Diagnostic approach to Hypercalcemia

Dr. zhila afshar

Assistant professor of pediatric endocrinology and metabolism

(Shiraz university of medical science)

CONFIRM HYPERCALCEMIA:

The first step in the evaluation of a patient with hypercalcemia:

- repeat measurement (ionized calcium)
- total calcium corrected for albumin
- distinguish hemoconcentration(eg, due to severe dehydration)
- thrombocythemia-associated hypercalcemia (due to release of intracellular calcium in vitro)
- preferably fasting and without venous occlusion
- previous values for serum calcium

should also be reviewed.

history and physical examination:

- kidney stones or fractures;
- weight loss;
- back or bone pain;
- fatigue or weakness;
- cough or dyspnea;
- ingestion of vitamins, calcium preparations, lithium, or thiazides;
- Facial and cardiovascular signs of Williams syndrome
- subcutaneous nodules consistent with fat necrosis,
- deformities of metaphyseal chondrodysplasia or infantile hypophosphatasia)
- efforts to assess chronicity by seeking prior results.

Laboratory evaluation:

- once hypercalcemia is confirmed, **the next step** is **measurement of serum PTH** .

- **(PTH)-mediated hypercalcemia:**
- primary and tertiary hyperparathyroidism
- familial hyperparathyroid syndromes
- familial hypocalciuric hypercalcemia
- lithium-induced hypercalcemia
- **non-PTH mediated hypercalcemia :**
- primarily malignancy
- vitamin D intoxication
- granulomatous disease

PTH:

- **Elevated parathyroid hormone:**

1-primary hyperparathyroidism .

- **Mid- to upper-normal or minimally elevated** :

1-primary hyperparathyroidism(10 to 20 percent)

2-familial hypocalciuric hypercalcemia

- **Low-normal or low** (below 20 pg/mL) :

1-non-PTH-mediated hypercalcemia(PTHrp and vitamin D metabolites)

Vitamin D metabolites :

25(OH)D ↑:

- vitamin D intoxication: ingestion of either vitamin D or calcidiol itself .
- many experts define vitamin D intoxication as a value >150 ng/mL

1,25-dihydroxyvitamin D↑:

- direct intake of this metabolite,
- extrarenal production in granulomatous diseases
- lymphoma
- increased renal production that can be induced by primary hyperparathyroidism but not by PTHrp .

PTHrp:

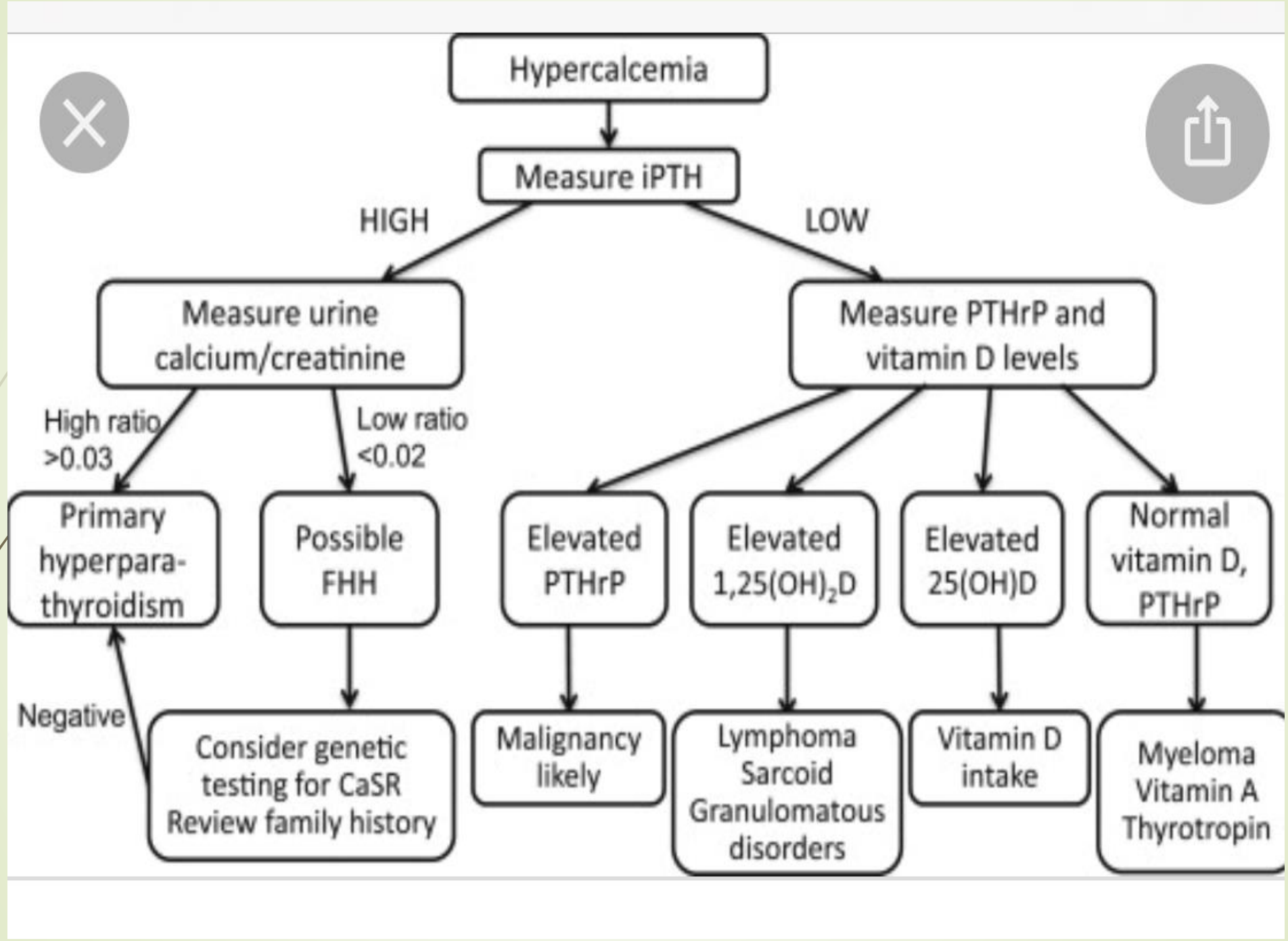
- PTH-related protein — Humoral hypercalcemia of malignancy
- one of the most common causes of non-(PTH)-mediated hypercalcemia.
- if there is clinical evidence of malignancy, usually a solid tumor
- the hypercalcemia is of relatively recent onset.
- However, this assay is usually not necessary for diagnosis, since most patients have clinically apparent malignancy. Levels of PTH and 1,25-dihydroxyvitamin D (calcitriol) are usually appropriately suppressed in these patients .
- Nevertheless, because the diagnosis of malignancy as the cause of hypercalcemia is usually clinically obvious, and the PTH assay can be used to diagnose primary hyperparathyroidism, the role of PTHrP assays in clinical practice is limited.

Other tests :

low serum levels of PTH, PTHrp, and low or normal vitamin D metabolites:

- multiple myeloma
- thyrotoxicosis
- immobilization
- vitamin A toxicity
- milk-alkali syndrome

(SPEP and urinary protein electrophoresis [UPEP] for possible multiple myeloma, TSH, vitamin A) will often provide the correct diagnosis.


Hypercalcemia
Measure iPTH
HIGH
LOW
Measure urine calcium/creatinine
Measure PTHrP and vitamin D levels
High ratio >0.03
Low ratio <0.02
Primary hyperpara-thyroidism
Possible FHH
Elevated PTHrP
Elevated 1,25(OH)2D
Elevated 25(OH)D
Normal vitamin D, PTHrP
Negative
Consider genetic testing for CaSR Review family history
Malignancy likely
Lymphoma Sarcoid Granulomatous disorders
Vitamin D intake
Myeloma Vitamin A Thyrotropin

serum phosphate concentration:

- ***frank hypophosphatemia or low-normal serum phosphate levels :***
- Hyperparathyroidism
- humoral hypercalcemia of malignancy (due to PTHrp)
- ***phosphate concentration is normal or elevated:***
- granulomatous diseases,
- vitamin D intoxication,
- immobilization,
- thyrotoxicosis,
- milk-alkali syndrome,
- metastatic bone disease.
- The serum phosphate concentration ***is variable:*** in familial hypocalciuric hypercalcemia.

Treatment of hypercalcemia

- Treatment for hypercalcemia should be aimed:

  1-lowering the serum calcium concentration

  2-treating the underlying disease

- The **degree of hypercalcemia**, along with the **rate of rise of serum calcium** concentration, often determines symptoms and the urgency of therapy.

