

# Hypercalcemia: Student Handout

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## Hypercalcemia: A Student Guide to High Calcium

### Learning Objectives

- Distinguish PTH-mediated from non-PTH hypercalcemia using lab interpretation
- Recognize severe hypercalcemia as medical emergency
- Implement hydration and bisphosphonate therapy safely
- Understand dose optimization and alternatives like denosumab

### Definition and Severity

**Hypercalcemia** = Total calcium >10.5 mg/dL (ionized >5.5 mg/dL)

Severity	Level	Symptoms	Urgency
<b>Mild</b>	10.5-12	Often asymptomatic	Outpatient evaluation
<b>Moderate</b>	12-14	Nausea, constipation, confusion	Admit, treat within hours
<b>Severe</b>	>14	Coma, arrhythmias, renal failure	ICU, immediate treatment

### The Diagnostic Puzzle: Two Main Causes

#### PTH-Mediated (30% of cases)

**Primary hyperparathyroidism** (most common outpatient cause) - Usually from adenoma (85%), rarely parathyroid cancer - Mild, asymptomatic at presentation - PTH elevated or normal (inappropriately normal for high calcium)

**Clinical clue:** Outpatient, discovered on screening, minimal symptoms

#### Non-PTH-Mediated (70%, especially inpatients)

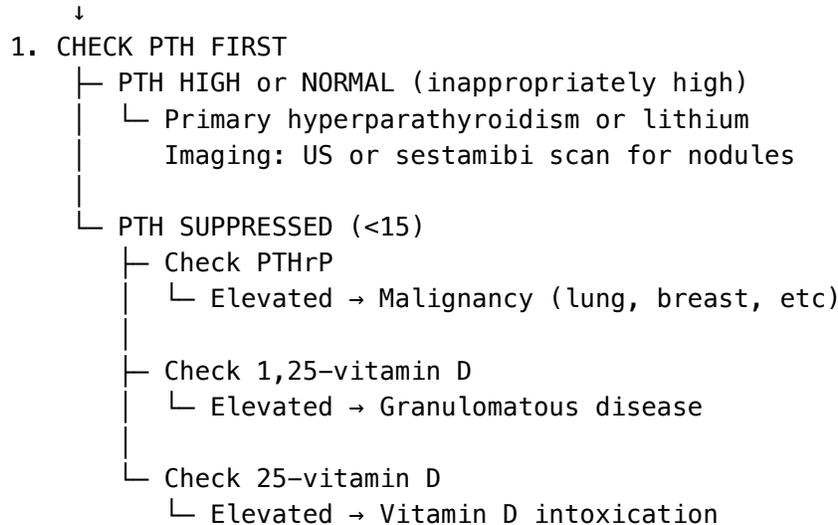
**Malignancy with PTHrP** (80% of non-PTH cases) - Lung cancer (squamous cell most common) - Breast, ovarian, renal cell, lymphomas - PTH suppressed, PTHrP elevated - Prognosis poor (median survival 2-3 months)

**Vitamin D-mediated** (granulomatous disease) - Sarcoidosis, tuberculosis, fungal infections - Macrophages make calcitriol (active vitamin D) - 1,25-vitamin D elevated despite PTH suppressed

## Thyroid toxicosis, vitamin D intoxication

### Diagnostic Algorithm

HYPERCALCEMIA detected (Ca >10.5)



### Acute Management (Severe Hypercalcemia)

#### Step 1: IV Hydration (Start Immediately)

- **Goal:** Enhance urinary calcium excretion
- **Regimen:** 200-300 mL/hour normal saline
- **Monitor:** Urine output, CVP, cardiopulmonary status
- **Caution:** Loop diuretics NO LONGER recommended (causes hemoconcentration)
- **Timeline:** Can lower calcium 2-4 mg/dL in first 24 hours

#### Step 2: Bisphosphonate (Effects appear in 2-4 days)

**Zoledronic acid (Zometa)** - PREFERRED - Dose: 4 mg IV over 15+ minutes - Efficacy: Normalizes calcium in 88% of patients - Peak effect: 2-4 days - Duration: 3-4 weeks - Monitor: Check creatinine before dose; adjust for renal impairment

**Pamidronate** - Alternative - Dose: 60-90 mg IV over 2-4 hours - Efficacy: 70% response rate - Slower but similar timeline to zoledronic acid

**Key limitation:** Bisphosphonate nephrotoxicity risk - Avoid if CrCl <30 mL/min - Use extended infusion times (30-60 minutes) - Monitor creatinine daily × 3 days - Hydrate well before administration

#### Step 3: Bridge Therapy While Awaiting Bisphosphonate Effect

**Calcitonin** (for urgent rapid lowering only) - Dose: 4-8 IU/kg IV/SC every 6-12 hours - Onset: 4-6 hours - Peak effect: 12-24 hours - Limitation: Tachyphylaxis within 48-72 hours - Use: Bridge therapy only, not maintenance

**Prednisone** (if granulomatous disease) - Dose: 40-100 mg daily - Inhibits macrophage calcitriol production - Works only for vitamin D-mediated hypercalcemia - Useless for malignancy-related

#### Step 4: Address Underlying Cause

- Treat malignancy
- Vitamin D intoxication: restrict vitamin D intake
- Granulomatous disease: treat infection

