Review & Update in Nephrolithiasis

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A Systemic Disorder

♦ CKD
♦ Bone disease with fractures
♦ CAD
♦ HTN
♦ Type 2- DM
♦ Metabolic Syndrome
♦ Stroke
♦ Malignancies
♦ IBD
Epidemiology

- Pandemic - doubled prevalence / past 3 decades
- $5 billion / yr in USA
- 2 - 3 X in males
- Peak incidence, 40 - 60 yr old in males, late 20s in females and decreases by age 50.
- 6 - 12% of Americans in their lifetime
- Caucasian male > Asian, Hispanic > A-A female
Recurrence Rate After First Kidney Stone

Ann Intern Med 111:1006, 1989
Risk Factors

♦ Geographic location: S.E.
♦ Peak: Late summer
♦ Life style: White collar worker with sedentary life style
♦ Diet
♦ Medications
♦ F. Hx. : 60% have a first degree relative with Hx of stone disease
Drug Induced Nephrolithiasis

- **Indinavir (protease inhibitor):** 20% crystalluria, 4-43% renal stone, ~5 months on Rx, more soluble in UpH< 5.5, radiolucent or opaque
- **Ephedrine (Ma-Huang extract):** “energy suppl., wt. loss”, 0.06% of stones
- **Star fruit (Chinese remedy):** Oxalidaceae family, acute oxalate nephropathy
- **Sulfonamides:** 1-4 wks on Rx, bladder stones; Rx, Alkaline diuresis
- **Loop diuretics:** Hypercalciuria
- **Acetazolamide:** Hypokal. met. Acid., hypocitraturia, hypercalciuria, 15% stone
- **Allopurinol:** Xanthine stone
- **Vit. D / Vit A, Ca, anti acids**
- **Salicylate / Probenecid / Chemotherapy:** Uric acid stone
- **Vit C., Triamterene, MTX, Acyclovir, Amphotericin B, Glucocorticoids, Theophylline, guaifenesin, anticonvulsants (felbamate, topiramate [topamax], zonisamide), Orlistat.**
Hereditary Nephrolithiasis

- Distal RTA (aut. dom. AE1; aut. rec. B1 subunit- H-ATPase)
- Bartter’s syndrome
- Adenine / Hypoxanthine phosphoribosyl transferase def.
- Xanthine oxidase deficiency
- Cystinuria
- Hereditary hyperoxaluria
- Familial hyperparathyroidism
- Multiple endocrine neoplasia
- Idiopathic hypercalciuria
- ADPKD
- Dent’s disease (X-linked recessive nephrolithiasis)
- Hereditary hypomagnesemia hypercalciuria (Paracellin-1)
## Stone Composition

<table>
<thead>
<tr>
<th>Compound</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca-oxalate</td>
<td>60%</td>
</tr>
<tr>
<td>Ca-phosphate</td>
<td>15%</td>
</tr>
<tr>
<td>Uric acid</td>
<td>5-10%</td>
</tr>
<tr>
<td>Struvite</td>
<td>10-15%</td>
</tr>
<tr>
<td>Cystine</td>
<td>1-2%</td>
</tr>
</tbody>
</table>
Initial sites of crystal deposition in common Ca Oxalate patients

JCI 111:607, 2003
Initial sites of crystal deposition in intestinal bypass patients

JCI 111:607, 2003
Ca Oxalate Stone Formation

Interstitial Apatite
(Ca Phosphate)
(Randall Plaque)
Intestinal Bypass & Ca Phosphate (Brushite) Stone Formation

Duct of Bellini (Ca Phosphate) (Randall Plug)
### Urinary abnormalities in pts evaluated for nephrolithiasis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria (M &gt; 250, F &gt; 225 mg / 24 hr)</td>
<td>51%</td>
</tr>
<tr>
<td>Hyperuricosuria (M &gt; 750, F &gt; 700 mg / 24 hr)</td>
<td>42%</td>
</tr>
<tr>
<td>Hypocitraturia (M &lt; 250, F &lt; 300 mg / 24 hr)</td>
<td>34%</td>
</tr>
<tr>
<td>Hyperoxaluria (&gt; 40 mg / 24 hr)</td>
<td>34%</td>
</tr>
<tr>
<td>Hypomagnesuria (&lt; 5 mEq / 24 hr)</td>
<td>26%</td>
</tr>
<tr>
<td>Low urine volume (&lt; 1500 ml / 24 hr)</td>
<td>61%</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>2%</td>
</tr>
</tbody>
</table>

