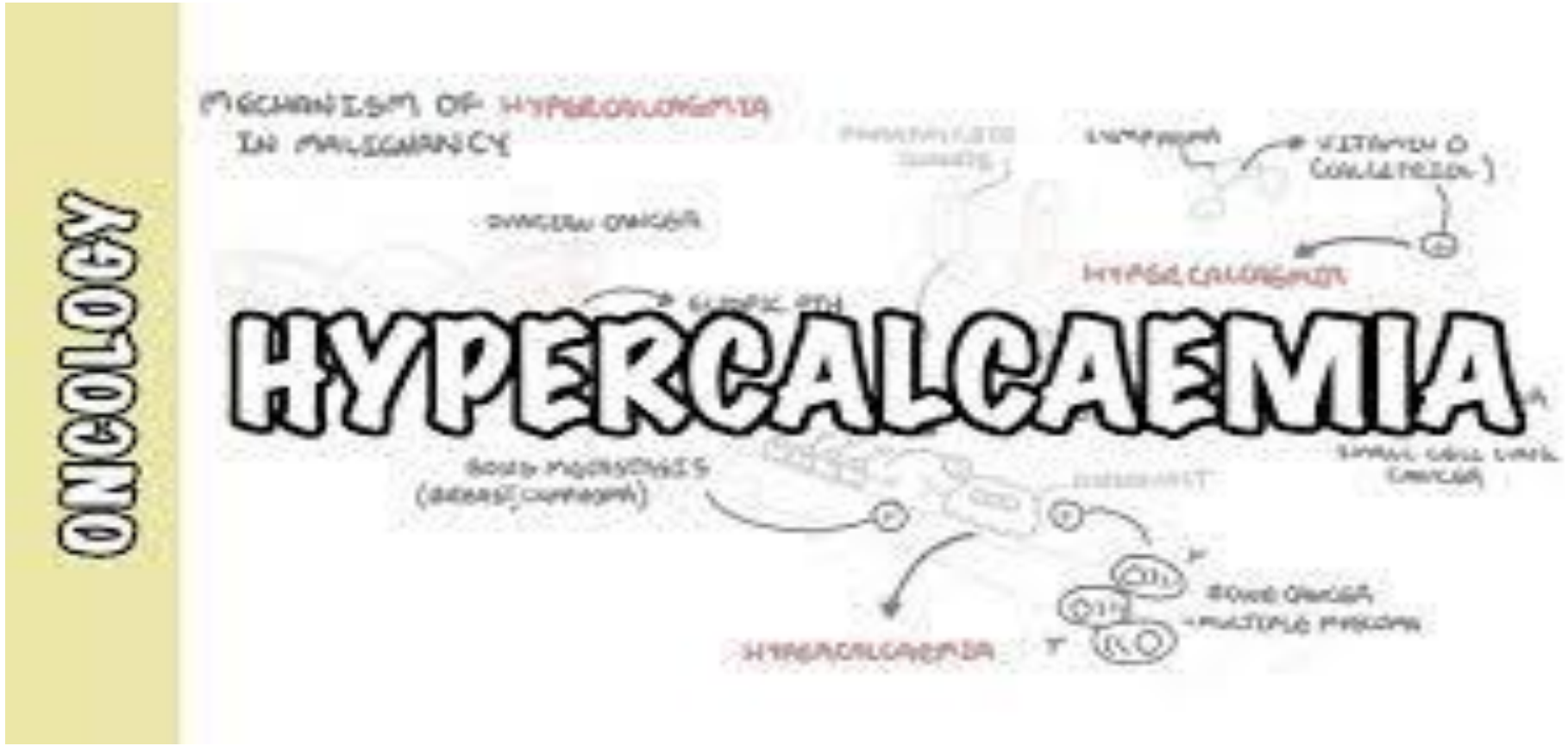


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Diagnostic approach & Treatment to Malignancy-Associated hypercalcemia



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CAUSES OF AKI IN CANCER PATIENTS

Metabolic causes?

