Calculus 101

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Class Questions

1. What imaging is not helpful to identify stones?
   - Renal ultrasound
   - KUB
   - CT
   - MRI

2. Which of the following urinary parameters determines the accuracy of a 24-hour urine collection?
   - Volume
   - Creatinine
   - Sodium

3. Calcium phosphate is the predominant stone in which of following conditions
   - Type 1 distal renal tubular acidosis
   - Gouty diathesis
   - Diabetes mellitus
Impact of Urinary Stones

- Estimated prevalence 8.8% in US, 19% men, 9% women (National Health and Nutrition Examination Survey)
- 75% of nephrolithiasis are calcium stones
- Recurrence rates 50% in 10 years in calcium stone formers
- Mortality rare, 28% renal deterioration with certain stones
Types of Stones: Most to least common

Calcium oxalate (monohydrate and dehydrate)
Uric acid
Struvite (magnesium ammonium phosphate)
Calcium phosphate
Cystine
Xanthine and drug related stones
Stones are solutes that occur in amounts too high to stay dissolved (supersaturating) in urine

- Calcium oxalate stones form from an initial calcium phosphate concretion that originates near the renal calyx epithelium of the terminal collection duct.
- The calcium phosphate concretion (Randall’s plaque) erodes through the urothelium, is exposed to urine, and forms a nidus of calcium oxalate deposition.
Types of Hypercalciuria

› **Absorptive**- inherited as a autosomal dominant trait, is excessive passive mucosal absorption of calcium in the jejunum, results in high normal serum calcium

› **Resorptive**- rare. Excessive PTH secretion from a parathyroid adenoma leads to bone resorption, increased renal synthesis of calcitrol, and enhanced intestinal absorption of calcium.
  – Primary hyperparathyroidism (5% of nephrolithiasis)
  – Sarcoidosis, malignancy associate

› **Renal Leak**- impaired renal tubular reabsorption of calcium, reduces serum calcium which causes increased PTH, that results in increased intestinal calcium absorption caused by enhanced VIT D synthesis and mobilization of calcium from bone all which results in hypercalciuria. Serum calcium remains normal because the loss of calcium in urine is offset by enhanced intestinal calcium absorption and bone resorption.
Renal Tubular Acidosis

› Type 11, in proximal, defect of bicarbonate retrieval caused by poorly characterized mechanisms in renal tubules (not associated with nephrolithiasis)

› Type 1, in distal tubule is not able to generate a steep H+ gradient results in metabolic acidosis and elevated urine PH. The elevated urine PH favors calcium phosphate crystals. Often have a urine PH>6.8 (Normal PH of urine 6.5-7.0 in morning and 7.5-8.0 in evening-food)
Hyperoxalurias

- **Primary**- rare inborn errors, autosomal recessive, secondary to decrease in activity of hepatic enzymes. Stones begin in childhood leads to renal failure-liver, kidney transplant

- **Increased substrate**- pyridoxine (vitamin B6 deficiency)

- **Enteric Hyperoxaluria**- most common-colonic hyperabsorption-increased amounts of fatty acids and bile salts result in increased permeability of oxalate in colon.
  - Malabsorption syndromes have a 7-10% chance of forming stones
Uric Acid Stones

- Product of purine metabolism
- Uric acid is 100 times more soluble at a PH > 6 compared to PH < 5.5
- Most common risk factor acidic urine including the lack of a normal postprandial alkaline tide
- Patients with persistent acidosis-distal tubular acidosis
- Gout (hyperuricemia) 20% cases
- Hyperuricosuria associated chemotherapy (lymphoma and leukemia) sudden lysis of millions of cells releases large quantity of purines
Struvite Stones

- Caused by UTI with urease producing organisms, most common Proteus mirabilis. (E coli is not a urease producing organism) Treat surgical, aggressive antibiotics
- Urease is responsible for making urine more alkaline. Cleaves urea into two moles of insoluble ammonium
- Phosphate is less soluble at alkaline urine and precipitates onto the insoluble ammonium, yielding magnesium ammonium phosphate
Cystine Stones

- Autosomal recessive gene for cystine transport by renal tubular and intestinal cells. Amino acids (cystine, ornithine, lysine, arginine) Decreased tubular reabsorption. Cystine is only one of 4 amino acids whose solubility is low enough to precipitate to form stones.