### Alternative Therapies

#### Denosumab (Prolia)

**When to use:** - Bisphosphonate-refractory disease - Severe renal impairment (CrCl <30 mL/min)  
- Patient intolerance to IV bisphosphonates

**Advantages:** - RANKL inhibitor (blocks bone resorption differently than bisphosphonates) - Single subcutaneous dose: 120 mg - Response in 2-4 days - No renal function adjustment needed

**Major risk:** REBOUND HYPERCALCEMIA after stopping - Can occur 4-9 months later - Severe hypercalcemia possible - Requires long-term management plan (oral bisphosphonates or re-dosing)

#### Dialysis

- For severe refractory cases
- Effective but last resort
- Most ICU patients respond to hydration + bisphosphonate

### Monitoring During Treatment

Timeframe	Parameter	Action
<b>Before treatment</b>	Creatinine, calcium	Baseline; guides bisphosphonate dose
<b>During hydration</b>	Daily Ca, Cr, input/output	Adjust rate, watch for overload
<b>Days 2-4</b>	Daily calcium	Monitor for bisphosphonate response
<b>After bisphosphonate</b>	Every 3-7 days × 3 weeks	Ensure sustained response
<b>Long-term</b>	Monthly (if applicable)	Monitor for relapse

### Management by Etiology

#### Primary Hyperparathyroidism

- **Definitive:** Parathyroidectomy (95%+ cure rate)
- **Medical:** Cinacalcet lowers calcium; bisphosphonates improve bone density

- **Surgical candidates:** Age <50, symptomatic, severe hypercalcemia
- **Non-surgical:** Monitor annually; treat when symptomatic

### Malignancy-Related

- **Prognosis:** Poor (median 2-3 months)
- **Treatment:** Aggressive: hydration + bisphosphonate + cancer therapy
- **Follow-up:** May need repeated bisphosphonate dosing (often becomes PTHrP-independent)

### Vitamin D-Mediated

- **Granulomatous disease:** Corticosteroids (40-100 mg daily)
- **Vitamin D intoxication:** Restrict D intake, hydrate
- **Usually self-limited** once underlying condition treated

### Dose Optimization Considerations

**Standard zoledronic acid 4 mg** is FDA-approved, but: - Some clinicians use **2 mg** in elderly, renal insufficiency, or mild hypercalcemia - Original trials showed no difference between 4 mg and 8 mg - **Lower doses warrant further investigation** but may reduce nephrotoxicity

Current practice: Use standard 4 mg with extended infusion (30-60 minutes) rather than dose reduction.

### Practice Questions

**Q1:** A 72-year-old with CrCl 25 has malignancy-related hypercalcemia (calcium 13.8, suppressed PTH, elevated PTHrP). How do you treat?

Answer

Aggressive hydration first (200-300 mL/hour saline). Given borderline renal function, consider denosumab 120mg SC instead of zoledronic acid (no renal adjustment needed). If using zoledronic acid, reduce dose, extend infusion to 60 minutes, and monitor creatinine carefully. Calcitonin can bridge while awaiting effect. Treat underlying cancer.

**Q2:** A patient received denosumab for malignancy-related hypercalcemia. One month later, she's asymptomatic with normal calcium. What's the long-term plan?

Answer

Don't stop and hope for the best! Rebound hypercalcemia occurs 4-9 months later in many patients. Start maintenance oral bisphosphonate (alendronate 70mg weekly) or plan for re-dosing denosumab. Educate patient on warning signs (thirst, nausea, confusion) and arrange close follow-up.

**Q3:** A 68-year-old with primary hyperparathyroidism has asymptomatic calcium 11.2. He doesn't want surgery. What's your management?

Answer

Observation with annual monitoring is safe for asymptomatic mild hypercalcemia (calcium <12, no symptoms). Monitor calcium, phosphate, PTH yearly. Surgery indicated only if: symptoms

develop, calcium rises significantly, kidney function declines, osteoporosis worsens, or patient changes mind. Cinacalcet can lower calcium if intervention needed but doesn't prevent progression.

## Key Takeaways

- **Check PTH first** to distinguish primary hyperparathyroidism from other causes
- **Hydration is foundation** of acute management
- **Bisphosphonates take 2-4 days** to work (need bridge therapy with calcitonin)
- **Denosumab alternative** for renal dysfunction or bisphosphonate failure
- **Rebound hypercalcemia risk** with denosumab—plan long-term management
- **Malignancy-related** usually requires aggressive treatment; prognosis poor
- **Granulomatous disease** responds to corticosteroids, not bisphosphonates
- **Primary hyperparathyroidism** = parathyroidectomy definitive treatment
- **Asymptomatic mild** hypercalcemia can be observed

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**Memory aid:** “CHIMPANZEES” = Calcium from Hypercalcemia Involves Malignancy, PTHrP, Adenoma, Nodules, Zoledronic (acid), Excess vitamin D, Endocrine, Sameness (similar labs with different causes)

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## See Also

### Related Student Handouts

- Calcium and Phosphorus Disorders
- CKD Complications

### Clinical Content (01-Clinical-Medicine/Nephrology)

- Electrolyte Disorders Hub
- Essential Renal Laboratory Tests

### Butler-COM Resources

- Butler COM - Nephrology Deep Dive