A Simplified Approach to the Metabolic Evaluation of the Stone Former
(Referencing the AUA Medical Management of Kidney Stones Guideline)

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# Classification of Stone Causes

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Classification of Stone Causes

**Infection**
- Struvite
- Carbonate apatite
- Matrix

**Metabolic**
- Calcium
- Calcium Oxalate
- Calcium Phosphate
- Uric Acid
- Cystine
When should a metabolic evaluation be considered?

- Recurrent stone disease
- Stone burden requiring invasive surgery
- Solitary kidney
- Family history
- Skeletal conditions (osteoporosis, fracture)
- Inflammatory bowel disease / bowel surgery
- Children
What is the rationale for a metabolic evaluation?

- The clinical stone may be the phenotypic expression of an underlying metabolic abnormality.

- We can identify and mitigate these abnormalities.

All pts with a newly diagnosed stone should undergo a screening evaluation (Clinical Principle).
What is the optimal timing of the 24 hour urine collection?

• Presence of stone material in collecting system will not affect results
• Ideally should be done 1 month following an intervention
  – When patient has resumed normal lifestyle

Clinicians should obtain metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers (Standard: Grade B)

24-hr urine testing can be used to inform and monitor treatment regimens
Practical Evaluation of the Metabolic Stone Former Calcium or Uric Acid Stones

• What tests can most hospitals perform?
  – 24 hour urine collections for:
    • Total volume
    • Calcium
    • Oxalate
    • Citrate
    • Uric Acid
    • Creatinine
    • Sodium
    • pH

Metabolic testing should consist of 1 or 2, 24-hr urine collections obtained on a random diet (Expert Opinion)
What tests can most hospitals perform?
- 24 hour urine collections for:
  - Total volume
  - Calcium
  - Oxalate
  - Citrate
  - Uric Acid
  - Creatinine
  - Sodium
  - pH

Commercial vendors simplify the process
- LithoLink
- Mission Pharmacal
Calcium Stone Disease
The Hypercalciurias

- Metabolic classification
  - Absorptive hypercalciuria
  - Renal hypercalciuria
  - Resorptive hypercalciuria

- 1º hyperparathyroidism

Clinicians should not routinely perform “fast and calcium load” testing to distinguish among types of hypercalciurias. (Recommendation: Grade C)
Absorptive Hypercalciuria

• Increased intestinal absorption of calcium
  – Type I – Occurs regardless of dietary calcium intake
  – Type II – Does not occur with calcium restriction
    • Different types likely only of academic interest

• Results in increased filtered calcium load and decreased renal reabsorption

• Excess renal losses preserve calcium homeostasis (zero sum balance)
Renal Hypercalciuria

- Impaired renal tubular calcium reabsorption
- Loss of calcium triggers parathyroid function
  - Mobilizes calcium from bone
  - Enhances GI absorption of calcium
- Increases renal filtered load of calcium
Resorptive Hypercalciuria

- Primary hyperparathyroidism
  - Hypersecretion of PTH
    - Excessive bone resorption
    - Increased GI calcium absorption
  - Results in increasing circulating calcium and increased renal filtered load of calcium
How to Treat Hypercalciuria
Thiazide Diuretics

• Increases tubular calcium reabsorption
  – Distal tubule
  – Proximal tubule

• Requires potassium supplementation to prevent:
  – Hypokalemia
  – Hypocitraturia
Thiazide Diuretics

- Absorptive hypercalciuria
  - Will reduce calcium excretion
  - Retained calcium stored in bone
- Renal hypercalciuria
  - Ideal treatment
  - Corrects the renal leak
- Resorptive hypercalciuria
  - Not appropriate treatment of 1\textsuperscript{o} hyperparathyroidism
    - May exacerbate hypercalcemia

Clinicians should offer thiazide diuretics to patients with high or relatively high urine calcium and recurrent calcium stones (Standard: Grade B)
Dietary Calcium Counseling

