



Hypercalcemia

PTH splits the differential · Saline first, then the antiresorptive

CHECK PTH EARLY

it does all the work

CONFIRM AND ASSESS *correct it, then grade it*

CORRECT FOR ALBUMIN

Corrected Ca = measured Ca + $0.8 \times (4.0 - \text{albumin g/dL})$. In hypoalbuminemic inpatients a "normal" calcium may be genuinely high. **Ionised calcium** is the definitive measure where available or where binding is unpredictable.

GRADE IT

Mild < 12 mg/dL · **Moderate** 12–14 · **Severe** > 14 mg/dL. Symptoms track the **rate of rise** as much as the absolute number — a rapid rise to 12 can be more symptomatic than a chronic 13.

SYMPTOMS

Stones, bones, abdominal groans, psychic moans — polyuria and dehydration, bone pain, constipation, nausea, pancreatitis, confusion and coma. **ECG: short QT**, and bradyarrhythmia at high levels.

PTH SPLITS THE DIFFERENTIAL *one test, two branches*

PTH result	What it means
PTH raised or inappropriately normal PTH-dependent	Primary hyperparathyroidism — the commonest cause in outpatients, usually an adenoma, often found incidentally and mildly raised for years. Also tertiary hyperparathyroidism in chronic kidney disease, lithium , and familial hypocalciuric hypercalcemia . Check a 24-hour urine calcium to exclude FHH, which is benign and must not be operated on.
PTH suppressed PTH-independent	Malignancy — the commonest cause in inpatients, and usually a rapid rise in an unwell patient. Then granulomatous disease (sarcoid, TB), vitamin D toxicity , thyrotoxicosis , immobilization, milk-alkali syndrome , thiazides, and excess vitamin A.
Then narrow further	Send PTHrP , 25- and 1,25-dihydroxyvitamin D , SPEP with free light chains , TSH, and imaging directed by the history. Raised 1,25-vitamin D points to granulomatous disease or lymphoma; raised PTHrP indicates humoral hypercalcemia of malignancy.

TREAT IT *volume, then block bone resorption*

- 1 Isotonic saline is the first and most important step.** These patients are profoundly dehydrated from calcium-induced nephrogenic diabetes insipidus. Restoring volume alone lowers calcium through dilution and restored renal excretion.
- 2 Do not give a loop diuretic routinely.** Reserve furosemide for **volume overload** once rehydrated — giving it early worsens dehydration and raises the calcium further. This is an outdated reflex worth unlearning.
- 3 Stop the contributors:** thiazides, lithium, calcium and vitamin D supplements, and excess vitamin A. Mobilize the patient, since immobilization drives resorption.
- 4 Calcitonin for rapid control** in severe disease. It works within hours but **tachyphylaxis limits it to 48–72 hours** — it is a bridge to the antiresorptive, not a treatment in itself.
- 5 Antiresorptive therapy is the definitive step.** Takes 2–4 days to work, which is exactly why calcitonin covers the gap.

HYPERCALCEMIA OF MALIGNANCY *Endocrine Society 2022 — a change worth knowing*

WHICH ANTIRESORPTIVE

Adults with hypercalcemia of malignancy should receive **denosumab** or an **intravenous bisphosphonate**, and the guideline **suggests denosumab over an IV bisphosphonate**. In severe disease (calcium > 14 mg/dL), use **calcitonin combined with denosumab or an IV bisphosphonate** as initial treatment. For **refractory or recurrent** hypercalcemia despite a bisphosphonate, **use denosumab**.

TWO EXCEPTIONS

Calcitriol-mediated hypercalcemia (granulomatous disease, some lymphomas) should be **treated first with glucocorticoids**, adding denosumab or a bisphosphonate only if steroids are insufficient. **Parathyroid carcinoma** may be treated with a **calcimimetic**, or an IV bisphosphonate or denosumab. **Denosumab is not renally cleared**, which makes it attractive in renal impairment — but it causes **more hypocalcemia**, so monitor closely.

PRIMARY HYPERPARATHYROIDISM *the outpatient half of the problem — who needs surgery*

Indication for parathyroidectomy	Detail
Symptomatic disease	Any patient with kidney stones , fragility fracture , or overt symptoms should be referred — surgery is curative in experienced hands.
Age under 50	Younger patients accumulate decades of exposure, so surgery is favored even when asymptomatic.
Calcium above the reference range	Serum calcium more than 1 mg/dL above the upper limit of normal .
Skeletal involvement	T-score ≤ −2.5 at any site, or a vertebral fracture on imaging.
Renal involvement	eGFR < 60 , nephrolithiasis or nephrocalcinosis on imaging, or 24-hour urine calcium > 400 mg/day with an increased stone risk.
If not operating	Monitor calcium and renal function annually and bone density every 1–2 years . Maintain adequate hydration and avoid thiazides and lithium. Cinacalcet lowers calcium where surgery is not possible, though it does not improve bone density.

REFRACTORY OR RECURRENT DISEASE *when the calcium will not come down*

RECHECK THE MECHANISM

If calcium rebounds quickly after an antiresorptive, the driver may not be bone resorption. **Calcitriol-mediated** disease needs steroids; **PTH-driven** disease needs a calcimimetic or surgery. Re-measure **PTH**, **PTHrP** and **1,25-vitamin D** rather than repeating the same drug.

LAST-LINE MEASURES

Hemodialysis with a low-calcium bath for severe, refractory hypercalcemia, particularly with renal failure or heart failure where saline loading is unsafe. **Denosumab** is the preferred antiresorptive when renal function precludes a bisphosphonate. Throughout, **treat the underlying malignancy** — hypercalcemia of malignancy is a poor prognostic marker and oncological control is the durable answer.

PEARLS & PITFALLS

- Do not reach for furosemide.** Fluid is the treatment; diuretics early make the dehydration and the calcium worse.
- Always correct for albumin**, or check an ionised calcium. Unrecognized hypercalcemia in a hypoalbuminemic patient is common.
- Check a urine calcium before referring for parathyroidectomy** — familial hypocalciuric hypercalcemia is benign and surgery does not help.
- Calcitonin buys 48–72 hours only.** Start the antiresorptive at the same time, not after.
- Denosumab is now suggested over IV bisphosphonates** for hypercalcemia of malignancy, and is preferred in renal impairment — but watch for hypocalcemia.
- Steroids first for granulomatous or lymphoma-related hypercalcemia**, since the mechanism is excess 1,25-vitamin D rather than bone resorption.

