Medical Approach to Nephrolithiasis

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ACP Meeting

Washington University in St. Louis
School of Medicine
DISCLOSURES

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Assistant Professor of Medicine

Research support
• Abbott
• Kadmon
• Otsuka
• Pfizer
Introduction

• Nephrolithiasis is a common disorder estimated to account for 1% of all hospital admissions

• Men are affected at a rate 3-4x that of women

• 1 in 12 men will experience a kidney stone at some point in his life
Introduction

• Despite the long history of nephrolithiasis, a unifying theory for stone formation has yet to emerge

Introduction

• The initial presentation most frequently involves the severe and sudden onset of unilateral flank pain, radiating to the groin and the finding of microscopic hematuria is common (90%)

• Plain x-rays may reveal most stone types if they are larger than 2mm in diameter (except for uric acid)

• Non-contrast CT is the preferred imaging modality
Introduction

• For the first episode... appropriate urologic treatment & general dietary recommendations

• But, resist the temptation to check an extensive stone-risk panel while the patient is in the hospital

• The risk of a second stone is ~50% in the next seven years
Introduction

- A second episode does merit a more complete evaluation, once the patient is back on his or her typical outpatient diet.
  
  1) Dietary assessment
  
  2) Stone analysis (if available)
  
  3) 24-hour urine stone battery
General Approach

• Regardless of the stone composition, there are a few common approaches that should be taken for the prevention of future episodes

• 1) INCREASE FLUIDS
• 2) RESTRICT SODIUM
• 3) “NORMAL” CALCIUM INTAKE
• 4) LOW PURINE DIET
Stone Types

- Calcium oxalate
- Calcium phosphate
- Uric acid
- Struvite (Mg-NH₄-PO₄)
- Cystine
Stone Types

- Calcium oxalate
- Calcium phosphate
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- Struvite (Mg-NH$_4$-PO$_4$)
- Cystine
Calcium Oxalate

• Calcium-based stones are, by far, the most commonly encountered stone type

• OXALATE > PHOSPHATE

• Precipitation of the oxalate does not vary much according to pH (as opposed to the phosphate variety)
Calcium Oxalate

www.monicasegal.com
Calcium Oxalate
Calcium Oxalate

- HYPER-CALCIURIA

- Excess calcium in the urine can obviously increase the risk of calcium stones

- But... this calcium is not generally derived from the diet
Calcium Oxalate

• HYPER-CALCIURIA

• Most of the body’s calcium is in the skeleton, and the amount in the serum (and thus the amount filtered) is tightly regulated by PTH (and Vitamin D).

• In patients prone to stone formation, restricting dietary calcium just means that the kidneys will get the calcium from somewhere else.
Calcium Oxalate

- Increases in urinary calcium can occur:
  
  1) Increased serum calcium
     - Increased PTH
     - Bone resorption / turnover
  
  2) Increased GI absorption
     - Excess vitamin D intake
     - Excess vitamin D production (granuloma)
  
  3) Decreased renal reabsorption
     - Increased sodium excretion
     - Loop diuretics
Calcium Oxalate

home.comcast.net/~llpellegrini
Calcium Oxalate

Na+, K+, 2Cl-

K+

Ca++

Claudins (16, 19)
Calcium Oxalate
Calcium Oxalate
Calcium Oxalate

- HYPER-OXALURIA

- DIET
  - Spinach, rhubarb, chocolate
  - Vitamin C

- GI ABSORPTION
  - Bariatric surgery
  - Fat malabsorption

- GENETIC
  - Primary hyperoxaluria
Calcium Oxalate
Calcium Oxalate

CaCO3 w/meals

Bile Acid Sequestration
Calcium Oxalate

- HYPO-CITRATURIA

- Citrate in the urine is protective against stone formation as it binds to calcium to form a soluble complex

- HypoK can predispose to hypo-citraturia

- Supplementation with oral citrate (K-citrate, Urocit-K) can lead to conversion to bicarbonate and urinary alkalinization…
Calcium Oxalate