• Prospective, randomized study
  – 400 mg calcium diet
  – 1200 mg calcium diet
• Primary outcome - time to first stone
• Results at 5 year follow-up
  – Low calcium diet – 38% recurrence
  – Normal calcium diet – 20% recurrence
Sodium Restriction

• Dietary sodium can influence renal calcium excretion
  – Increase of 100 mEq/day of sodium will increase urinary calcium by 50 mg/day
  – Excess dietary sodium will attenuate hypocalciuric effect of thiazides

Clinicians should counsel patients with calcium stones and relatively high urinary calcium to limit sodium intake and consume 1000-1200 mg/d of dietary calcium (Standard: Grade B)
Calcium Supplements

• Can promote hypercalciuria
  – Especially at initiation of therapy
  – Magnitude of effect is variable

• What is recommended?

• Calcium citrate
  – No significant effect on CaOx/CaP supersaturation
  – Check 24 hour urine calcium following initiation
    • If elevated, can begin thiazide treatment

• What about Vitamin D?
  – No definitive evidence yet
  – There are health benefits from normalizing Vitamin D
    • Repletion is probably ok
The Hyperoxalurias

Idiopathic hyperoxaluria
Enteric hyperoxaluria
Primary hyperoxaluria

All associated with calcium oxalate stone disease
Idiopathic Hyperoxaluria

- Most common type of hyperoxaluria
- Initial treatment is dietary modification
  - Refrain from high oxalate foods
    - Ascorbate (Vitamin C) megadoses
  - Limit animal protein consumption
    - May increase oxalate excretion
  - Normal dietary calcium intake
    - Will reduce oxalate excretion

Clinicians should counsel patients with calcium oxalate stones and relatively high urinary oxalate to limit intake of oxalate-rich foods and maintain normal calcium consumption. (Expert Opinion)
Enteric Hyperoxalururia

• Fat is malabsorbed
  – Ordinarily little fat reaches the colon
• In malabsorptive states fatty acids reach colon and bind calcium
  – Calcium normally binds oxalate in gut
  – Once complexed to fatty acids, calcium is unable to bind oxalate
  – Increased oxalate load absorbed and delivered to kidney
  – Urinary oxalate rises
  – Calcium oxalate stones form
Enteric Hyperoxaluria

Suspect with hyperoxaluria and bowel disease
Enteric Hyperoxaluria

• Other associated lithogenic factors
  – Low urine volume
    • Increased intestinal fluid losses
  – Hypocitraturia
    • Metabolic acidosis due to bicarbonate losses
    • Hypokalemia
  – Hypomagensiuria
    • Poor intestinal magnesium absorption
Enteric Hyperoxaluria

• **Treatment**
  – Correction of bowel pathology if possible
  – Increased fluid consumption
  – Low fat, low oxalate diet
  – Calcium citrate substitution
    • Promotes enteric calcium oxalate complexation
  – Magnesium supplementation
    • Will complex with oxalate
  – Cholestyramine
    • Will bind fatty acids, bile acids, oxalate
  – Potassium citrate
    • Correct underlying acidosis and hypokalemia
The Effect of Citrate
Citrate

- Inhibitor of calcium oxalate stone formation
- Forms soluble complexes with calcium
- Inhibits crystallization of calcium salts

- Low urinary citrate seen in:
  - 5-10% of patients as isolated finding
  - 50% of patients as one of multiple finding

- Can be repleted with potassium citrate
Etiology of Hypocitraturia

- Idiopathic
- Distal Renal Tubular Acidosis (Type I)
- Chronic Diarrheal States
- Thiazide-induced
- UTI
  - Loss of citrate lyase

- Really, any state with a metabolic acidosis
  - Decreases renal citrate synthesis
  - Increases renal citrate reabsorption
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Clinicians should offer potassium citrate therapy to patients with recurrent calcium stones and low or relatively low urinary citrate (Standard: Grade B)
Uric Acid Stones