- More soluble at a pH of 9.6 and higher, difficult to achieve.

Normally excrete <100 mg cystine/day. Cystine stone formers excrete >200mg/day.

1% of stone formers.
Medications

- 10% HIV patients on Indinavir develop stones, risk is higher for those who have Hepatitis B, C, or hemophilia and those who take SMX-TMPX
- Topamax, Laxatives, Guafenison
- Xanthine stones
  - Nitrogen compound, extremely rare genetic disorder.
Who is at Risk for Stones?

Number of factors for calcium stone formers including metabolic, anatomic, urinary, climate, and dietary factors.

1. Southern states, stone belt of America, Caucasian males, age 40-70.
2. 2.6 relative risk of a stone with a positive family hx
3. Obesity-purine excess, salt, urine found to have a lower PH
4. Diabetes – insulin resistance causes defects in renal production of ammonia, lowering the PH of urine, increased calcium excretion
5. Chronic diarrhea-excess oxalate, calcium may bind with fat instead of oxalate
What are the Symptoms?

› Flank pain, one sided abdominal pain, renal colic from obstruction
› UVJ stones often associated with bladder symptoms, frequency, urgency
› Gross or microscopic hematuria are present on 90% of patients.
› Hydronephrosis/obstruction may cause nausea and vomiting
› Fever with obstruction, pyelonephritis
CT Abdomen/Pelvis non contrast gold standard, low dose in future

Predictive values: positive and negative are 100% and 91% with CT, and 97% and 74% with IVP

KUB 75%-90% if stones are radiopaque stones

Ultrasound insensitive to ureteral stones, able to visibly see hydronephrosis, no radiation.

Describe location of stone either renal, ureteropelvic junction (UPJ), proximal ureter, mid ureter, distal ureter, ureterovesical junction (UVJ)
CT ABD/Pelvis non-contrast
2/3 of ureteral stones pass within 4 weeks of onset of symptoms.

MET (Medical Expulsion Therapy) ureteral smooth muscle relaxation includes alpha blockers (29% increase in passage) and calcium channel blockers (9%).

Reasons to treat — uncontrolled pain with oral narcotics, fever, vomiting, job.

### Chance of Passing Ureteral Stones

<table>
<thead>
<tr>
<th>Size of Ureteral Stone</th>
<th>Days to pass (mean)</th>
<th>% likelihood of need for intervention</th>
</tr>
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<tbody>
<tr>
<td>3 mm</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>4-6 mm</td>
<td>22</td>
<td>50</td>
</tr>
<tr>
<td>&gt; 6 mm</td>
<td>-</td>
<td>99%</td>
</tr>
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</table>
ESWL (Extracorporeal Shockwave Lithotripsy)

- Work by a sharp peak in positive pressure followed by a trailing negative wave
- The change in density and acoustic impedance from water to calculus results in stone fragmentation
- All lithotripters have (1) an energy source, (2) device to focus shock wave at a local point, (3) coupling medium, and (4) stone localization.
ESWL cont.

- Size does matter (less than 2 cm); stone composition
- Treatment option for renal and proximal, mid ureteral stones, not pelvic stones
- Stone free rates 56% to 80% (Less success lower pole renal stones) Randomized trial 35%
- Joseph, et al- Stone density (HU) success 54.5% for stones 1000 HU or greater; 87% success 500 HU-1000; and 100% less than 500 HU
- Obesity- Skin to stone distance greater than 10 cm predictive of failure
- Complications: Steinstrasse 3-6%, hematoma 4.1-19%, symptomatic less than 1%
- larger renal stones require stent
- Contraindications to ESWL: bleeding, UTI, pregnancy
Ureteroscopy laser lithotripsy, stent

› Holmium lasers, electrohydraulic
› Major downside is the requirement of stent, ESWL better patient acceptance as a result
› Complications infection, bleeding obstructing visual field, injury to ureter, ureteral stricture
› Difficult to reach lower pole renal stone
Percutaneous Nephrolithotomy (PCNL)

