Stones, Bones and other Potential HPN Complications

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Disclosures

- Excerpts from "Bacteria, Bones, and Stones: Managing Challenging Complications of SBS"
- ASPEN 2018
- E Johnson, L Matarese, D Seidner
- No relevant financial disclosures
HPN Complications that will not be covered*

- Infection: Systemic, tunnel, exit $^{1,2}$
- Hyper and hypoglycemia $^{1,2}$
- Dehydration $^1$
- Catheter: Clot, tear, cracked hub $^1$
- Vein inflammation $^1$
- Air emboli $^1$
- PNALD (use webpage search engine)

*Available at https://Oley.org
1. On HPN complication chart
2. Resources: My HPN- Online Education
Presentation Outline

• Stones = Nephrolithiasis (kidney stones)
• Bones = Osteoporosis and osteomalacia
• Bacteria = SIBO & D-Lactic Acidosis
Nephrolithiasis
Nephrolithiasis

• General Population: 8.4%
  – Calcium, Oxalate, Urate, Cysteine, Xanthine, Phosphate

• Prevalence of symptomatic stones 42-50% after GI ops
  – Colon-in-continuity: calcium oxalate
  – End-jejuno- or ileostomy: calcium oxalate and uric acid

Gut 1992;33:1493-97
NEJM 2004;350:684
Risk Factors for Stone Formation

<table>
<thead>
<tr>
<th>Surgical anatomy</th>
<th>Stone type</th>
<th>Predisposing factors</th>
</tr>
</thead>
</table>
| Jejuno-colic anastomosis              | Calcium oxalate  | - Dehydration / Low Urine Volume (all stones)  
- Increased amount of luminal oxalate d/t low calcium concentrations d/t steatorrhea.  
- Enhanced colonic absorption d/t unabsorbed bile salts, especially if TI resection <100 cm.  
- Decreased bacterial degradation  
- Enhanced production  
  Pyridoxine deficiency  
  Thiamine deficiency  
  Gut bacteria ? |
| *** Colon in continuity ***           |                  |                                                                                                                                                     |
| 25% incidence of stones               |                  |                                                                                                                                                     |
| Jejunostomy or ileostomy              | Calcium oxalate  | - Hypocitraturia  
- Hypomagnesuria (minor)                                                                                                                                 |
| 10-15% incidence of stones            | Uric acid        | - Low urine pH                                                                                                                                       |

Tomson CRV, Nephrocalcinois and nephrolithiasis.  
**Oxalate Nephropathy**

- **Enteric Hyperoxaluria**
  - Ca Ox
  - FA
  - Short bowel no colon
  - Ca FA
  - Ox
  - Short bowel with colon
  - Ca Ox stones
  - Ox
  - Bile salts
  - Ox
  - Ca FA

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* From AGA

Silberg DG et al. Biol Chem 1995;270:11897
Urinary Oxalate Excretion after Ileal Resection

- 24-hour urinary oxalate excretion
- 12/18 (66%) of resected patients had hyperoxaluria
- 3 patients passed stones
- Patients with the largest resections (or most extensive disease) had the greatest degree of hyperoxaluria

NEJM 1973;289(4):172
Effect of Oxalate Free Diet on Urinary Oxalate Excretion

- 4 subjects w/ ileal resection and high U oxalate.
- 24 hr urine on three consecutive 5 day periods
- Oxalate excretion fell to normal values within 24 hours of starting low oxalate diet (< 4 gm vs 100-200 mg)
- Returned to high values on resumption