- Accounts for 5-10% of all stones
- Most common in patients with no obvious uric acid metabolism abnormality
  - Associated with certain uric acid disorders, though
    - Purine gluttony
    - Metabolic syndrome (insulin resistance)
    - Gouty diathesis
- Also associated with:
  - Chronic diarrheal states
  - Myeloproliferative disorders
Uric Acid Stones

• Pathogenesis
  – Increased urinary uric acid is helpful, but not mandatory
  – Relatively acidic urine pH is required
    \[ \text{H}^+ + \text{Urate}^- \leftrightarrow \text{Uric Acid} \]
    • Low pH drives soluble urate salt to insoluble uric acid
    • pKa of uric acid is 5.75
Treatment of Uric Acid Calculi

• Increase urinary pH with alkali therapy
  – Potassium citrate
    • Generally begin at 20-30 mEq BID dosing
    • Follow urinary pH
      – At pH 6.5 most uric acid will be soluble

• If hyperuricosuria is present:
  – Allopurinol will decrease uric acid production
    • Blocks ability of xanthine oxidase to convert xanthine to uric acid

• Dietary purine reduction
Treatment of Uric Acid Calculi

- Increase urinary pH with alkali therapy
  - Potassium citrate

Clinicians should offer potassium citrate to patients with uric acid and cystine stones to raise urinary pH to an optimal level. (Expert Opinion)

If hyperuricosuria is present:
  - Allopurinol will decrease uric acid production
    - Blocks ability of xanthine oxidase to convert xanthine to uric acid

Clinicians should *not* routinely offer allopurinol as first-line therapy to patients with uric acid stones. (Expert Opinion)
Pharmacologic Take Home Points

• Hypercalciuria
  (Absorptive or renal leak – both treated the same)
  – Managed with thiazides / potassium supplement
    • HCTZ or chlorthalidone or indapamide
    • Potassium citrate 10-20 mEq q D
      or (if stone composition is calcium phosphate)
    • Potassium chloride 10-20 mEq q D
  – Check BMP 2-3 days after starting therapy
  – Check 24 hour study 3-4 weeks later
Pharmacologic Take Home Points

• Hypocitraturia
  – Replete with potassium citrate 10-20 mEq BID
  – Check BMP 2-3 days after starting therapy
  – Check 24 hour urine study 3-4 weeks later

• Uric acid stones
  – Potassium citrate 20 mEq BID
  – Check BMP 2-3 days after starting therapy
  – Check 24 hour urine study 3-4 weeks later
  – +/- patient self-monitoring with pH paper
  – Allopurinol ONLY if urine uric acid is elevated
Dietary Take Home Points

• Fluid intake to maintain urine volume > 2L per day
• Normal calcium intake
  – 1000-1200 mg per day
  – If calcium supplement required - calcium citrate with meals
  – Check 24 hour urine on supplement – may require thiazide
• Strict low salt diet
  – 2300-3300 mg per day
    • 1 tsp = 2300 mg
• Moderate animal protein
  – 6-8 oz meat per day (size of deck of cards)
• Low oxalate
  – Compliance is challenging
  – Appreciate high oxalate foods and maximize fluid intake
Dietary Take Home Points

Clinicians should recommend to all stone formers a fluid intake that will achieve a urine volume of at least 2.5L daily (Standard: Grade B)

• Fluid intake to maintain urine volume > 2L per day
• Normal calcium intake – 1000-1200 mg per day
  – If calcium supplement required - calcium citrate with meals
  – Check 24 hour urine when on supplement - may require thiazide
• Strict low salt diet – 2300-3300 mg per day
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• Low oxalate
  – Compliance is challenging
  – Appreciate high oxalate foods and maximize fluid intake

Clinicians should encourage patients with calcium stones and relatively low urinary citrate to increase their intake of fruits and vegetables and limit non-dairy animal protein. (Expert Opinion)

Clinicians should counsel patients with uric acid stones or calcium stones and relatively high urinary uric acid to limit intake of non-dairy animal protein. (Expert Opinion)