- **Hypercarbia?/ hypoxemia?**

Pco2= 38 / spo2=98%

- **Hypo/hyper glycemia?**

BS=118

- **Liver failure?**

AST=24, ALT=6, Alkp= 270 , INR=1.1

- **Cardiac failure?**

No evidence

- **Renal failure?**

Cr=4.5, Urea= 200, k=5, flapping tremor present

- **Electrolyte disturbance?**

Na=135, Mg=2.0, P=4.5, *Ca+=6…7*



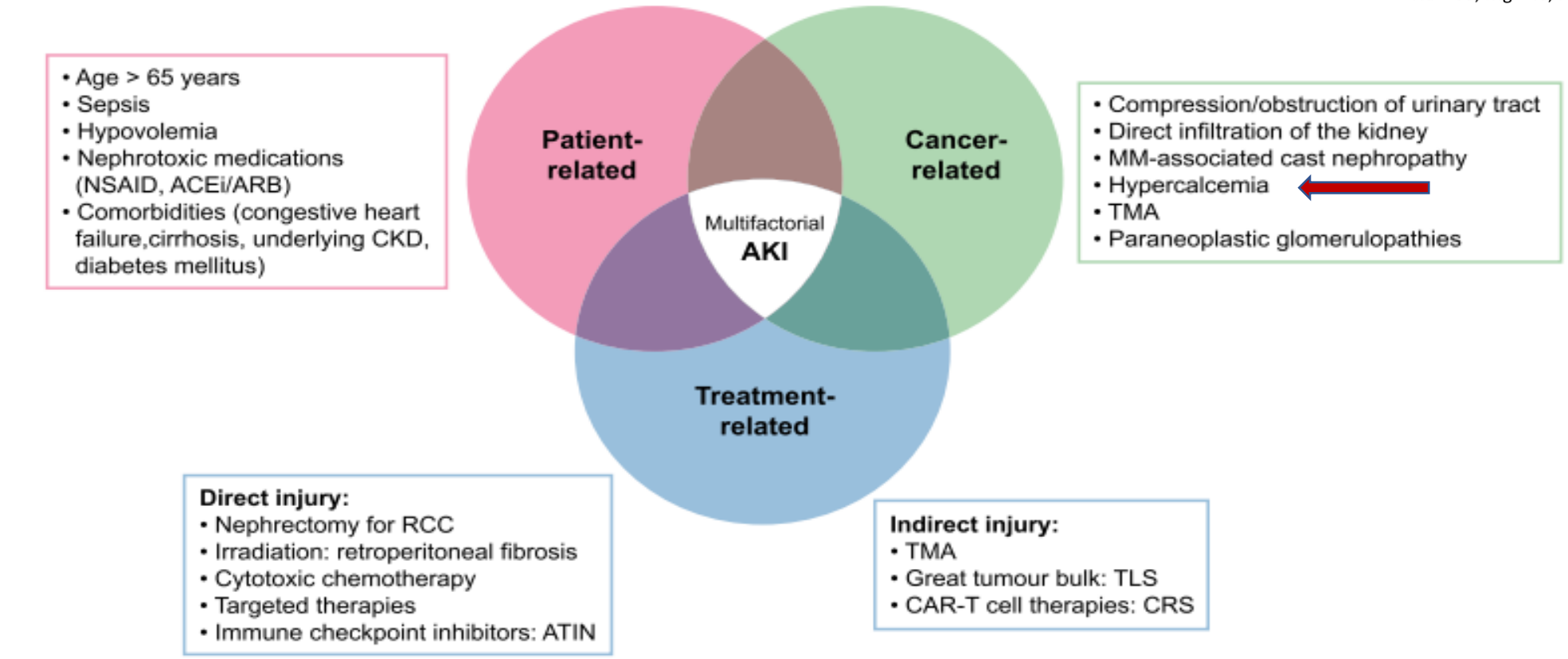


FIGURE 1: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATIN, acute tubulointerstitial nephritis.

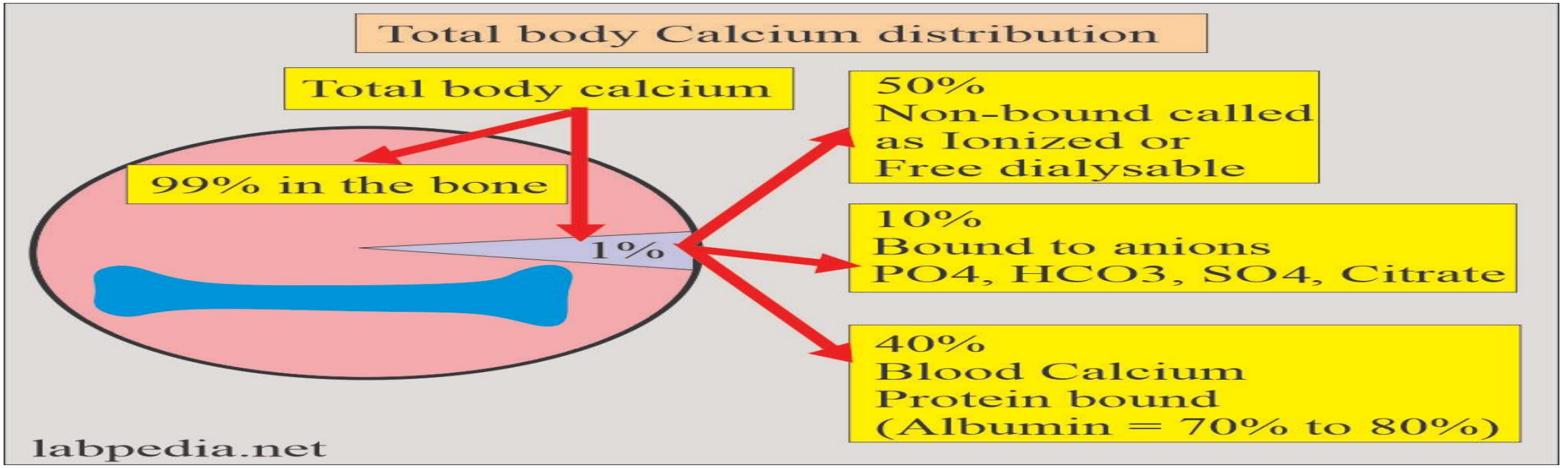
Serum calcium



❖Normal range

➢Total Ca:8.8 to 10.3 mg/dL (corrected for serum albumin)

➢Ionized Ca: 4.8 to 5.3 mg/dL or 1.20 to 1.40 millimol/L



Measurement calcium concentration

- Total plasma or serum calcium concentration

  (colorimetric assays)

