Hypercalcemia (11)

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- **Incidence**
  - Found in ~15% of hospitalized adult patients (often incidentally)
- **Pathophysiology**
  - 1% of total body Ca circulates in the body and is exchangeable with extracellular fluid; the rest resides in bone
    - ~50% of extracellular calcium is ionized → physiologically active
    - ~40% bound to protein (mostly albumin) → affected by protein levels
      - Correction of total serum Ca for hypoalbuminemia: Add 0.8 mg/dL to measured serum Ca for every 1 g/dL decrease in albumin (with normal albumin value of 4 mg/dL)
    - Remainder complexed with anions to form calcium salts
- **Etiology**
  - Entry of Ca into the circulation exceeds excretion in urine/deposition into bone
    - Accelerated bone resorption, increased gastrointestinal absorption, decreased renal excretion (or combination of these factors)
  - #1 cause → primary hyperparathyroidism (usually due to parathyroid adenoma)
    - Activated osteoclasts resorb bone + increased intestinal absorption of Ca
  - #2 cause → malignancy (this is the most common cause in hospitalized patients)
    - Bone metastases cause local osteolysis; multiple myeloma causes release of osteoclast activating factors; solid tumors secrete PTHrp; lymphoma causes PTH-independent extrarenal production of calcitriol
  - Less common causes
    - Increased bone resorption → thyrotoxicosis, immobilization (several weeks), Paget disease, vitamin A intoxication
    - Increased calcium absorption in intestine → increased calcium ingestion, milk-alkali syndrome, increased endogenous production of $1,25(OH)_2D$ (granulomatous disease, vitamin D excess)
    - Misc: Lithium, thiazide diuretics, tamoxifen, adrenal insufficiency, theophylline toxicity, familial hypocalciuric hypercalcemia (FHH)
- **Presentation**
  - Symptoms depend on degree and acuity of increase in Ca level
  - Mild hypercalcemia (up to 11-11.5 mg/dL)
    - Symptoms, if present at all, are nonspecific (fatigue, constipation, depression)
  - Moderate/severe hypercalcemia (>12-14 mg/dL)
    - Chronic elevation may be well tolerated
      - Patient may still develop nephrolithiasis (from chronic hypercalciuria) and type 1 renal tubular acidosis
    - Acute rise can cause marked symptoms
      - Polyuria (decreased concentrating ability of distal tubule), polydipsia, **dehydration**, acute renal insufficiency, anorexia, nausea, muscle weakness, bone pain, altered mental status
      - EKG may show shortened QT interval, AV block, bradycardia

- Neuropsychiatric disorders most common in patients with primary hyperparathyroidism (anxiety, depression, cognitive dysfunction)

No characteristic physical exam findings

- **Diagnosis**
  - **First**, **confirm elevated calcium level**
    - Recheck value. Correct for albumin vs. check ionized Ca.
  - **Second**, **check PTH**
    - Elevated or high normal PTH indicates PTH-mediated cause → primary hyperparathyroidism (and very rarely FHH)
      - PTH at the upper end of normal range is inappropriate as the PTH should be *suppressed* in patients with high serum Ca
    - Low serum PTH indicates non-PTH mediated cause→ continue workup
  - **If PTH is low, then check**
    - Parathyroid hormone-related peptide (PTHrp)
    - Vitamin D (1,25-dihydroxyvitamin D and 25-hydroxyvitamin D)
      - Elevated 25(OH)D suggests vitamin D intoxication
      - Elevated $1,25(OH)_2D$ suggests granulomatous disease/lymphoma
  - **If PTHrp and Vitamin D levels are normal, then check**
    - Serum and urine protein electrophoresis, TSH, Vitamin A
  - Other clues
    - Mild elevation in PTH can also be due to familial hypocalciuric hypercalcemia (low urine Ca level confirms)
    - Thiazide diuretics enhance Ca resorption in distal tubule → low urine Ca
    - Low or low-normal serum phosphorous →hyperparathyroidism and humoral hypercalcemia of malignancy
      - PTH inhibits proximal tubule phosphate reabsorption
    - Calcium > 13 mg/dL usually due to malignancy; <11 mg/dL or high normal typical of hyperparathyroidism
- **Treatment**
  - Indicated if Ca > 14 or Ca > 12 in symptomatic patient (if asymptomatic then only hydration necessary for Ca of 12)
  - Hydration, usually aggressive, is mainstay of treatment
    - Normal saline at 200-300 cc/hour if severe/symptomatic
  - Consider furosemide 20-100 mg IV after volume replete
    - Mainly to avoid volume overload (does not reduce Ca quickly)
  - Bisphosphonates indicated in malignancy-associated hypercalcemia
    - Pamidronate or zoledronic acid (peak effect takes 48-72 hours)
  - Calcitonin useful if rapid lowering not accomplished with hydration
    - Rapid onset but short duration, patients can develop tolerance (tachyphylaxis within 48-72 hours).
  - Glucocorticoids are first line after hydration in hematologic malignancies or vitamin D intoxication (suppress $1,25(OH)_2D$)
  - Hemodialysis can be used for resistant, life-threatening hypercalcemia
  - And, of course, treat the underlying condition

- Consider parathyroidectomy in patients with primary hyperparathyroidism who meet criteria set forth by National Institutes of Health (age <50, T score < -2.5, Creat clearance < 60, calcium > 1mg/dl above normal).

- **References for Further Reading**

  - Carroll Mary F and Schad David S. A Practical Approach to Hypercalcemia. *Am Fam Physician* 2003; 67:1959-66. (**Contains a great diagnostic algorithm!)**
  - French Sarah, Subauste Jose, Geraci Stephen. Calcium Abnormalities in Hospitalized Patients. *Southern Medical Journal* 2012; 105(4):231-7.
  - Khosia, Sundeep. Hypercalcemia and Hypocalcemia. In: Longo, Dan L et al, eds. *Harrison's Principles of Internal Medicine* – 18th ed. New York, NY: McGraw-Hill; 2012:360.