic metabolic panel shows serum calcium 10.2 mg/dL (normal), PTH 85 pg/mL (normal 15–65). 24-hour urine shows: Uric acid 950 mg/day (elevated), Oxalate 35 mg/day (normal), Citrate 280 mg/day (low), pH 5.2 (acidic), Volume 1.5 L/day. What is the stone type likely to form, and what is first-line therapy?**

   - A) Calcium oxalate; start potassium citrate
   - B) Uric acid; start potassium citrate and allopurinol
   - C) Calcium phosphate; start thiazide
   - D) Struvite; start prophylactic antibiotics

   Answer: B. The clinical picture clearly indicates **URIC ACID stones:** elevated uric acid (950 mg/day), acidic urine pH (5.2), hypocitraturia, and recurrent stones. First-line therapy

is: (1) **Potassium citrate 20 mEq BID–TID** to alkalinize urine to pH 6.0–6.5 (uric acid is insoluble at pH <5.5); (2) **Allopurinol 100–300 mg daily** to reduce uric acid excretion; (3) Dietary purine restriction. Importantly, the patient's hyperuricosuria likely reflects either gout or high purine diet (red meat, shellfish). Uric acid stones are special because they can DISSOLVE with alkalinization—unlike CaOx or struvite stones, making potassium citrate critical.

Clinical Pearls Summary

- **CT KUB is the gold standard** for diagnosis (97–99% sensitivity); detects all stone types including radiolucent ones
- **Calcium restriction is harmful** in stone-formers (☐ oxalate absorption); maintain 800–1000 mg/day
- **Uric acid stones can dissolve** with potassium citrate and allopurinol; aggressive therapy indicated
- **All first-time stone-formers <50 years need 24-hour urine workup** to identify metabolic abnormalities
- **Medical management fails in struvite stones**; surgery mandatory; antibiotics alone won't cure
- **Cystine stones require aggressive hydration** (3–4 L/day urine output); fluids > medications
- **Asymptomatic stones <4 mm pass spontaneously 90% of the time**; observation reasonable
- **Stone-free rates:** ESWL 70–85%, URS >90%, PCNL >95%
- **Volume is the most important modifiable risk factor**; all patients should aim for 2–3 L/day urine

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