- Exploited in blood gas

- Measure the ionized calcium

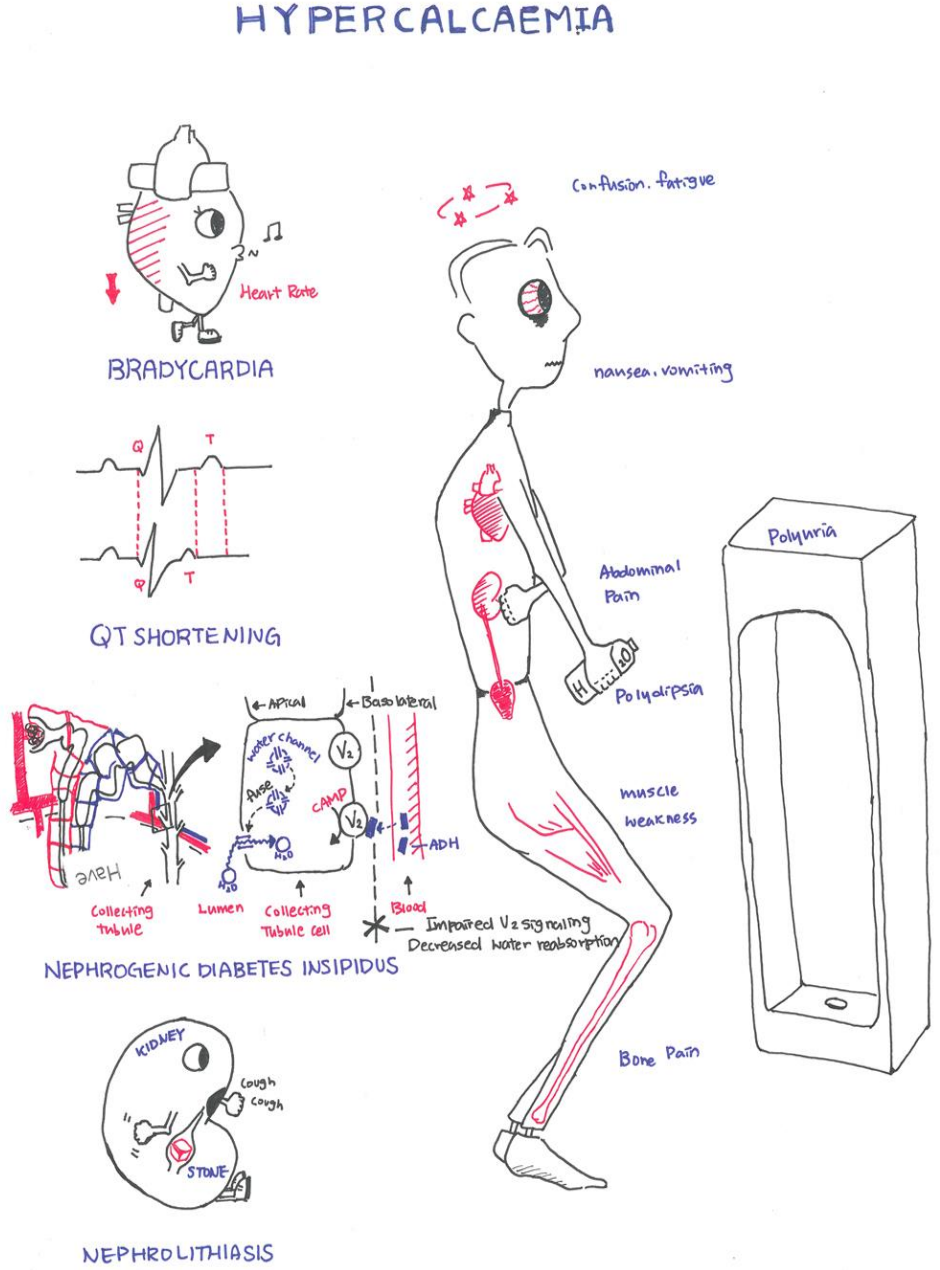
Hypercalcemia

- Hypercalcemia as a laboratory value is defined as a serum total calcium level greater than 10.3 mg/dl (corrected for albumin)

- Mild: Ca concentration = 10.4 to 11.9 mg/dL
- Moderate: Ca concentration = 12.0 to 13.9 mg/dL
- Severe (hypercalcemic crisis): Ca concentration = 14.0 to
- 16.0 mg/dL

TABLE 18-2 Clinical Features of Hypercalcemia

General
Malaise, tiredness, weakness
Neuropsychiatric
Impaired concentration, loss of memory, headache, drowsiness, lethargy, disorientation, confusion, irritability, depression, paranoia, hallucinations, ataxia, speech defects, visual disturbances, deafness (due to calcification of the eardrum), pruritus, mental retardation (infants), stupor, coma
Neuromuscular
Muscle weakness, hyporeflexia or absent reflexes, hypotonia, myalgia, arthralgia, bone pain, joint effusion, chondrocalcinosis, dwarfism (infants)
Gastrointestinal
Loss of appetite, dry mouth, thirst, polydipsia, nausea, vomiting, constipation, abdominal pain, weight loss, acute pancreatitis (calcifying), peptic ulcer, acute gastric dilation
Renal
Polyuria, nocturia, nephrocalcinosis, nephrolithiasis, interstitial nephritis, acute and chronic renal failure
Cardiovascular
Arrhythmia, bradycardia, first-degree heart block, short QT interval, bundle branch block, cardiac arrest (rare), hypertension, vascular calcification
Metastatic Calcification
Band keratopathy, red eye syndrome, conjunctival calcification, nephrocalcinosis, vascular calcification, pruritus



Classification of Causes of Hypercalcemia

I. Parathyroid-related

A. Primary hyperparathyroidism
   1. Solitary adenomas
   2. Multiple endocrine neoplasia

B. Lithium therapy

C. Familial hypocalciuric hypercalcemia

II. Malignancy-related

A. Solid tumor with metastases (breast)

B. Solid tumor with humoral mediation of hypercalcemia (lung, kidney)

C. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)

III. Vitamin D–related

A. Vitamin D intoxication

B. ↑1,25(OH)2D; sarcoidosis and other granulomatous diseases

C. Idiopathic hypercalcemia of infancy

IV. Associated with high bone turnover

A. Hyperthyroidism

B. Immobilization

C. Thiazides

D. Vitamin A intoxication

V. Associated with renal failure

A. Severe secondary hyperparathyroidism

B. Aluminum intoxication

C. Milk-alkali syndrome

Laboratory Evaluation of Hypercalcemia

❖Confirm hypercalcemia:

✓Serum total calcium (recheck if only one measurement)

✓Serum corrected calcium equation

or

➢Ionized calcium (if total estimated calcium is believed to be unreliable)