NEJM 1973;289(4):172
## High Oxalate Foods

<table>
<thead>
<tr>
<th>Food Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruits</td>
<td>Blackberries, black raspberries, blueberries, red currants, dewberries, figs, grapes, gooseberries, kiwi, lemon peel, orange peel, red raspberries, rhubarb, strawberries, tangerines, any juice made from above fruits</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Beans (green, wax, dried), beets (tops, roots, greens), celery, chives, collards, dandelion, eggplant, escarole, kale, leeks, mustard greens, okra, parsley, parsnips, peppers (green), pokeweed, rutabagas, sorrel, summer squash, sweet potatoes, Swiss chard, tomato soup, vegetable soup, watercress, yams</td>
</tr>
<tr>
<td>Meat substitutes, beans, nuts, seeds</td>
<td>Almonds, baked beans canned in tomato sauce, cashews, green beans (waxed and dried), peanut butter, peanuts, pecans, sesame seeds, sunflower seeds, tofu (soybean curd), walnuts</td>
</tr>
<tr>
<td>Beverages</td>
<td>Any juice made from high oxalate fruits, draft beer, chocolate (plain), chocolate milk, cocoa, coffee powder (instant), Ovaltine, tea (brewed)</td>
</tr>
<tr>
<td>Starches</td>
<td>Fig Newtons, fruit cake, graham crackers, grits, white corn, kamut, soybean crackers, wheat germ</td>
</tr>
<tr>
<td>Condiments</td>
<td>Ground cinnamon, raw parsley, pepper (&gt;1 tsp/day), ginger, soy sauce</td>
</tr>
</tbody>
</table>
Ability of Different Probiotic Strains to Metabolize Oxalates In Vitro

- Oxalate-degrading activity of 13 lactobacilli and 5 bifidobacteria tested
- Lactobacillus strains were more efficient than bifidobacteria in degrading oxalates.
- L. paracasei LPC09 (DSM 24243) gave the best result, with 68.5% of ammonium oxalate conversion followed by L. gasseri and L. acidophilus species.
- Clinical utility unclear

J Clin Gastroenterol 2014;48:591
Symptoms

• Pain in the lower back, flank, groin
• Nausea / vomiting
• Blood in the urine
• Pain when urinating
• Unable to urinate, urinary frequency
• Fever / chills.
• Foul smelling or cloudy urine
Other Risk Factors

• Medical conditions
  – HBP, DM, Gout, Obesity, Malabsorption, Parathyroid disease, Hypercalciuria

• Medications
  – Diuretics, Ca antacids, Dilantin, Cipro, Ceftriaxone and others

• Family history of kidney stones

• Blockage or repeat infections of the UT
Evaluation and Management

- Blood tests
- Urine sample test
- Stone analysis
- Imaging study
  - CT
  - US
  - IVP
  - Plain film
- IVF
- Pain medication
- Medication to relax the ureter
- Minimally-invasive procedures
- Surgery
# Minimize Stone Formation in SBS

<table>
<thead>
<tr>
<th>Methods</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate fluid and salt intake (consider NaCl suppl)</td>
<td>In SBS urine volume and urine sodium are reduced due to malabsorption. Increase fluid and salt intake to increase urine output to prevent stone formation.</td>
</tr>
<tr>
<td>Low fat diet</td>
<td>Reduce fatty acids that binds intraluminal calcium → leads to that leads to an increase in free oxalate, (unbound) → increased absorption of dietary oxalate.</td>
</tr>
<tr>
<td>Calcium supplementation</td>
<td>Bind oxalate in the gut.</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Binds bile salts and oxalate, reducing oxalate absorption in the colon.</td>
</tr>
<tr>
<td>Low oxalate diet</td>
<td>Reduce oxalate intake to reduce oxalate excretion.</td>
</tr>
<tr>
<td>Low sodium and animal protein intake</td>
<td>Reduce urinary calcium excretion. (most helpful with intact GI tract)</td>
</tr>
<tr>
<td>Potassium citrate supplements</td>
<td>Alkalinize urine and can prevents urinary calcium oxalate, urate and phosphate crystal formation.</td>
</tr>
<tr>
<td>Avoid systematic acidosis (consider NaHCO3 suppl)</td>
<td>Acidosis reduces citrate excretion and urine pH which can cause calcium oxalate crystal formation in the urine.</td>
</tr>
<tr>
<td>Magnesium supplements</td>
<td>Hypomagnesemia leads to reduced citrate excretion (minor effect, difficult in SBS)</td>
</tr>
<tr>
<td>Probiotics ??</td>
<td>Oxalate degrading.</td>
</tr>
</tbody>
</table>
Metabolic Bone Disease