1-Mild hypercalcemia :<12 mg/dL

2-Moderate hypercalcemia :12 and 14

3-Severe hypercalcemia :>14 mg/dL

PREFERRED APPROACH

- ***Mild hypercalcemia*** — asymptomatic or mildly symptomatic (<12 mg/dl) do not require immediate treatment.
- **they should be advised to avoid factors:**

1-thiazide diuretics

2- lithium carbonate therapy,

3-volume depletion,

4-prolonged bed rest or inactivity

5-high calcium diet (>1000 mg/day).

- **Adequate hydration** (at least six to eight glasses of water per day) is recommended to minimize the risk of nephrolithiasis.

Moderate hypercalcemia :

- **Moderate hypercalcemia** — between 12 and 14 mg/dL
- ***chronic moderate hypercalcemia:*** Asymptomatic or mildly symptomatic
- may not require immediate therapy
- they should follow the same precautions
- ***acute rise to these concentrations:*** marked changes in sensorium
- requires more aggressive therapy. (saline hydration and bisphosphonates.)

Severe hypercalcemia :

- ***Severe hypercalcemia*** — (>14 mg/dL) require more aggressive therapy.
- hydration
- Administration of salmon calcitonin
- bisphosphonates

Hydration:

- —**with 0.9% saline (twice maintenance volume over 24 to 48 hours)—**
- restores intravascular volume
- dilutes and decreases serum Ca
- increases glomerular filtration of Ca
- decreases reabsorption of Ca21 in the proximal and distal renal tubules
- **hydration alone usually lowers the total serum calcium concentration 1 to 3 mg/dL.**
- In the absence **of renal failure or heart failure**, loop diuretic therapy to directly increase calcium excretion is not recommended, because of potential complications and the availability of drugs that inhibit bone resorption, which is primarily responsible for the hypercalcemia.

salmon calcitonin :

- Administration of salmon calcitonin (4 international units/kg)
- repeat measurement of serum calcium in several hours. (calcitonin sensitive)
- repeated every 6 to 12 hours (4 to 8 international units/kg).
- tachyphylaxis to calcitonin after 24 to 48 hours
- Calcitonin generally is well tolerated
- transient nausea, vomiting, abdominal cramps, flushing, and local skin reactions may occur.

Bisphosphonates:

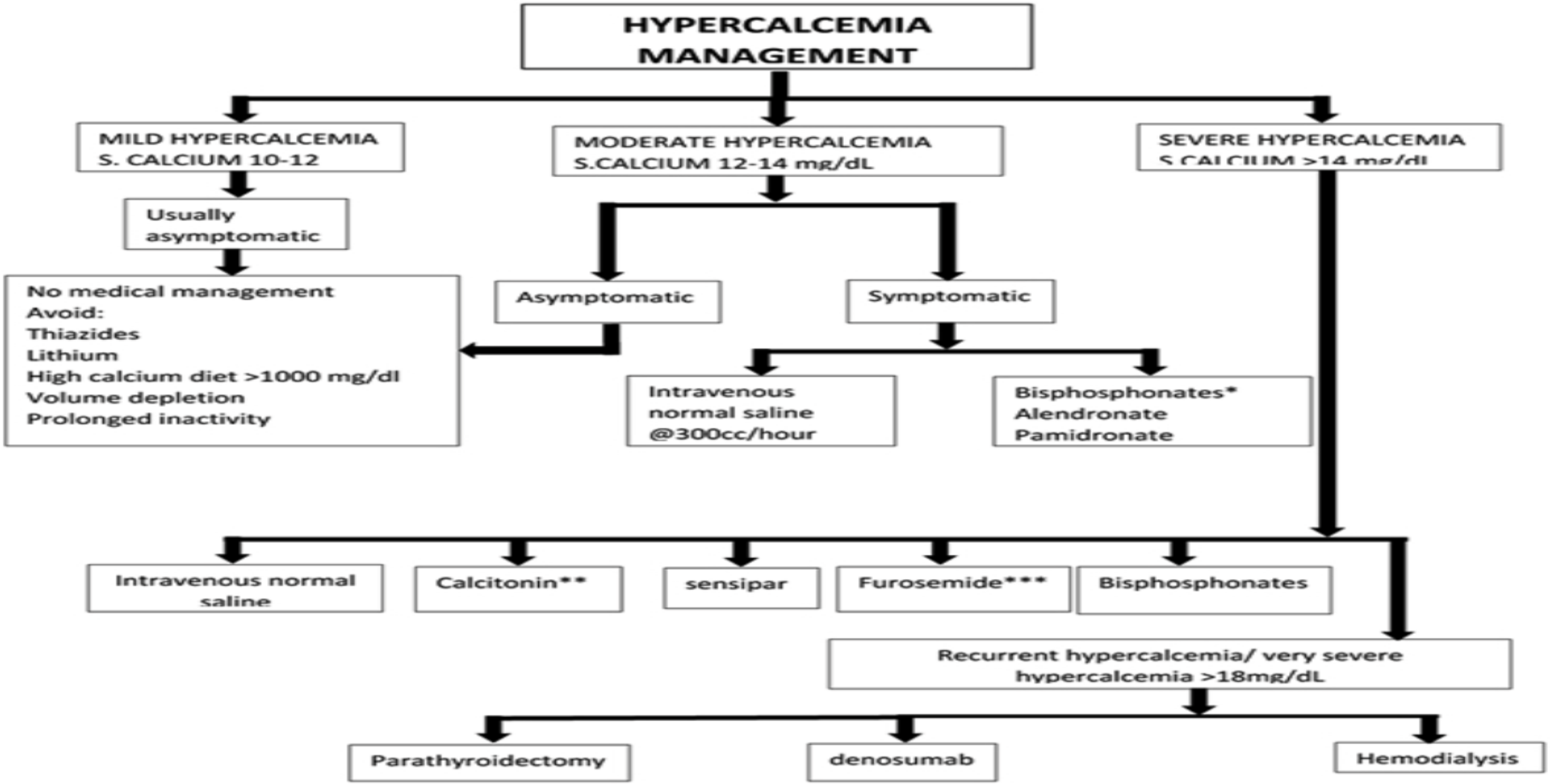
- zoledronic acid
- pamidronate (0.5 to 2 mg/kg in 30 mL normal saline IV over 4 hours)
- ZA is preferable because it is superior to pamidronate in reversing hypercalcemia related to malignancy.
- Contraindicated: (due to severe renal impairment) (GFR <30 mL/minute)