• HYPER-URICOSURIA

• Even in calcium-based stones, uric acid in the urine can create a nidus on which calcium salts can precipitate (heterogeneous nucleation)

• Treatment can focus on dietary purines and allopurinol
Calcium Oxalate

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Flag</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREATININE, 24 HOUR URINE</td>
<td>1.4 G/24 HRS</td>
<td></td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>24 HOUR URINE POTASSIUM</td>
<td>12 mmol/24HR</td>
<td></td>
<td>7.7-91.3</td>
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<tr>
<td>SODIUM, 24 HOUR URINE</td>
<td>191.4 mmol/24HR</td>
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<td>26.4-243.8</td>
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<tr>
<td>MAGNESIUM, 24 HOUR URINE</td>
<td>65 MG/24HRS</td>
<td></td>
<td>65-120</td>
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<tr>
<td>PHOSPHORUS, 24 HOUR URINE</td>
<td>0.88 G/24 HRS</td>
<td></td>
<td>0.34-1.00</td>
</tr>
<tr>
<td>URIC ACID, 24 HOUR URINE</td>
<td>925.6 mg/24hr</td>
<td>H</td>
<td>250.0-750.0</td>
</tr>
<tr>
<td>CALCIUM, 24 HOUR URINE</td>
<td>517 mg/24hr</td>
<td>H</td>
<td>50-300</td>
</tr>
<tr>
<td>24 HOUR URINE VOLUME</td>
<td>1700.0 ML/24HRS</td>
<td>L</td>
<td>&gt;=2000.0</td>
</tr>
<tr>
<td>URINE pH</td>
<td>6.0 pH</td>
<td></td>
<td>5.5-7.1</td>
</tr>
<tr>
<td>OXALATE, 24 HOUR URINE</td>
<td>0.56 mmol/24 hr</td>
<td>H</td>
<td>0.08-0.49</td>
</tr>
<tr>
<td>24 HOUR URINE CITRATE</td>
<td>125.6 mg/24hr</td>
<td>L</td>
<td>200.0-1000.0</td>
</tr>
<tr>
<td>TOTAL URINE VOLUME</td>
<td>1700 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIME IN MINUTES</td>
<td>1440 minutes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Calcium Oxalate

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Decreased Risk</th>
<th>Increasing Risk for Stone Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Volume (liters/day)</td>
<td>4.05</td>
<td></td>
</tr>
<tr>
<td>SS CaOx</td>
<td>3.18</td>
<td></td>
</tr>
<tr>
<td>Urine Calcium (mg/day)</td>
<td></td>
<td>521</td>
</tr>
<tr>
<td>Urine Oxalate (mg/day)</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Urine Citrate (mg/day)</td>
<td>830</td>
<td></td>
</tr>
<tr>
<td>SS CaP</td>
<td></td>
<td>2.32</td>
</tr>
<tr>
<td>24 Hour Urine pH</td>
<td></td>
<td>6.430</td>
</tr>
<tr>
<td>SS Uric Acid</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Urine Uric Acid (g/day)</td>
<td></td>
<td>1.113</td>
</tr>
</tbody>
</table>
### Calcium Oxalate

<table>
<thead>
<tr>
<th>DATE</th>
<th>SAMPLE ID</th>
<th>Vol 24</th>
<th>SS CaOx</th>
<th>Ca 24</th>
<th>Ox 24</th>
<th>Cit 24</th>
<th>SS CaP</th>
<th>pH</th>
<th>SS UA</th>
<th>UA 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/09/16</td>
<td>S18416969</td>
<td>4.05</td>
<td>3.18</td>
<td>521*</td>
<td>33</td>
<td>830</td>
<td>2.32</td>
<td>6.430</td>
<td>0.23</td>
<td>1.113</td>
</tr>
</tbody>
</table>

**Reference Range**
- Vol: 0.5 - 4L
- SS CaOx: 6 - 10
- Ca: male <250, female <200
- Ox: 20 - 40
- Cit: male >450, female >550
- SS CaP: 0.5 - 2
- pH: 5.8 - 6.2
- SS UA: male <0.800, female <0.750