- Check of serum Alb

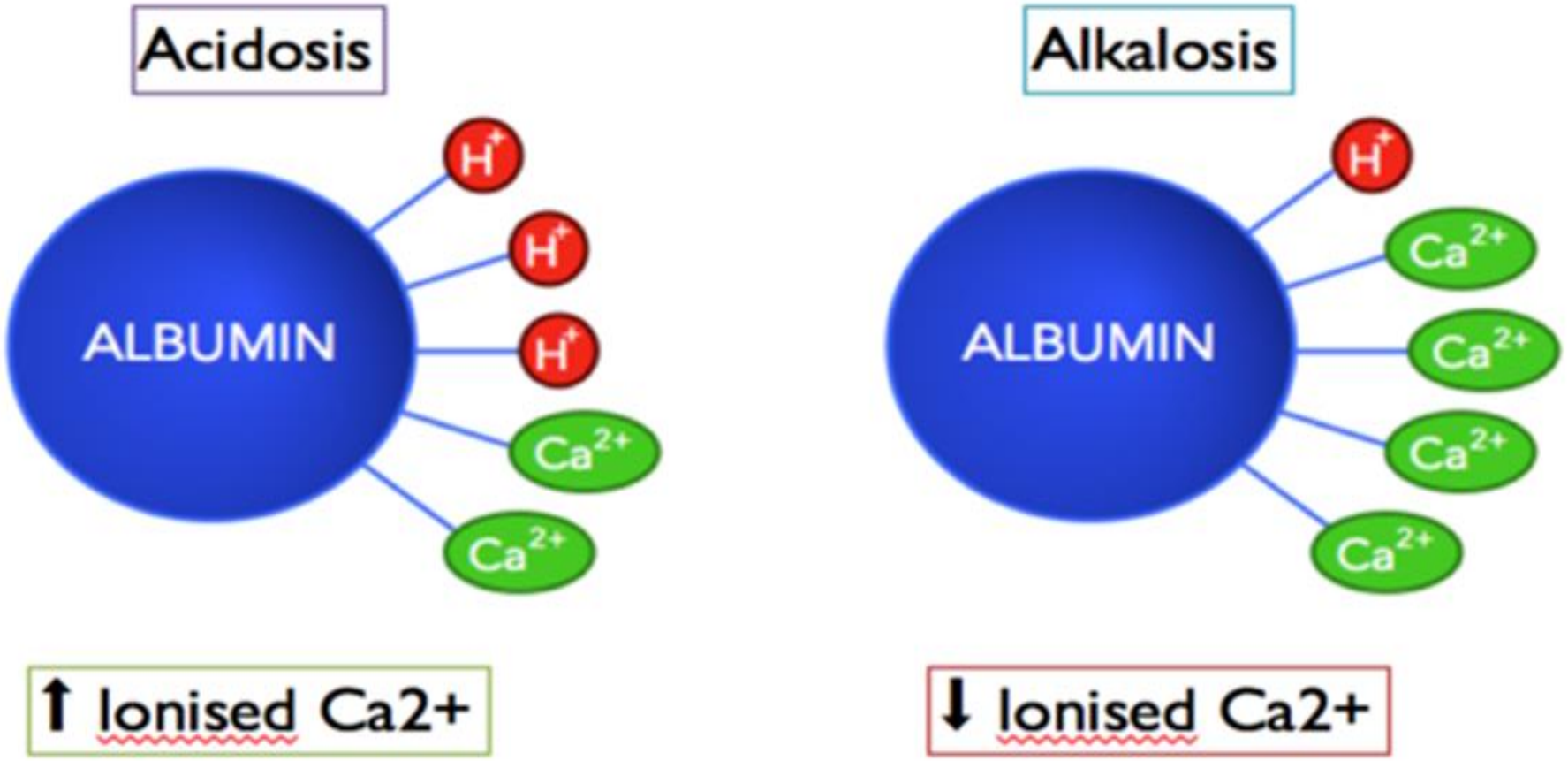
Albumine effect

Serum total calcium concentration needs to be corrected based on patient's serum albumin level using the following formula:

Adjusted total calcium (mg/ dL) = total calcium(mg/ dL) + 0.8(4 – albumin(g /dL))

- Check of Ca2+

Acid-base effect



Laboratory Evaluation of Hypercalcemia

❖Laboratory evaluations after hypercalcemia is established:

✓Serum phosphorus

✓Creatinine with estimated GFR

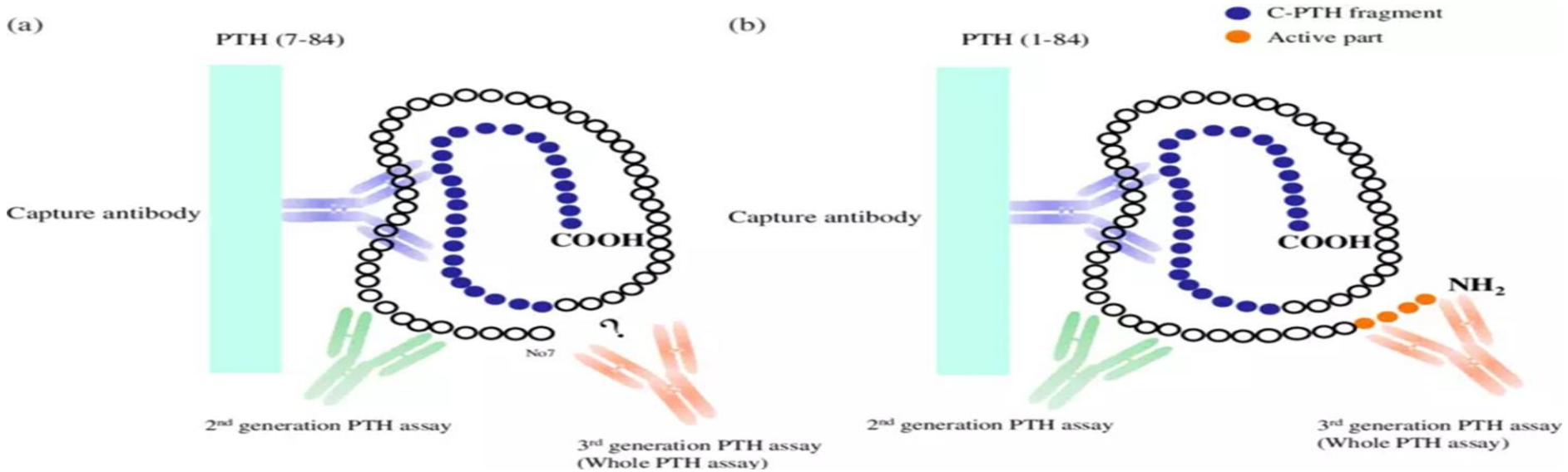
✓PTH

Parathyroid hormone assay

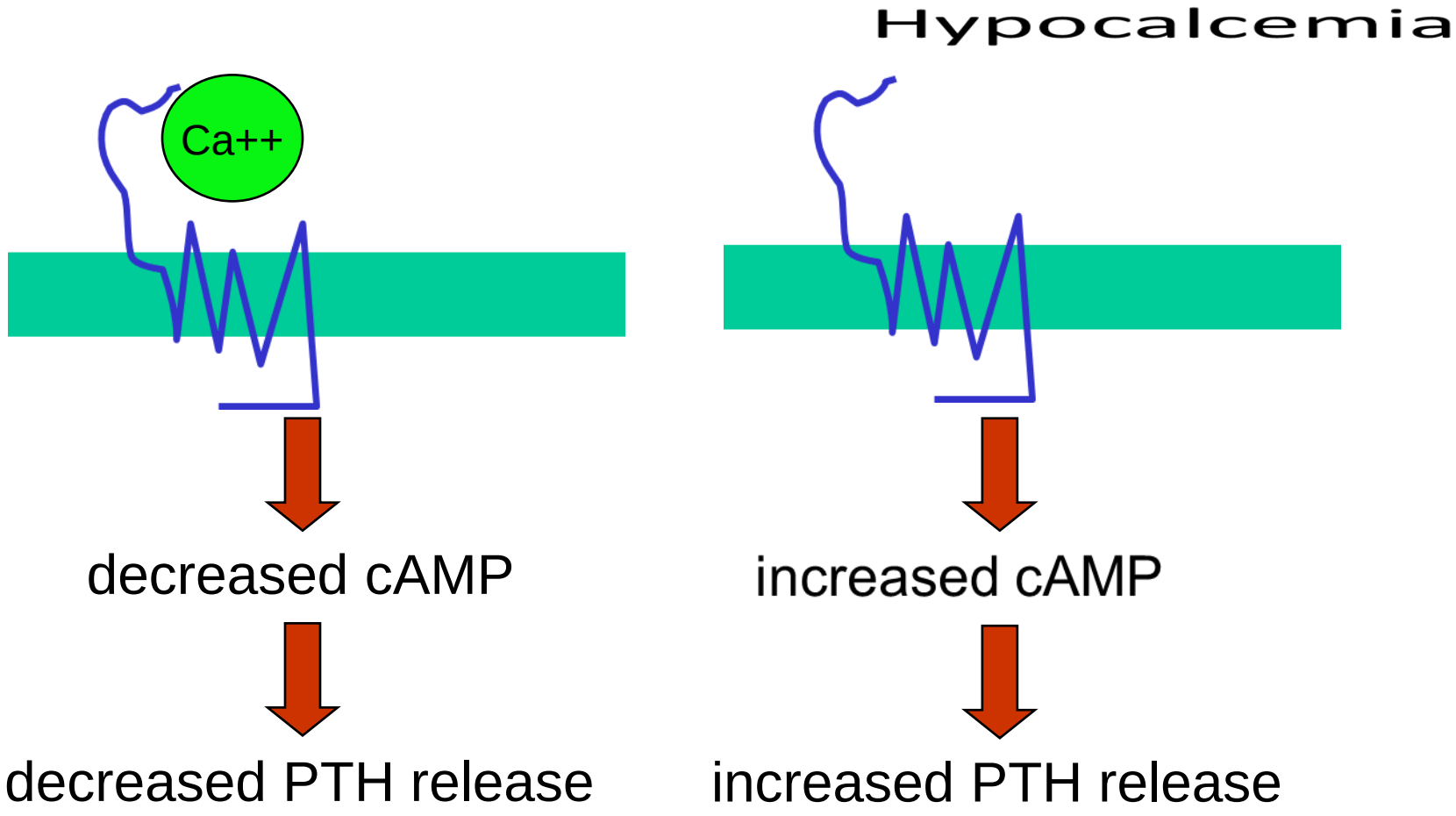
- **first generation** PTH assays. starting from residues 34, 37, 41, and 43
- **Second-generation PTH assays** use two monoclonal antibodies:
- 1-against the N-terminal region
- 2-against the C-terminal region

This combination of antibodies recognizes PTH fragments lacking the N-terminal amino acids 1-4, such as PTH (7-84).

- **Third-generation PTH assays**
- 1-polyclonal antibody that exclusively recognizes whole PTH (1-84)
- 2- a combination of two monoclonal antibodies that recognize PTH (39-84) and the N-terminal amino acids 1-4 of PTH



