Medical Management of Nephrolithiasis

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Disclosures

- Nothing to disclose
Aims

• Provide recommendations for prevention and follow-up of adult patients with kidney stones
• Emphasis on EBM
• Highlight the AUA Guideline 2014
Need for Guideline?

- Common and costly problem
- High rate of recurrence
  - Strong motivation to avoid
- Effective established treatment regimens
  - Widespread mis-information
- Evidence of under-utilization
Overview

• Evaluation
• Diet Therapies
• Pharmacologic Therapies
• Follow-up
Evaluation

- Screening eval for all with a newly diagnosed stone
  - Detailed medical and dietary history
  - Serum chemistries
  - Urinalysis (pH, microscopic crystals)
  - Urine culture (high pH and urease splitting → struvite)

- When stone available, chem analysis at least once
- Obtain/review available imaging to assess stone burden (anatomic anomalies, UPJ obstruction, medullary sponge)
Evaluation

Medical History
• Obesity
• Type II DM
• 1° hyperparathyroidism
• Hyperthyroidism
• Distal RTA (type 1)
• Gout
• Bariatric Surgery
• Bowel resection/disease with malabsorption

Dietary History
• Low fluid intake
• High Na intake
• Low or high Ca intake
• Excessive intake of animal protein
• Limited fruits and vegetables
Evaluation

Medications

- Topiramate
- Acetazolamide
- Zonisamide
- Probenecid
- Triameterene
- Protease inhibitors
- Vitamin C
- Vitamin D
- Calcium

Serum Chemistries

- BMP, Phos, uric acid
  - $\uparrow$Ca, $\downarrow$Phos $\rightarrow$ 1° HPT
  - $\downarrow$CO2, $\downarrow$K+, $\uparrow$Cl $\rightarrow$ dRTA
  - $\uparrow$Uric acid $\rightarrow$ low pH or hyperuricosuria

- Serum PTH if 1° HPT is suspected (high Ca in serum or urine) *Vit D
Evaluation

• Perform **metabolic testing** in high-risk or interested first-time stone formers and recurrent stone formers (Standard; Grade B)
  – Urine saturation of stone-forming salts highly correlate with stone composition
  – 24-hour urine testing allow us to inform/monitor treatments

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• Recurrent/multiple SFs
• Children/Adolescents
• Solitary kidney
• “Interested” 1st time SFs

• High-risk 1st time SFs
  – Family history
  – GI disease/resection
  – Gout
  – Type II DM
  – Obesity
  – dRTA
  – 1° HPT
  – Nephrocalcinosis
  – Recurrent UTIs
Evaluation

• Metabolic testing should consist of one or two 24-hour urine collections obtained on random diet (Expert Opinion)
  – Total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium and creatinine
  – SS, UUN
  – Urine cystine

• Clinicians should not routinely perform "fast and calcium load" testing to distinguish among types of hypercalciuria (Recommendation; Grade C)
Dietary Therapies

- Best available EBM on dietary therapies is poor
- Few well designed studies
- Many existent studies flawed:
  - Lack a group who continue without any dietary recommendations
  - Utilize a multicomponent diet
    - Independent effects of individual components cannot be determined
- Compliance with dietary recommendations often low
Hydration, Hydration, Hydration

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

At 5 yrs: 12% vs 27% recurrence in 199 CaOx formers

Large, retrospective cohort & observational studies show greater benefit (29-45% risk reduction)

• No specific fluid volume intake can be recommended
Does fluid type matter?

- Only 1 RCT has shown benefit with avoiding soda, specifically phosphoric-acid based (Colas)
  - 1009 SFs randomized, at 3 yrs: those avoiding soda had 6% fewer recurrences and 15% fewer with the previous cola drinkers

- Observational studies have been less clear
  - Health Professionals Follow-up Study, Nurses’ Health Study
    - Find no association with soda consumption
    - Coffee, Tea, Beer and Wine associated with reduced RR
    - Apple, grapefruit juices associated with increased RR
**NL Ca, low protein, Low Na**

- Counsel patients with Ca stones and relatively high urinary Ca to limit Na intake & consume 1,000-1,200 mg per day of dietary Ca (Standard; Grade: B)

**NL Ca, low protein, low Na diet**

At 5 yrs: **20% vs 38%** recurrence in 120 CaOx formers (men)
- Borghi L et al. NEJM 346:77, 2002

Low Ca intake → ↑oxalate absorption → urinary oxalate excretion

Dietary Na is strongly linked to urinary Ca excretion (Na <2.3g/d)