### Dietary Factors

<table>
<thead>
<tr>
<th>DATE</th>
<th>SAMPLE ID</th>
<th>Na 24</th>
<th>K 24</th>
<th>Mg 24</th>
<th>P 24</th>
<th>Nh4 24</th>
<th>Cl 24</th>
<th>Sul 24</th>
<th>UUN 24</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/09/16</td>
<td>S18416969</td>
<td>316</td>
<td>140</td>
<td>152</td>
<td>2.442</td>
<td>66</td>
<td>305</td>
<td>100</td>
<td>25.54*</td>
<td>2.2</td>
</tr>
</tbody>
</table>

**Reference Range**
- Na: 50 - 150
- K: 20 - 100
- Mg: 30 - 120
- P: 0.6 - 1.2
- Nh4: 15 - 60
- Cl: 70 - 250
- Sul: 20 - 80
- UUN: 6 - 14
- PCR: 0.8 - 1.4

### Normalized Values

<table>
<thead>
<tr>
<th>DATE</th>
<th>SAMPLE ID</th>
<th>WEIGHT</th>
<th>Cr 24</th>
<th>Cr 24/Kg</th>
<th>Ca 24/Kg</th>
<th>Ca 24/Cr 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/09/16</td>
<td>S18416969</td>
<td>79.4</td>
<td>2596*</td>
<td>32.7</td>
<td>6.6</td>
<td>201</td>
</tr>
</tbody>
</table>

**Reference Range**
- Cr 24: male 18-24, female 15-20
- Cr 24/Kg: <4
- Ca 24/Kg: <140
- Ca 24/Cr 24: <140
Calcium Oxalate

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper-Oxaluria</td>
<td></td>
</tr>
<tr>
<td>Hypo-Citraturia</td>
<td></td>
</tr>
<tr>
<td>Hyper-Uricosuria</td>
<td></td>
</tr>
<tr>
<td>Hyper-Calciuria</td>
<td></td>
</tr>
</tbody>
</table>

Prevention of Calcium Phosphate nephrolithiasis is essentially the same
Stone Types

- Calcium oxalate
- Calcium phosphate
- Uric acid
- Struvite (Mg-NH$_4$-PO$_4$)
- Cystine
Calcium Phosphate

- As opposed to Calcium Oxalate stones, these are preferentially formed in ALKALINE urine
- Notably, the conditions are perfect in a DISTAL RTA, where systemic acidosis leads to:
  - Bone resorption
  - Citrate reabsorption from urine
  - And along with inability to acidify urine…
Calcium Phosphate
Calcium Phosphate

- Treatment is ALMOST the same as for calcium oxalate stones... just be cautious about over-alkalinizing the urine

- Urine pH should not exceed 7.0
Calcium Phosphate

• Trickier are the patients suspected of having an incomplete distal RTA
  – There is an inability to acidify the urine, tending towards a metabolic acidosis
  – However, the serum bicarbonate is normal, thanks in part to the reabsorption of citrate from the urine
  – However, there is typically profound hypocitraturia, with an already-elevated urine pH.
    . . . the therapeutic window for citrate administration is small
Stone Types

• Calcium oxalate
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• Cystine
Uric Acid

- Uric acid accounts for ~5% of stones

- More than anything else, urine pH will determine the precipitation of uric acid, becoming insoluble in acidic urine, with pH<5.5

- Low urine volume is #2 on the list

- Hyper-uricosuria is not necessary for uric acid stone formation (gout, myeloproliferative disease, diet)
Uric Acid

These stones are notable for being **RADIOLUCENT**
Uric Acid

• In addition to increased fluid intake (at least 3L of UOP), urine alkalinaization is the mainstay of therapy

• Potassium citrate (10-20 mEq TID) is preferred, titrated up to a urine pH of 6.5; acetazolamide can also help alkalinize the urine

• If hyper-uricosuria is present, purine dietary restriction and allopurinol can be initiated (if above failed to work)
**Uric Acid**