Calcium Receptor and PTH Release

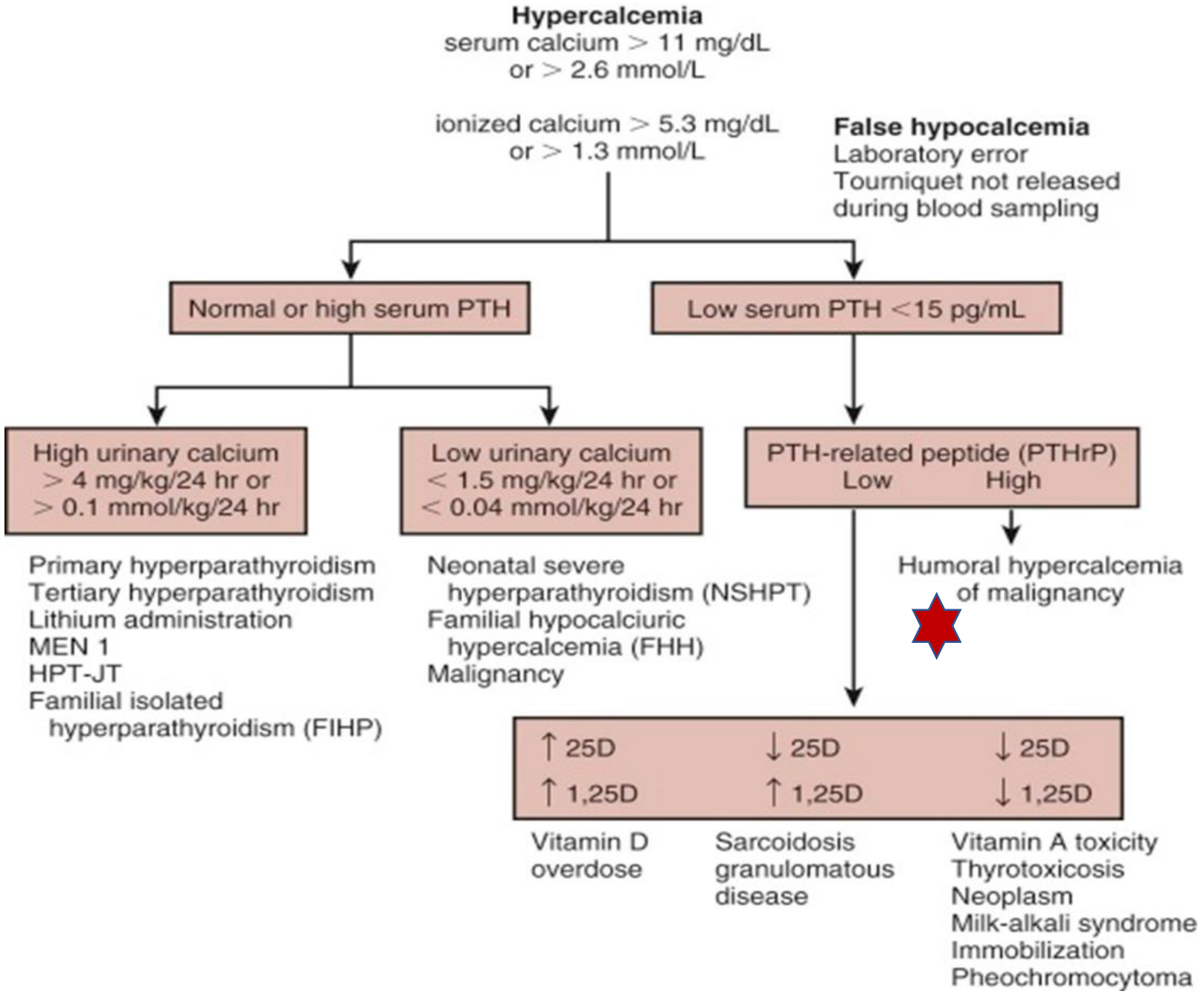


Laboratory Evaluation of Hypercalcemia

- Additional laboratory evaluations to consider if diagnosis is still uncertain:

- PTHrP
- 25(OH)D
- 1,25(OH)2D

- ✓SPEP, UPEP serum-free light chains, serum and urine IFE
- ✓Skeletal survey
- ✓Vitamin A levels



WBC	17.000							
HB	7.8							
PLT	224							
Na	135							140
K	5							4
Ca	7+	6.6	6.7	6.7	6	4.8	4.1	4
Mg	2							
P	4.5							3.9
Cr	4.5	2.9	1.9	1.5	1.2	0.7	1.1	0.9
PH	7.40							
PCO2	38							
HCO3	20							
PTH	6.25							
Vit D	17							

Cancer-Related Hypercalcemia

- Hypercalcemia occurs in approximately 10% to 25% of patients with some cancer, especially during the last 4 to 6 weeks of life.
- It can be classified into four categories:

1. humoral hypercalcemia of malignancy (HHM)
2. local osteolytic hypercalcemia (LOH)
3. 1,25(OH)2D-induced hypercalcemia
4. ectopic secretion of authentic PTH

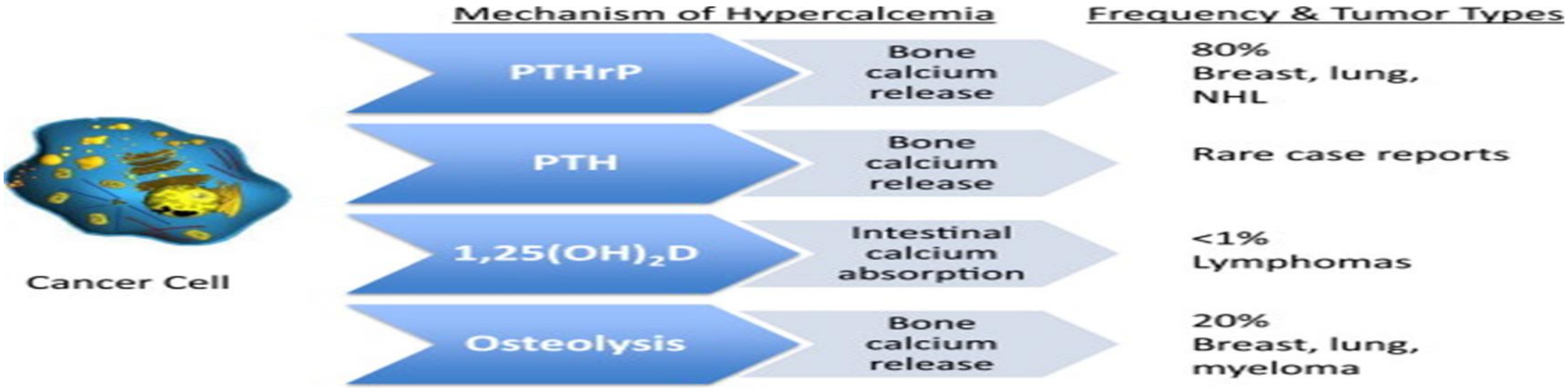
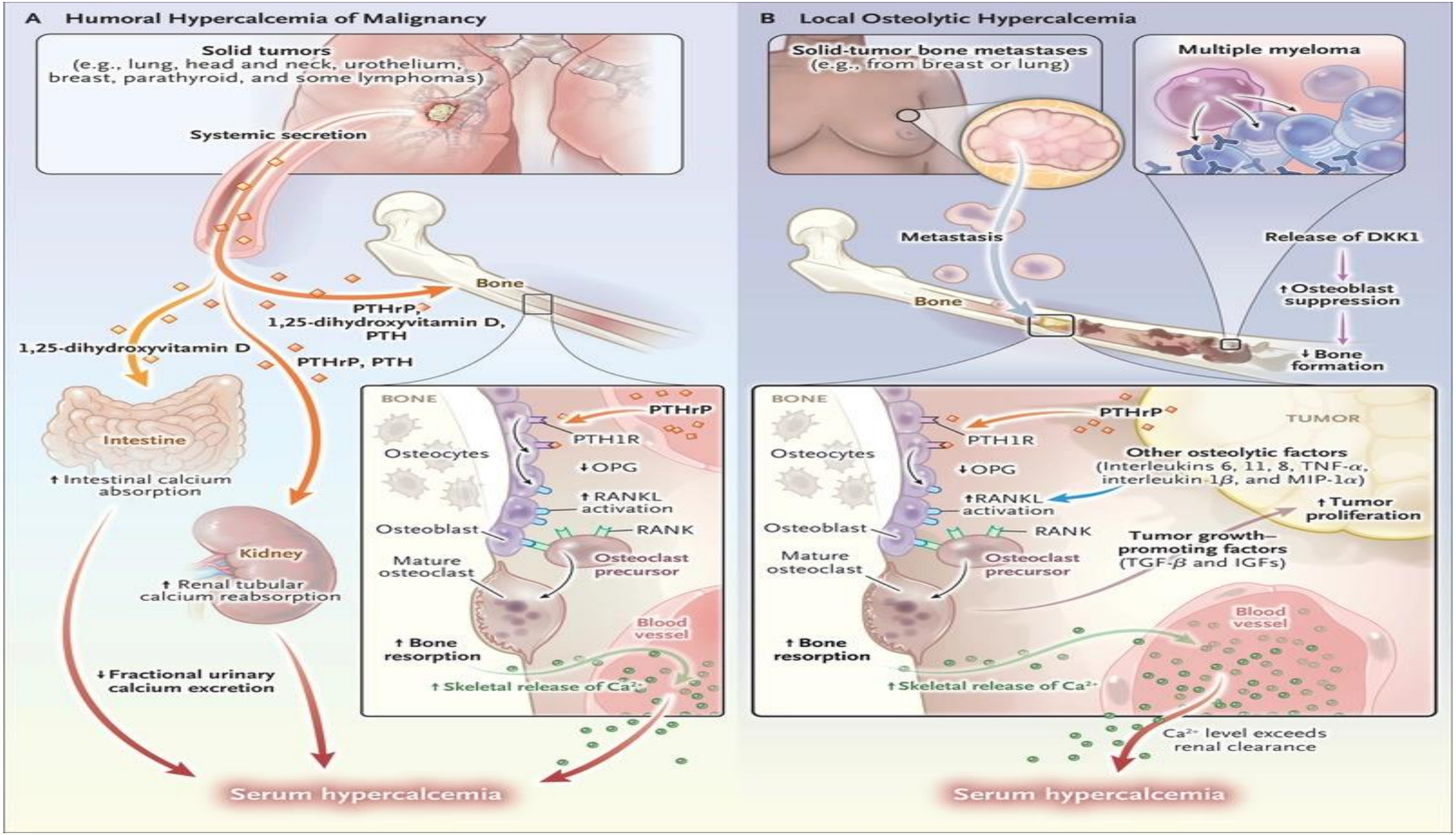