- Calcium supplements- typically should be stopped
  - Supplement users often exceed RDA upper limit (1200mg)
  - Collect 24-hour urine samples on and off the supplement
  - Calcium citrate (?better than Ca chloride, Ca carbonate?)
### Low Oxalate Diet

- Counsel patients with CaOx stones and relatively high urinary oxalate to limit intake of oxalate-rich foods and maintain normal Ca consumption (Expert Opinion)

<table>
<thead>
<tr>
<th>Fruits/Veggies</th>
<th>Bread/Grains</th>
<th>Nuts/seeds</th>
<th>Candies</th>
<th>Beverages</th>
<th>Misc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avocados</td>
<td>French Toast</td>
<td>Dates</td>
<td>Brownies</td>
<td>Carrot Juice</td>
<td>Tofu</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>Flour</td>
<td>Almonds</td>
<td>Cake</td>
<td>Hot Chocolate homemade</td>
<td>Soy</td>
</tr>
<tr>
<td>Kiwi</td>
<td>Brown Rice</td>
<td>Cashews</td>
<td>Candies with Nuts</td>
<td>Lemonade (frozen from concentrate)</td>
<td>Chocolate Syrup</td>
</tr>
<tr>
<td>Orange</td>
<td>Grits</td>
<td>Peanuts</td>
<td>Chocolate Syrup</td>
<td>Rice Dream</td>
<td>Fudge Sauce</td>
</tr>
<tr>
<td>Raspberries</td>
<td>Cornmeal</td>
<td>Pistachios</td>
<td>Fudge Sauce</td>
<td>Tea, Brewed</td>
<td>Miso</td>
</tr>
<tr>
<td>Navy Beans</td>
<td>Wheat</td>
<td>Mixed Nuts</td>
<td>Potato chips</td>
<td>Tomato Juice</td>
<td>Peanut Butter</td>
</tr>
<tr>
<td>Okra</td>
<td>Couscous</td>
<td>Pumpkin Seeds</td>
<td></td>
<td>V8 Juice</td>
<td>Stuffing</td>
</tr>
<tr>
<td>Rhubarb</td>
<td>Rice Bran</td>
<td>Trail Mix</td>
<td></td>
<td></td>
<td>Tahini</td>
</tr>
<tr>
<td>Spinach</td>
<td></td>
<td>Walnuts</td>
<td></td>
<td></td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Yams</td>
<td></td>
<td>Pecans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beets</td>
<td></td>
<td>Sunflower seed</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Potatoes</td>
<td></td>
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</tr>
</tbody>
</table>
Dietary Therapies

• Encourage patients with Ca stones and relatively low urinary citrate to increase intake of fruits/vegetables and limit non-dairy animal protein (Expert Opinion)

• Urinary citrate excretion is determined by acid-base status
  – Metabolic acidosis or dietary acid loads $\rightarrow$ ↑renal citrate resorption $\rightarrow$ ↓urinary excretion

• Hypocitraturia: common risk factor (~prevalence 20-60%)
  – Associated with RTA, chronic diarrhea, medications (carbonic anhydrase inhibitors), high acid load in diet
  – Foods with acid load: meats, fish, poultry, cheese, eggs, and to a lesser extent, grains
  – Foods with alkali load: nearly all fruits and vegetables
Dietary Therapies

- Counsel patients with uric acid stones or Ca stones and relatively high urinary uric acid to limit intake of non-dairy animal protein (Expert Opinion)
  - Diet-derived purines account for an estimated 30% of urinary uric acid (majority is endogenous)
  - High purine foods (>150 mg/3-oz)
    - Some fish/seafood: anchovies, sardines, herring, mackerel, scallops, mussels
    - Water fowl, organ meats, glandular tissue, gravies and meat extracts
  - Moderately-high
    - Other shellfish and fish, game meats, mutton, beef, pork, poultry and meat-based soups/broths
Dietary Therapies

• Counsel patients with cystine stones to limit sodium and protein intake (Expert Opinion)
• Cystinurics have very high rates of stone recurrence despite medical management (combined dietary and pharmacological therapy)

• High fluid intake is particularly important (cystine concentration <250 mg/L)
  – At least four liters/day
• Dietary sodium restriction (<2,300 mg/day)
• All foods of animal origin are rich in cystine & methionine (metabolized to cysteine)
• Increased intake of fruits and vegetables promote urinary alkalinization and favor cystine solubility
## Diet-Summary