### Summary Stone Risk Factors

<table>
<thead>
<tr>
<th>SAMPLE ID: S18416969</th>
<th>PATIENT COLLECTION DATE: 06/09/2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANALYTE</strong></td>
<td><strong>DECREASED RISK</strong></td>
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<tr>
<td>Urine Volume (liters/day)</td>
<td>4.05</td>
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<td>Urine Uric Acid (g/day)</td>
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Stone Types

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- Cystine
Struvite

- Struvite stones go by a variety of names
  - Struvite
  - Magnesium-ammonium-phosphate
  - “Triple phosphate”
  - Staghorn calculi

Rajaian S, Kekre NS, NEJM, 2009
Struvite

- Struvite precipitates in alkaline urine, and can be worsened by high magnesium excretion

- Strongly associated with urea-splitting organisms in urinary tract infections
  - *Proteus*
  - *Providencia*
  - *Pseudomonas*
  - *Klebsiella*
  - *Staphylococcus*
  - *Mycoplasma*
Struvite

- The bacteria produce supersaturation in their immediate surroundings, with crystallization forming around clusters of bacteria

- Treatment is typically surgical

- Bacterial eradication with abx is rare
Stone Types

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- Calcium phosphate
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- Cystine
Cystine

- Cystine stones result from an autosomal recessive genetic mutation in amino acid transport (~1% of stones)
- Solubility increases as pH increases (>7.0-7.5)
- At normal urine pH, 4L/day of urine would be needed to maintain solubility
- Sodium restriction to lowest possible level ($U_{Na} < 100$ mEq/d)
Cystine

- 24-hour urine cystine is normally <75 mg/d; most cystinuric patients have levels >300 mg/d

- Sulfhydryl drugs (Thiola/tiopronin, D-penicillamine, captopril) form cross-links with cystine to increase solubility

- For patients on these medications, a cystine capacity assay may be measured (Litholink) rather than actual excretion/supersaturation
Summary

- **ACIDIC URINE**
  - Uric Acid
  - Cystine

- **ALKALINE URINE**
  - Calcium Phosphate
  - Struvite

- **ANY pH**
  - Calcium Oxalate
A patient with a history of calcium phosphate nephrolithiasis is diagnosed with a distal renal tubular acidosis. Which of the following is most likely to be present on the 24-hour urine specimen?

- A) Hyperuricosuria
- B) Urine pH < 5.5
- C) Hyperoxaluria
- D) Hypocitraturia
- E) Hypocalciuria
Answer 1

- Correct answer: (D)
- A distal renal tubular acidosis would lead to a systemic acidosis, resulting in bone resorption, and ultimately, hypercalciuria (not hypocalciuria). The defect in urinary acidification leads to a high urine pH. In order to attempt to correct the systemic acidosis, citrate is reabsorbed by the proximal nephron, resulting in hypocitraturia. The combination of the above factors strongly predisposes to formation of calcium phosphate nephrolithiasis. Uric acid and oxalate excretion are not typically altered in this disease state.
Question 2

- A patient presents with recurrent nephrolithiasis. No prior stone has been submitted for chemical analysis. Plain films of the abdomen reveal radio-opaque stones bilaterally in the area of the kidneys. Which dietary intervention is most recommended?
  - A) Fluid restriction
  - B) Calcium restriction
  - C) Diet high in animal proteins
  - D) Supplemental vitamin C
  - E) Sodium restriction
Answer 2

- Correct answer: (E)
- Calcium-based stones are by far the most common and the radio-opaque stones are suggestive of this composition. Fluid intake to produce at least 2 liters of urine output is recommended, as is a diet low in sodium and animal proteins (purines). Calcium restriction was associated with INCREASED stone formation, likely related to the lack of oxalate-binding in the diet. Sodium intake, rather than calcium, is the prime determinant of calcium urinary excretion. Vitamin C supplementation is not recommended as it may be converted to oxalate and increase the risk of calcium oxalate stone formation.