Excluding cystinuria and infection stones
Causes of Secondary Hypercalciuria
( < 10% of patients with hypercalciuria )

♦ With Hypercalcemia
  - Primary hyperparathyroidism
  - Granulomatous dis. ( sarcoidosis, TB, histiocytosis, histoplasmosis, etc. )
  - Lymphoma, MM
  - Bone metastasis
  - Paget’s disease
  - Prolonged immobilization

♦ Endocrine disorders
  - Hyperthyroidism
  - Cushing’s syndrome
Causes of Secondary Hypercalciuria
(< 10% of patients with hypercalciuria)

♦ Medications:
  - Furosemide
  - Acetazolamide
  - Vit. D intoxication
  - Milk - alkali syndrome

♦ Metabolic acidosis
  - Distal RTA

♦ Medullary sponge kidney
Causes of Secondary Hypercalciuria
( < 10% of patients with hypercalciuria )

♦ Medications:
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  - Acetazolamide
  - Vit. D intoxication
  - Milk - alkali syndrome

♦ Metabolic acidosis
  - Distal RTA

♦ Medullary sponge kidney
Medullary Sponge Kidney

In retrograde pyelogram there is reflux of contrast material into distended tubules in medullary pyramids.
Medullary Sponge Kidney

Clusters of calcifications in the upper and lower calyces
Resorptive Hypercalciuria of Hyperparathyroidism
Distal RTA

♦ Ca-phosphate stone
♦ Mechanism:
  – Acidosis induces bone loss → hypercalciuria
  – Alkaline urine pH → Ca-phosphate precipitation
  – Acidosis & hypokalemia → hypocitraturia
Idiopathic Hypercalciuria

- Absorptive hypercalciuria
  - Type I (24%)
  - Type II (30%)
- Renal phosphate leak (absorptive hypercalciuria type III) (19%)
- Renal Ca leak (8%)
- Bone resorption
Absorptive Hypercalciuria

- ↑ Ca absorption
- ↓ PTH
- ↑ Serum Ca

Hypercalciuria
Hypercalciuria

↓ Serum Ca

↑ 1,25 (OH)2 D

↑ Ca absorption

↑ PTH

↑ Bone resorption

Renal Hypercalciuria
Urinary Ca Excretion as a Function of Intestinal Ca Absorption

- **Normal adults**
- **Idiopathic Hypercalciuria**

Urine Ca (mg/d) vs Net intestinal Ca absorption (mg/d)
Mechanisms of Hypercalciuria in the Genetic Hypercalciuric Stone-Forming (GHS) Rats

- Increased intestinal Ca absorption
- No increase in serum vit. D level
- High urine calcium excretion rate on a very low Ca diet
- Increased bone resorption
- Primary defect in renal Ca reabsorption
- Increased number of vit. D receptors in intestine, bone and kidney
Hyperoxaluria

- Primary hyperoxaluria
  - Type I (80%): Hyperoxaluria & Glycolic aciduria
    (Alanine : Glyoxylate aminotransferase def. = AGT)
  - Type II (10%): Hyperoxaluria & L-glyceric aciduria
    (Glyoxylate reductase/Hydroxypyruvate reductase def. = GRHPR)
  - Type III (5%): Hyperoxaluria & Hypercalciuria & 4-hydroxyglutamate
    (Mutation in HOGA1 gene)

- Secondary hyperoxaluria
  - Dietary source / substrate (vit. C)
  - GI absorption:
    - Small bowel resection / bypass / pathology
    - Chronic pancreatic / biliary disease
    - Dietary Ca / Mg
Enteric Hyperoxaluria

- Dietary oxalate
  - Absorbed in colon
  - Ca availability
    - Ca complexed to fatty acids
      - Malabsorption of fatty acids & bile salts
        - Small bowel disease or resection
      - Dietary Ca
  - Insoluble CaOx
  - Dietary Ca

- 10% absorbed in colon
- 90% dietary Ca
<table>
<thead>
<tr>
<th>Condition</th>
<th>Typical urinary oxalate excretion rates (mmol/1.73 m²/24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal population</td>
<td>&lt;0.45 (&lt;40 mg)</td>
</tr>
<tr>
<td>Dietary and idiopathic hyperoxaluria</td>
<td>0.46–0.6 (40-60 mg)</td>
</tr>
<tr>
<td>Enteric hyperoxaluria</td>
<td>0.7–1.0 (60-90 mg)</td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>&gt;1.0 (90-270 mg)</td>
</tr>
</tbody>
</table>