Osteoporosis

Risk
- Genetic susceptibility
- Inactive lifestyle
- Age (over 45)
- Insufficient mass
- Growth

1 in 3 women and 1 in 5 men over 50 will experience osteoporosis fracture

Prevention and treatment
- Diet
- Dairy products
- Restful sleep
- Calcium and Vitamin D
- Limit coffee
- Stop smoking
- Limit alcohol
Osteoporosis vs. Osteomalacia

2001 NIH definition OP: A skeletal disorder characterized by **compromised bone strength** (integration of bone density and bone quality) predisposing of present increased risk of fracture. [fragility fracture]

OM: Defective bone mineralization at the bone-osteoid interface with Increased bone volume but increased fracture risk

- Altered vitamin D nutrition or metabolism
- Phosphate wasting disorders
- Metabolic acidosis
- Defective bone mineralization
- Inhibitors of bone mineralization
Normal Trabecular Bone
Osteoporosis
Osteomalacia
Prevalence of *Osteoporosis* in Intestinal Failure and Insufficiency


P<0.001 comparing Controls to IF and II for O’osis and O’penia
Risk Factors for IF-MBD

Disease Associated Factors

- Short bowel syndrome
  - Malabsorption
  - Renal calcium wasting
  - Metabolic acidosis
    - Diarrhea (non-anion gap)
    - D-lactic acidosis (anion gap)
- Malignancy
  - Disease and Rx associated
    - Anorexia
    - Malabsorption
- Malignancy-cont’d
  - Hypogonadism
  - Paraneoplastic
- IBD
  - Vitamin D deficiency
    - Avoidance of dairy
    - Malabsorption
  - Corticosteroids
  - Hypogonadism
  - Inflammatory cytokines

Seidner DL JPEN 2002
Risk Factors for IF-MBD

• Documented deficiency
  – Protein, vitamin D, calcium, magnesium

• Theoretic deficiency
  – Vitamin K, vitamin C, copper, fluoride, boron

• Potential PN toxicity
  – Vitamin A, vitamin E, cadmium, strontium, vanadium, fluoride (mineral water)

Ferrone M, Geraci M. NCP 2007
Vitamin D Status in IF / II

• Vitamin D deficiency in intestinal failure
  – 96 pts: 28% mild 25-50 nmol/l, 14% mod <25 nmol/l, Nygaard ‘17
  – 186 pt: 50% mod, 26% severe, Napartivaumnuay N. Nutrients ‘17

• Vitamin D deficiency in intestinal insufficiency
  – 71 pts: 31% mild 25-50 nmol/l, 17% mod <25 nmol/l, Nygaard ‘17
  – 77 pts: 44% mod, 25% severe, Ellegard L. Clin Nutr ‘13
  – 60 pts: 65% mod 10-20 ng/ml, 30% sevr <10 ng/ml, Fan S. NCP ‘17
PN Factors that Affect Bone Mineral Density

• Increase calcium excretion
  – Amino acid (titratable acid)
  – Sodium (increase GFR)
  – Calcium
  – Dextrose (insulin)
  – Cycled infusion

• Decrease calcium excretion
  – Phosphorus

Seidner DL JPEN 2002
Ferrone M, Geraci M. NCP 2007
PN Factors that Affect Bone Mineral Density

- Adversely alters bone metabolism
  - Magnesium (low)
    - PTH secretion and renal activity
    - Abnormal vitamin D metabolism
  - Metabolic acidosis
    - Amino acids produce weak organic acids
    - Chronic diarrhea, d-lactic acidosis
  - Heparin (modest doses)
  - Vitamin D (low, inactive)
  - Aluminum (any)