- IR places nephrostomy access, Urologist laser lithotomy, usually requires overnight stay in hospital
- Stone free rates 85-100%
- Highest rate of complications and longest convalescence, 4-8% infections/ urosepsis, pain, pulmonary complication related to percutaneous access
- Contraindications: bleeding, UTI, body habitus
Treatment Decisions

- Stones greater than 2 cm should be treated with PCNL
- Stones between 1 cm and 2 cm, density >1000 HU, skin to stone distance >10 cm or cysteine stones, ureteroscopy felt to be safer more efficacious for stones in all locations recommended.
- Newer ureteroscopes and improved laser, ureterscopy
- Complication rates for URS ureteral perforation rates less than 2% or less. Overall stone free rates 81-94% and vast majority of patients stone free after one procedure
Renal ultrasound: done one to two months after stent removal to ensure hydronephrosis has resolved (7%)

- KUB- calcium stones but does not evaluate hydro

- Referral to Stone Prevention Clinic, first time stone formers option

- High Risk should be evaluated-multiple stones, advanced age, comorbidities, anatomic-solitary kidney, duplex ureter, horseshoe kidney (fused kidney 20% increased risk), medullary sponge kidney (rare congenital disorders small cysts form in tubules which reduce outward flow of urine)

- All children refer to a nephrologist/stone prevention
Stone Prevention

› 2, 24 hour urine collections is recommended, 4-6 weeks post treatment

› Quest or Litholink-clear, easy to read, recommendations for treatment

› Creatinine is measured to assess accuracy of collection
  – Males- 18-24 mg/kg daily
  – Females 15-20 mg/kg daily
Metabolic Stone Evaluation

- 24 hr urine for total volume, PH, calcium, oxalate, sodium, uric acid, citrate, phosphate, magnesium, sulfate, creatinine, cystine-option
- Serum calcium, phosphorus, uric acid, BUN and creatinine, bicarbonate, albumin, alkaline phosphate, intact PTH, 1,25-di-OH-vitamin D2 (optional)
- Stone composition analysis
Most Common Factors

› Low urine volume
› Hypercalciuria
› Hypocitraturia
Supersaturation

› Saturation describes the ability of urine to keep minerals dissolved

› Supersaturation describes a state above formatting product or the estimation of the concentration product of ions in urine relative to their solubility product in aqueous solution.

› Solubility of calcium oxalate is 4 X higher in urine than in water

› Once solubility is exceeded, crystals can form

› Presence of inhibitors ie. Citrate and magnesium, increases solubility by 7-11 X
Altering Supersaturation

› Increase volume/water: 2.5 liters of urine a day
  – (De Silverio, et al) Supersaturation was not significantly influenced by water type, tap water vs. purified water

› Decrease solutes ie oxalate

› Alter PH

› Add inhibitors
AUA Recommendations

- All calcium stone formers should increase fluid intake to maintain adequate urine volume (2.5 liter/day for adults) and to consume a DASH diet (Dietary Approaches to Stop Hypertension) based on more fruits, vegetables, whole grains, nuts, legumes, low fat dairy products, fewer sweetened beverages, sodium, and red or processed meats.

- Increased water intake has decreased risk of stone recurrence by up to 50% in idiopathic calcium stone formers.

- Sugar sweetened beverages including cola and non-cola beverages associated with increased risk by 23%-33% based on 3 large prospective studies.
Dietary cont.

- Reduced dietary calcium consumption and increased oxalate consumption increases risk for forming a stone (also increased risk of fracture risk-osteopenia)
- Dietary calcium better than supplemental possibly due to time of day they are taken and not with meals not binding with dietary oxalate.
  - Calcium: Milk-300 mg, yogurt-450 mg
- Increased sodium consumption augments calcium excretion and reduces citrate excretion
- Animal protein consumption amplifies calcium and uric acid excretion
- Subjects consuming 1.2 liters of orange juice daily, increased urinary citrate excretion similar to 60 meq potassium citrate daily
Oxalate found in food and is generated from metabolism of glycine, hydroxyproline and Vitamin C. It is estimated that 10-50% of urinary oxalate is derived from dietary oxalate. Recommend no more than 500 mg Vitamin C day.