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparator</th>
<th>Mode of Detection</th>
<th>ARR</th>
<th>NNT</th>
<th>RR (95% CI)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing fluids to maintain urine output &gt; 2 L per day (for individuals with a single previous calcium stone episode)</td>
<td>No increase in fluids</td>
<td>Composite*</td>
<td>15%</td>
<td>7</td>
<td>0.45 (0.24 to 0.84)</td>
<td>●●●</td>
</tr>
<tr>
<td>Eliminating soft drinks (based on a single study in men)</td>
<td>No advice to reduce intake of soft drinks</td>
<td>Symptomatic</td>
<td>7%</td>
<td>14</td>
<td>0.83 (0.71 to 0.98)</td>
<td>●●●</td>
</tr>
<tr>
<td>Eliminating soft drinks acidified solely with phosphoric acid but not citric acid: a subgroup analysis of participants who frequently consumed such soft drinks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.65 (0.49 to 0.87)</td>
<td>●●●</td>
</tr>
<tr>
<td>Low-animal protein, low-sodium, decreased-oxalate, increased-water, and normal-calcium diet†</td>
<td>Low calcium, decreased oxalate, and increased water intake</td>
<td>Composite</td>
<td>18%</td>
<td>6</td>
<td>0.52 (0.29 to 0.95)</td>
<td>●●●</td>
</tr>
<tr>
<td>Low-animal protein, high-fiber, increased-bran, low-purine, adequate-calcium, and increased-fluid diet</td>
<td>Adequate calcium and increased fluid</td>
<td>Composite</td>
<td>-20%</td>
<td>5</td>
<td>5.88 (1.39 to 24.92)</td>
<td>●●●</td>
</tr>
<tr>
<td>Tailored diet based on a metabolic evaluation””</td>
<td>Empirical dietary recommendations</td>
<td>Composite</td>
<td>13%</td>
<td>8</td>
<td>0.32 (0.14 to 0.74)</td>
<td>●●●</td>
</tr>
</tbody>
</table>

Fink HA et al. AHRQ Comparative Effectiveness Reviews 2012
Pharmacologic Therapies

- Offer **thiazide diuretics** to patients with high or relatively high urine calcium & recurrent calcium stones (Standard; Grade B)

- Several RCTs have shown that thiazide diuretics reduce the formation of recurrent calcium kidney stones
  - HCTZ 25mg bid or 50mg qday
  - Chlorthalidone 25mg qday
  - Indapamide 2.5mg qday

- Act directly at the DRT and indirectly at the PRT to promote Ca resorption

- Dietary Na restriction needed to maximize the hypocalciuric effect and limit potassium losses
Pharmacologic Therapies

**Thiazide diuretics**

- Dietary sources of potassium (fruits/vegetables low in oxalate) encouraged
- Potassium supplementation (potassium citrate) may be needed due to hypokalemic effects
- No RCTs have specifically targeted Caphos SFs but included
- Thiazide therapy is appropriate for CaOx and CaPhos SFs
- Some high-risk first-time stone formers might also benefit from thiazide therapy
- ARR 29%, NNT 3, RR 0.53
- Fink HA et al. AHRQ Comparative Effectiveness Reviews 2012
Pharmacologic Therapies

• Offer potassium citrate therapy to patients with recurrent Ca stones and low or relatively low urinary citrate (Standard; Grade B)
  – Provides alkali load that promotes citrate excretion in the PRT
  – Prospective, RCTs have demonstrated reduced risk of recurrent Ca stones
    • Low or low normal urine citrate
    • Normal citrate excretion but low urinary pH
  – Caphos SFs with hypocitraturia (observational studies; no RCTs)
    • Risk that higher urine pH can promote Caphos stone formation
  – Preferred over sodium citrate (Na can increase urine Ca excretion)
    • Should be considered if the patient is at risk for hyperkalemia
  – Typically 30-60mEq/day divided bid or tid
  – Monitor urine pH and serum K+

• ARR 41%, NNT 3, RR 0.25
  – Fink HA et al. AHRQ Comparative Effectiveness Reviews 2012
Pharmacologic Therapies

- Offer **allopurinol** to patients with recurrent Ca oxalate stones who have hyperuricosuria and normal urinary calcium (Standard; Grade B)
  - Limit non-dairy animal protein to maximize the efficacy of allopurinol