Seidner DL JPEN 2002
Ferrone M, Geraci M. NCP 2007
• Prevention & Treatment of IF-MBD*
  – Diagnosis and monitor MBD with DEXA and biochemistry. (#109-110. grade: low)
  – Promptly address risk factors for OP in all patients on LT-HPN. (#111. grade: very low)
  – The primary step is to optimize PN with required vitamin D, calcium, and phosphate. Medical treatment may increase BMD and lower fracture risk. (#112. grade: low)

*Strength of recommendations are all strong
DXA Measurement
(Dual-energy X-ray Absorptiometry)

- Considered the clinical standard “Gold Standard”
- Measures BMD at multiple sites
  - Spine
  - Hip
  - Forearm
  - Total body

- Cannot ddx OP vs OM
# Patient Evaluation

## Evaluation

<table>
<thead>
<tr>
<th>Serum</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMP, Mg, Phos</td>
<td>Initial followed qwk for ~3 months</td>
</tr>
<tr>
<td>iPTH</td>
<td>Malabsorption or hyperpara suspect</td>
</tr>
<tr>
<td>25-OH vitamin D (1, 25 OH vitamin D)</td>
<td>Malabsorption suspect</td>
</tr>
<tr>
<td>TSH</td>
<td>Hyperthyroidism suspect</td>
</tr>
<tr>
<td>C-telopeptide (CTX)</td>
<td>Measures bone resorption, monitor response to tx. (fragments of type I collagen)</td>
</tr>
</tbody>
</table>

## Radiographic

| DEXA**                        | Baseline, every 1 to 3 years, prn                |

## Urine

| 24-hour Ca, Mg                | Monitor every 6 to 12 months                    |

**Optimally on the same scanner**
Management of MBD

- **Eliminate secondary causes of MBD**
  - Treat underlying disease, infections, chronic inflammation
  - Diagnose and treat hyperthyroidism, hypogonadism, hyperparathyroidism
  - Discontinue tobacco use
  - Minimize alcohol intake
  - Taper or stop glucocorticoids
  - Encourage weight bearing exercise
PN Preparation

• Calcium gluconate - 15 meq (3 gm salt)
• Phosphate - serum conc mid-range
  – Ca:PO$_4$ ratio or 5meq:10 mmol
  – 10-14 mmol / 1000 kcal dextrose
• Acetate - serum bicarb mid-range
• Sodium – balance intake with output
• Amino acids - 1.5 g/kg/d, reduce when visceral proteins normalize and patient is well
ESPEN Guideline Caveats

• PN Aluminum less than 25 mcg/L Klein GL AJCN ’95
• Supplement vit D if elevated PTH and low 25-hydroxy vit D Ellegard L. Clin Nutr ’13
• Consider temporary withdrawal of vit D if low BMD, PTH and 1, 25-OH D Verhage AH JPEN ’95
  – Provide Vitamin D 200 IU/d = MVI-13
• Consider IV clodronate, pamidronate, zolindronic acid (bisphosphonates)
Medications FDA Approved for OP

- Inhibits osteoclasts (bone resorption)
  - Conjugated estrogens
  - Selective estrogen receptor modulators
  - Bisphosphonates
  - Calcitonin
  - RANKL inhibitors
- Stimulates osteoblasts (bone anabolism)
  - Parathyroid hormone
Long-term PN Does Not Exacerbate OP

- 56 HPN 5.5 ± 1.2 y
- 67% with OP
- T-scores improved, esp if SBS onset >21yo

Cohen-Solal M.
J. Bone Miner. Res. ‘03
Long-term PN Does Not Exacerbate OP

- 75 HPN 4.1 + 1.9 y, 4.4 + 2.9 scans,
  - BMD loss of 1% annual (p< .005) no different than age- and sex-matched healthy subjects.
  - Model estimates of BMD for CD was significantly lower than non-CD. Haderslev KV. JPEN 2004

- 65 HPN 18.1 + 5.5 mos
  - Increase lumbar spine (P = 0.04).
  - Multiple regression found LS Z-score to correlate negatively with female sex age starting HPN. Pironi L. Clin Nutr 2004
Small Intestinal Bacterial Overgrowth