Foods high in oxalate: rhubarb, spinach, swiss chard, cocoa, pepper, beets, wheat bran

Reduced oxalate consumption decreases urinary excretion recommend- <100 mg daily for adults
Pharmacologic Therapy—indicated for pt who do not respond to dietary therapy or need a more aggressive approach

- **Hypercalciuria**—Level one evidence—Thiazide diuretics
  - Inhibit sodium reabsorption in distal convoluted tubule, promoting water and sodium loss, resulting in volume contraction which promotes passive reabsorption of calcium in proximal tubule leading to diminished urinary excretion—30-50% reduction in calcium excretion in 7 days
    - HCTZ 12.5 to 50 mg BID
    - Indapamide 12.5 mg–2.5 mg QD (long acting)
    - Chlorthalidone 25–50 mg QD (long acting)

- Fish oil—studies vary (has been shown to decrease oxalate excretion)
- Hypercalciuria due to renal phosphate leak—rare—treat with K-Phos Neutral QID
Hypocitraturia—several etiologies distal RTA, bowel disturbances, use of thiazide diuretics

- Therapy of choice for CaOX stone formers is potassium citrate as it increases urine PH and urinary citrate excretion, corrects or improves metabolic acidosis and inhibits precipitation of calcium oxalate crystals.
- Potassium citrate reduces risk of uric acid crystals
- Dosage 20-30 meq BID (Pt’s with 1 RTA may require higher doses) Liquid or pill; use liquid with small bowel issues
- Sodium citrate or sodium bicarbonate is used in patients who do not tolerate potassium preparation (alternative in pt with elevated K, kidney dz—should not be used with 1 RTA, have hypokalemia
Hyperuricosuria in calcium nephrolithiasis and normal urinary calcium

- allopurinol 100 mg QD to TID-xanthine oxidase inhibitor that blocks conversion of hypoxanthine to xanthine, a uric acid precursor-Stephen-Johnson syndrome, gout, rash, increased liver enzymes

- Febuxostat-new ono-purine inhibitor with lower risk of hypersensitivity may be an alternative in future, clinical effectiveness unknown
Primary Hyperparathyroidism

› Hypercalcemia and increased parathyroid hormone level, PTH
  – Do not initiate thiazide if hypercalcemia
› May not be readily apparent – diagnosis unmasked in those who are started on a thiazide diuretic to reduce calcium excretion and found to have hypercalcemia
› Surgical removal of offending parathyroid gland
Augmenting Magnesium excretion

› Increases solubility of calcium, oxalate and phosphate in urine and theoretically increases citrate excretion

› No level one evidence

› Magnesium 500 mg BID, causes diarrhea
Hyperoxaluria

- Majority of patients have idiopathic/dietary hyperoxaluria and for those who do not respond to dietary measures
- pyridoxine 50-100 mg QD can be considered, neurotoxicity
  No well controlled studies

Calcium supplements consider if low normal calcium excretion (calcium citrate)

Enteric hyperoxaluria-pt with anatomic or functional small bowel problem resulting in malabsorption. Treat with calcium supplements

Calcium citrate 1 to 2 GM TID with meals
Uric Acid stone formers

› Alkalinizing urine first line therapy
› Treat with potassium citrate, as long as PH controlled can’t have too much citrate
› Consider allopurinol for persistent stones or failed citrate therapy
Cystine Stone formers

› Alpha-MPG, tiopronin 300 to 1200 mg day in adults
› Work by promoting a disulfide exchange reaction with cysteine creating a more soluble compound
› Refer to nephrologist
Follow-up

› Repeat single 24 hour urine after change in therapy and annually
› Check serum studies for patients on medications
› Periodically do follow-up imaging
› Monitor for infections (struvite)
Questions?

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Title and Content Layout with Chart
Two Content Layout with SmartArt

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- Second bullet point here
- Third bullet point here

- **Group A**
  - Task 1
  - Task 2

- **Group B**
  - Task 1
  - Task 2

- **Group C**
  - Task 1