*Table 1. Expected urinary oxalate excretion in various states.*
Hyperoxaluria

- The role of **Oxalobacter Formigenes**:
  - Oxalate degrading, colonic G⁻ anaerobic bacteria
  - Natural colonization at age ~ 1 yr
  - 100% colonization by age 3 - 10 yrs
  - 75% colonization by adult age
  - Completely absent in the majority of patients with:
    - cystic fibrosis
    - enteric hyperoxaluria
    - prolong Ab Rx
Hypocitraturia

♦ Citrate inhibits precipitation / crystallization / aggregation of Ca-oxalate & Ca-phosphate

♦ Etiologies:
  – Intracellular acidosis (dRTA)
  – Thiazides (hypokalemia)
  – Chronic diarrhea (hypokalemia & acidosis)
  – Animal protein intake
  – UTI
  – Idiopathic
Infection Stones (Struvite Stones)

- Magnesium ammonium phosphate & carbonate apatite stones
- Urease producing bacteria (proteus, klebsiella, citrobacter, pseudomonas, enterococci)
  - Urea $\rightarrow$ CO$_2$ + NH$_3$ $\rightarrow$ ↑ Urine pH > 8
  - Precipitates MgNH$_4$PO$_4$
- Women, paraplegics, quadriplegics
- Involves > 1 renal calyx $\rightarrow$ “staghorn stone”
Cystinuria

- Autosomal recessive
- Heterozygous (1/200), homozygous (1/20,000)
- Homozygotes are stone formers
- AA transport defect: Cystine, ornitine, argenine & lysine
- Risk factors:
  - Low urine volume
  - Urine pH < 7
  - Diet: salt & methionine
Patients Evaluation

♦ Family Hx
♦ Dietary Hx
♦ Medication Hx
♦ Past medical Hx
♦ Occupational Hx
Relative Probability of Forming a Kidney Stone in Relation to 24 hr Urine Volume
Effect of high water intake (>2 L/d) on stone recurrence rate and time to recurrence in CaOxalate stone formers

J Urol 155:839,1996
Urinary Ca Excretion Rate in Relation to Diets Containing Different Quantities of Protein & Ca

<table>
<thead>
<tr>
<th>Diet protein</th>
<th>Urine Ca (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg/d</td>
<td>50</td>
</tr>
<tr>
<td>800 mg/d</td>
<td>100</td>
</tr>
<tr>
<td>1400 mg/d</td>
<td>200</td>
</tr>
</tbody>
</table>
Ca balance in Relation to Diets Containing Different Quantities of Protein & Ca

<table>
<thead>
<tr>
<th>Diet protein (g/d)</th>
<th>Ca balance (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>100</td>
<td>140</td>
</tr>
</tbody>
</table>

Graph showing the relationship between diet protein (g/d) and Ca balance (mg/d) for different Ca intake levels: 1400 mg/d, 800 mg/d, 500 mg/d.
Daily Urinary Ca Excretion Rate in Relation to NAE Rate in Healthy Adults Fed 75 g Protein / Day, From Different Sources

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>Urine Ca (mg/24h)</th>
<th>Urine NAE rates (mEq/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetarian diet</td>
<td>100-120</td>
<td>12 mEq/d</td>
</tr>
<tr>
<td>Ovo-vegetarian diet</td>
<td>120-140</td>
<td>26 mEq/d</td>
</tr>
<tr>
<td>Animal protein diet</td>
<td>140-160</td>
<td>40 mEq/d</td>
</tr>
</tbody>
</table>
Urinary Ca Excretion in Relation to NAE Rates

Urine Ca (mg/d)

Urine NAE rate (mEq/d)
Dietary Protein Intake and Uric Acid Excretion

The graph shows a linear relationship between dietary protein intake (g/kg/24 hr) and uric acid excretion (mg/kg/24 hr). As dietary protein intake increases, the amount of uric acid excreted also increases linearly.
Effect of a short term increase in dietary animal protein (34 g/24 hr, above baseline) intake on urinary parameters of 6 normal males
Low Ca* vs. Normal Ca**, Low Protein, Low Salt Diet for Prevention of Recurrent Stones in Idiopathic Hypercalciuria