Table 1. Types of Hypercalcemia Associated with Cancer.*

Type	Frequency (%)	Bone Metastases	Causal Agent	Typical Tumors
Local osteolytic hypercalcemia	20	Common, extensive	Cytokines, chemokines, PTHrP	Breast cancer, multiple myeloma, lymphoma
Humoral hypercalcemia of malignancy	80	Minimal or absent	PTHrP	Squamous-cell cancer, (e.g., of head and neck, esophagus, cervix, or lung), renal cancer, ovarian cancer, endometrial cancer, HTLV-associated lymphoma, breast cancer
$1,25(OH)_2D$-secreting lymphomas	<1	Variable	$1,25(OH)_2D$	Lymphoma (all types)
Ectopic hyperparathyroidism	<1	Variable	PTH	Variable

* PTH denotes parathyroid hormone, PTHrP PTH-related protein, $1,25(OH)_2D$ 1,25-dihydroxyvitamin D, and HTLV human T-cell lymphotrophic virus.


A Humoral Hypercalcemia of Malignancy
Solid tumors
(e.g., lung, head and neck, urothelium, breast, parathyroid, and some lymphomas)
Systemic secretion
Bone
PTHrP, 1,25-dihydroxyvitamin D, PTH
1,25-dihydroxyvitamin D
PTHrP, PTH
Intestine
↑ Intestinal calcium absorption
Kidney
↑ Renal tubular calcium reabsorption
↓ Fractional urinary calcium excretion
BONE
PTHrP
PTH1R
Osteocytes
↓OPG
↑RANKL activation
Osteoblast
RANK
Mature osteoclast
Osteoclast precursor
Blood vessel
↑ Bone resorption
↑ Skeletal release of Ca2+
Serum hypercalcemia
B Local Osteolytic Hypercalcemia
Solid-tumor bone metastases
(e.g., from breast or lung)
Multiple myeloma
Metastasis
Release of DKK1
↑Osteoblast suppression
↓ Bone formation
Bone
BONE
TUMOR
PTHrP
PTH1R
Osteocytes
↓OPG
↑RANKL activation
Other osteolytic factors
(Interleukins 6, 11, 8, TNF-α, interleukin-1β, and MIP-1α)
↑Tumor proliferation
Osteoblast
RANK
Mature osteoclast
Osteoclast precursor
Tumor growth–promoting factors
(TGF-β and IGFs)
Blood vessel
↑ Bone resorption
↑ Skeletal release of Ca2+
Ca2+ level exceeds renal clearance
Serum hypercalcemia

Tumor Types Producing PTHrP

Common

- Breast cancers
- Lung cancers
- Non-Hodgkin lymphoma
- Adult T-cell leukemia/lymphoma associated with human T-lymphotropic virus type 1 (HTLV-1)

Less Common

- Head and neck tumors
- Renal cell carcinoma
- Bladder cancer
- Pancreatic cancer
- Hepatocellular carcinoma
- Carcinoid tumors
- Melanoma

Abbreviation: PTHrP, parathyroid hormone–related peptide.
Source: Wysolmerski.[8]

- PTHrP is a large protein encoded by a gene on chromosome 12.
- It is similar to PTH only at the N terminus, where the initial eight amino acids are identical.
- PTHrP is widely expressed in a variety of tissues, including keratinocytes, mammary gland, placenta, cartilage, nervous system, vascul
- Normal circulating levels of PTHrP are negligible; it is probably unimportant in normal calcium homeostasis. However, mice with a targeted disruption in the PTHrP gene show a lethal defect in bone development, which demonstrates its importance in normal development

Major Differences in the Effects of PTH and PTHrP on Their Target Organs

Table 2. Major Differences in the Effects of PTH and PTHrP on Their Target Organs

	PTH	PTHrP
PTHR1	Higher affinity binding compared to PTHrP	Lower affinity binding compared to PTH
Bone	Increases bone resorption via activation of osteoclasts Greater increase in osteoblast activity	Increases bone resorption via activation of osteoclasts Lesser increase in osteoblast activity
Kidney	Increases reabsorption of calcium Increases $1,25(OH)_2D$ production Increases phosphorus excretion	Increases reabsorption of calcium Minimal to no increase in $1,25(OH)_2D$ production Increases phosphorus excretion
GI tract	Increases absorption of calcium by the ileum	No increase in absorption of calcium by the ileum

Abbreviations: $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; GI, gastrointestinal; PTH, parathyroid hormone; PTHrP, PTH-related peptide.

	Blood[a]			
	Ca	P_i	$1,25(OH)_2D$	iPTH
Primary hyperparathyroidism	↑	↓	↑↔	↑(↔)
Malignancy-associated hypercalcemia:				
★ Humoral hypercalcemia ★	↑↑	↓	↓↔	↓
Local destruction (osteolytic metastases)	↑	↔	↓↔	↓

[a]Symbols in parentheses refer to values rarely seen in the particular disease.