- Offer **thiazide diuretics and/or potassium citrate** to patients with recurrent Ca stones without metabolic abnormalities or ones appropriately addressed and stone formation persists (Standard; Grade B)
  - Potassium citrate is preferred first-line therapy (low side effect profile)
  - No trials have directly compared targeted vs empiric medical therapy for stone prevention
  - Several RCTs have shown benefit in pts regardless

- **ARR 22%, NNT 5, RR 0.59**
  - Fink HA et al. AHRQ Comparative Effectiveness Reviews 2012
Pharmacologic Therapies

• Offer potassium citrate to patients with uric acid and cystine stones to raise urinary pH to an optimal level (Expert Opinion)
  
  – Solubility of uric acid and cystine is increased at higher urinary pH
  – Uric acid: goal pH > 6.0
  – Cystine stone: goal pH 7.0-7.5
  – Persistent alkalinization may dissolve existing uric acid and cystine stones
Pharmacologic Therapies

• Do not routinely offer allopurinol as first-line therapy to patients with uric acid stones (Expert Opinion)
  – Main risk factor is low urine pH (not hyperuricosuria)
  – First line therapy is potassium citrate
  – Allopurinol is an adjunct to potassium citrate in refractory cases

  – 2 RCTs show benefit selectively for pts with hyperuricosuria (others show no benefit)
Pharmacologic Therapies

- **Offer cystine-binding thiol drugs** to patients with cystine stones who are unresponsive to dietary modifications and urinary alkalinization, or have large recurrent stone burdens (Expert Opinion)
  - Increase fluid intake, restriction of sodium and protein intake, and urinary alkalinization

- **When conservative measures fail (urine cystine >500mg/day)**
  - **Alpha-mercaptopropionylglycine (tiopronin)*** 300-600mg po tid
  - **D-penicillamine** 250-1000mg po qid
  - Captopril has not been shown to be effective for the prevention of recurrent cystine stones
    - Excretion at maximal doses not sufficient to effect cystine binding
Pharmacologic Therapies

• Offer acetohydroxamic acid (AHA) to patients with residual or recurrent struvite stones only after surgical options have been exhausted (Option; Grade B)
  – When stone removal is not feasible (consider antibiotics)
  – AHA: urease inhibitor
    • Close monitoring for phlebitis and hypercoagulability
  – 250mg po tid or qid

  – RCT of 94 pts with chronic UTI and struvite stones
    • Stone growth: 17% AHA vs 46% placebo (p<0.005)
  – RCT of 37 pts
    • Effective to prevent stone growth but 50% discontinuation due to side effects
Medical-Summary

Pharmacologic Therapies

• Need more study
  – *Oxalobacter formigenes* (probiotic) for hyperoxaluria
    • Colonize the bowel & decrease intestinal oxalate
    • RCT 80 pts: 30meq bid KMgCit or probiotic (Ochek) bid
    • At 1 month, urine oxalate decreased 10 vs 14.7 mg

• Widespread exposure to antibiotics in the food supply → elimination of *Oxalobacter formigenes*
Follow Up

- Obtain a single 24-hour urine specimen for stone risk factors **within six months** of the initiation of treatment to assess response to dietary and/or medical therapy (Expert Opinion)

- After the initial follow-up, obtain a single 24-hour urine specimen **annually** or with greater frequency, depending on stone activity, to assess patient adherence and metabolic response (Expert Opinion)
Follow Up

• Obtain **periodic blood testing** to assess for adverse effects in patients on pharmacological therapy (Standard; Grade: A)
  
  – Thiazides: hypokalemia and glucose intolerance
  – Allopurinol and tiopronin: ↑LFTs
  – AHA and tiopronin: anemia and other hematologic abnormalities
  – Potassium citrate: hyperkalemia
  
  – Thiazides: hypercalcemia (may unmask undiagnosed 1° HPT)
Follow Up

• Obtain a **repeat stone analysis**, when available, especially in patients not responding to treatment (Expert Opinion)

• Monitor patients with struvite stones for **reinfection** with urease-producing organisms and utilize strategies to prevent such occurrences (Expert Opinion)
  – Surveillance urine cultures
    • Recurrences may be reduced with long-term, prophylactic antibiotics

• Periodically obtain **follow-up imaging** studies to assess for stone growth or new stone formation based on stone activity (KUB, US or CT) (Expert Opinion)
  – Annual
Future Needs

- Stone rates are increasing
  - Changes in diet: more salt, less dairy, less fruits/veggies
  - Epidemics of metabolic syndrome, diabetes and obesity
  - Global warming?
  - Elimination of Oxalobacter formigenes
- Research in kidney stone prevention needed