NEJM 346:77, 2002

*Ca 400 mg/d

** Ca 1200 mg, protein 1.17 g / Kg, salt 3 g/d

RR= 0.5
Laboratory Evaluation

♦ Strain all urine samples - stone analysis
♦ Urinalysis ± urine culture
♦ KUB / IVP / spiral CT / ultrasound
♦ Abbreviated study:
  – Chem 7, Ca, PO4, uric acid
  – +/- 24 hr urine “stone risk profile” X 1
Laboratory Evaluation

♦ Comprehensive study:
  - Not to be performed within 3 - 4 wks of an acute stone episode or during UTI
  - Chem 7, Ca, PO4, Mg, uric acid, PTH
  - Urine screen for cystine
  - Follow up 24 hr urine for response to dietary / drug interventions
Laboratory Evaluation

♦ Specialized testing:
  – One 24 hr urine after 1 wk of restricted diet: Ca < 400 mg / day, Na < 100 mEq / day, low oxalate, low purine
  – Fasting urine: Ca / Cr ratio
  – Oral Ca load: urine Ca / Cr ratio
Patient Work Up

♦ Low risk patient (first single stone, no F HX, no bowel disease)
  – Abbreviated study

♦ High risk patient (second stone, multiple stones, increasing size, + F HX, bowel dis., children)
  – Comprehensive study
Management

♦ Acute episode
  – Pain relief (narcotic analgesics / NSAIDS)
  – Tamsulosin, Ca Channel blockers
  – Hydration

♦ Reasons for urology consult:
  – UTI / urosepsis
  – Stone > 7mm
  – Complete ureteral obstruction
  – Solitary kidney
  – ARF
  – Persistent pain, no passage / movement of stone
Radiological Evaluation of Acute Flank Pain

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncontrast Helical CT Scan</td>
<td>96-100%</td>
<td>92-100%</td>
</tr>
<tr>
<td>US</td>
<td>24-61%</td>
<td>90-100%</td>
</tr>
<tr>
<td>IVP</td>
<td>64%</td>
<td>92%</td>
</tr>
<tr>
<td>KUB</td>
<td>46-54%</td>
<td></td>
</tr>
</tbody>
</table>

Both Helical CT and IVP were 100% sensitive to detect ureteral obstruction

*J Urol* 161:534, 1999
*Radiology* 217:792, 2000
Prevention of Further Stones

♦ Dietary modification:
  – High fluid intake ( urine out put > 2.5 L )
  – Low oxalate diet ( hyperoxaluria )
  – Low salt diet ( < 6 g salt; hypercalciuria, cystinuria )
  – Moderate Ca restriction ( hypercalciuria )
  – Low protein / purine diet ( hyperuricosurria, hypercalciuria, hypocitraturia )
Prevention of Further Stones

♦ **Pharmacological Rx:**
  - K- citrate (Urocit-K, Polycitra)
    - Corrects acidosis
    - Alkalinizes urine
    - Increases urine citrate
    - Dose: 20 mEq bid - tid
  - Thiazide diuretics (+ salt restriction)
    - Reduce hypercalciuria
    - Cause hypokalemia    hypocitraturia
    - Add K - citrate ± Amiloride
Prevention of Further Stones

♦ Pharmacological Rx:
  - K- phosphate (Neutral phosphate)
    • Rx phosphaturic patients
    • Suppresses 1, 25 (OH)2 D3
    • Increases urine citrate & pyrophosphate
    • Dose: 500 mg tid
Prevention of Further Stones

Pharmacological Rx:

- Allopurinol (hyperuricosuria)
- Mg supplement (hypomagnesuria)
- Ca supplement (enteric hyperoxaluria)
- Pyridoxine (B6) (PH-Type I)
- Captopril, D-penicillamine, Tiopronin (cystinuria)
- Acetohydroxamic acid (Lithostat) (urease inhibitor)
Prevention of Further Stones

Φ Pharmacological Rx:
   - Mercaptopropionyl glycine (Tiopronin = Thiola)
     • A complexing, reducing thiol compound
     • Forms soluble disulfide complex with cystine
     • Less side effects than D - penicillamine
     • More effective in alkaline urine
     • Given with K - citrate
     • Keep urine cystine concentration < 250 mg / L
     • 400-1200 mg/day
     • Side effects:
       - B6, Zn, Fe deficiency

Side effects:
   - B6, Zn, Fe deficiency