• Predisposing factors
  – Blind loop, stricture, internal fistula
  – Increased intestinal transit
  – Decreased gastric acid, pancreatic secretions
  – Absence of ileocecal valve

• Consequences
  – Bacteria metabolize luminal nutrients AND cause mucosal injury → diarrhea, gas, bloat/pain
  – D-lactic acidosis → neurologic symptoms
• Diagnosis of SIBO
  – Intestinal aspirate: >$10^5$ CFU/mL of bacteria grown from jejunal fluid or the presence of colonic or oropharyngeal bacterial species
  – Hydrogen Breath Test: Undigested sugar in colon produce excess hydrogen (unreliable in SBS d/t rapid GI transit)

• Consequences
  – Nutrient Malabsorption
    • Mucosal inflammation, villous atrophy
    • Deconjugate bile salts, produce lithochoholic acid
  – Toxins:
    • Ammonia, D-lactate, alcohol, peptidoglycans
  – Symptoms: Poor appetite, diarrhea, gas, bloating
Symptoms with D-lactic acidosis

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>100</td>
</tr>
<tr>
<td>Slurred speech</td>
<td>52</td>
</tr>
<tr>
<td>Ataxia</td>
<td>32</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>29</td>
</tr>
<tr>
<td>Weakness</td>
<td>16</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>13</td>
</tr>
<tr>
<td>Aggressive behavior</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
</tr>
<tr>
<td>Acute CHF</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>3</td>
</tr>
<tr>
<td>Blurry vision</td>
<td>3</td>
</tr>
<tr>
<td>Explosive speech</td>
<td>3</td>
</tr>
<tr>
<td>Echolalia</td>
<td>3</td>
</tr>
<tr>
<td>“Feeling drunk”</td>
<td>3</td>
</tr>
<tr>
<td>Depression</td>
<td>3</td>
</tr>
</tbody>
</table>

- Postulated mechanisms for neurologic symptoms
  - Direct effect on brain
  - Other organic compounds


Oh. NEJM 1979;301249

Bongaerts Clin Chem 1995;41:107

Godey. AJG 2000;95:3675
Clinical D-Lactic Acidosis

- Metabolic acidosis with ≥ 1 of the following:
  - Typical neurologic symptoms
  - Serum D-lactic acid > 3mmol/L, normal L-lactate
  - Acidosis induced by food intake that improves with restriction
  - Recent completion of antibiotics or initiation of probiotics
  - Negative urine Acetest / ketone bodies
  - Culture bacteria capable of producing D-lactate

Uribarri. Medicine 1998;77(2):73
Acute Treatment of D-Lactic Acidosis

- IV hydration with sodium bicarbonate
- Avoid Ringer’s lactate solution
- Restrict enteral CHO, PN as needed
- Thiamine (B1) supplementation for increased pyruvate dehydrogenase activity
- Antibiotics and Probiotics unpredictable
- In rare cases hemodialysis
SIBO Management

• Surgical intervention if partial SBO or bowel tapering/lengthening if dilated
• Diet modification
  – High complex carbohydrates (CHO), low simple sugar, low fat as needed (SBS diet)
  – Low lactose, as needed
  – Treat vitamin and mineral deficiencies (B12, etc.)
  – In D-lactic acidosis, cautiously reintroduce CHO

Quigley, E. Infect Dis Clin N Am 2010;24:943
SIBO Management

• Antibiotics (off label) – 7 day course
  – Amox/Clavulanate 500/125 mg po tid, #21, $63
  – Metronidazole 250 mg po tid, #21, $24
  – Rifaximin 550mg po bid, #14, $$$$$

• Probiotics (over the counter)

• Limit anti-secretory and anti-diarrheal meds

Quigley, E. Infect Dis Clin N Am 2010;24:943
Conclusion

• Diet modification, oral supplements, and medications may be helpful in nephrolithiasis, PN associated-MBD, and SIBO
• Only medications for MBD are FDA approved
• Modify PN to optimize bone metabolism
• Treat all underlying associated diseases
THANK YOU