- **denosumab** :
- RANKL Inhibitor(monoclonal antibody directed against RANKL)
- can be administered concurrently with calcitonin.
- The administration of calcitonin plus saline: within 12 to 48 hours.
- The bisphosphonate :by the second to fourth day

Hemodialysis:

- very severe, symptomatic hypercalcemia. (18 to 20 mg/dL)
- neurologic symptoms but a stable circulation
- severe hypercalcemia complicated by renal failure.

MANAGEMENT OF HYPERCALCEMIA



Disease-specific approach

- ***Parathyroid carcinoma:***
- surgery.
- When the tumor is no longer amenable to surgical intervention:
- bisphosphonates
- calcimimetic agents
- denosumab.
- ***lymphoma, sarcoidosis, or other granulomatous causes:***
- low calcium diet,
- corticosteroids,
- treatment of the underlying disease.

- **ingestion of calcitriol:** usually lasts only one to two days
- stopping the calcitriol,
- increasing salt and fluid intake,
- perhaps hydrating with IV saline may be the only therapy that is needed.
- ***parent vitamin D or calcidiol:*** lasts longer
- glucocorticoids :(IV or oral) hydrocortisone(I mg/kg intravenously every 6 hours)
- ZA or pamidronate
- Ketoconazole(3 to 9 mg/kg/day in three divided doses)
- ***familial hypocalciuric hypercalcemia:*** elevation in serum calcium is typically mild and produces few if any symptoms.

Treatment of hypercalcemia

Intervention	Mode of action	Onset of action	Duration of action
Isotonic saline hydration	Restoration of intravascular volume Increases urinary calcium excretion	Hours	During infusion
Calcitonin	Inhibits bone resorption via interference with osteoclast function Promotes urinary calcium excretion	4 to 6 hours	48 hours
Bisphosphonates	Inhibit bone resorption via interference with osteoclast recruitment and function	24 to 72 hours	2 to 4 weeks
Loop diuretics*	Increase urinary calcium excretion via inhibition of calcium reabsorption in the loop of Henle	Hours	During therapy
Glucocorticoids	Decrease intestinal calcium absorption Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells in patients with granulomatous diseases or lymphoma	2 to 5 days	Days to weeks
Denosumab	Inhibits bone resorption via inhibition of RANKL	4 to 10 days	4 to 15 weeks
Calcimimetics	Calcium-sensing receptor agonist, reduces PTH (parathyroid carcinoma, secondary hyperparathyroidism in CKD)	2 to 3 days	During therapy
Dialysis	Low or no calcium dialysate	Hours	During treatment


Thank you