Abbreviations: P_i, inorganic phosphate; iPTH, immunoreactive parathyroid hormone.

Source: JT Potts Jr: HPIM-12, p. 1911.

Treatment

❖The therapy for hypercalcemia must be tailored to the degree of hypercalcemia, the clinical condition, and the underlying cause

1. urinary excretion
2. augmenting net movement of calcium into bone
3. inhibiting bone resorption
4. reducing intestinal absorption of calcium
5. removing calcium from the ECF by other means

Treatment

- ❖ Patients with mild hypercalcemia (<12 mg/dL)
  - ➢ do not require immediate treatment.
  - ✓ stop any medications implicated in causing hypercalcemia
  - ✓ avoid volume depletion and physical inactivity
  - ✓ maintain adequate hydration.
- ❖ Moderate hypercalcemia (12 to 14 mg/dL), especially if acute and symptomatic, requires more aggressive therapy.
- ❖ Patients with severe hypercalcemia (>14 mg/dL), even without symptoms, should be treated intensively

Volume Repletion and Loop Diuretics

❖Correction of the ECF volume is the first and the most important step in the treatment of severe hypercalcemia from any causes.

✓It can be achieved with infusion of normal isotonic saline at 200 to 500 mL/hr, adjusted to obtain a urine output of 150 to 200 mL/hr and accompanied by appropriate hemodynamic monitoring.

✓ Volume repletion can lower calcium concentration by approximately 1 to 3 mg/dL by increasing GFR and decreasing sodium and calcium reabsorption in proximal and distal tubules

Volume Repletion and Loop Diuretics

- Once volume expansion is achieved, loop diuretics can be given concurrently with saline to increase the calciuresis by blocking the Na+-K+-2Cl– cotransporter in the TAL.

Volume Repletion and Loop Diuretics

- Most commonly furosemide is used at a dosage of 40 to 80 mg every 6 hours, and this treatment together with saline therapy may decrease serum calcium concentration by 2 to 4 mg/dL.
- Urinary losses of fluid, potassium, and magnesium should be evaluated at intervals of 2 to 4 hours and quantitatively replaced to prevent ECF volume contraction, hypokalemia, and hypomagnesemia.

Volume Repletion and Loop Diuretics

- Care must be taken to monitor the patient's volume status closely during the administration of large amounts of saline and diuretic, particularly in hospitalized patients with cardiac or pulmonary or renal disease.

Inhibition of Bone Resorption

- The increase in bone resorption, as the most common pathologic process leading to hypercalcemia, must be addressed concurrently with volume expansion and hydration.
- Bisphosphonates are currently the agents of choice in the treatment of mild to severe hypercalcemia, especially that associated with cancer. They are pyrophosphate analogs with a high affinity for hydroxyapatite and inhibit osteoclast function in areas of high bone turnover

Bisphosphonates



- approved two bisphosphonates for treatment of hypercalcemia:
1. zoledronate (4 mg intravenously over at least 15 minutes)
2. pamidronate (60 to 90 mg intravenously over 2 to 24 hours).
- The clinical response takes 48 to 96 hours and is sustained for up to 3 weeks.
- Doses can be repeated no sooner than every 7 days.
- Both agents are effective in lowering calcium level.
- Zoledronate was slightly more efficacious than pamidronate in a randomized clinical trial
- Other bisphosphonates such as clodronate and ibandronate are also approved.

Table 1. Dosing guidelines for intravenous bisphosphonates in the treatment of acute hypercalcemia

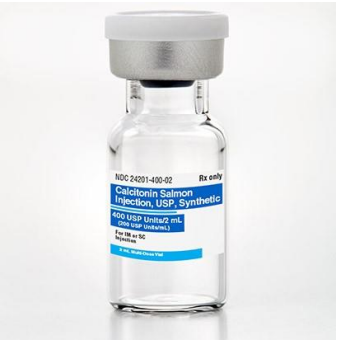
Bisphosphonate per CrCl	Dose and Infusion Rate	Dosing Interval
CrCl >60 ml/min		
pamidronate	90 mg over 2–3 hr	Every 3–4 wk
zoledronate	4 mg over 15 min	Every 3–4 wk
ibandronate	Not FDA approved	
CrCl 30–60 ml/min		
pamidronate	60–90 mg over 2–3 hr Reserve higher doses for more severe hypercalcemia	Every 3–4 wk
zoledronate		Every 3–4 wk
CrCl 50–60 ml/min	3.5 mg	
CrCl 40–49 ml/min	3.3 mg	
CrCl 30–39 ml/min	3 mg	
ibandronate	Not FDA approved	
CrCl < 30 ml/min		
pamidronate	60–90 mg over 4–6 hr Reserve higher doses for more severe hypercalcemia	Every 3–4 wk
zoledronate	Not recommended	Not recommended
ibandronate	Not FDA approved	

Data obtained from reference 61. CrCl, creatinine clearance; FDA, Food and Drug Administration.

Bisphosphonates

- Fever is observed in about one fifth of patients taking bisphosphonates;
- Rare side effects include acute renal failure, collapsing glomerulopathy, and osteonecrosis of the jaw.
- The dosage of bisphosphonates should be adjusted in patients with preexisting kidney disease.
- The renal component of hypercalcemia, which includes increased distal tubular calcium reabsorption driven by PTH-PTHrP, does not respond to bisphosphonates.

Calcitonin



- Calcitonin is also an effective inhibitor of osteoclast bone resorption.
- It has a rapid onset of action (within 12 hours), its effect is transient, and it has minimal toxicity.
- Calcitonin is usually given at a dosage of 4 to 8 U/kg subcutaneously, every 6 to 12 hours.
- Its role is mainly to provide initial treatment of severe hypercalcemia while waiting for the more sustained effect of bisphosphonates to begin.

Gallium nitrate



- Gallium nitrate inhibits bone resorption by increasing the solubility of hydroxyapatite crystals.
- The usual dosage is 200 mg/m2 intravenously over 24 hours with adequate hydration for 5 consecutive days, and the hypocalcemic effect is not generally observed until the end of this period.
- Gallium nitrate is effective, but can be nephrotoxic

Plicamycin

- Plicamycin (mithramycin) (25 µg/kg intravenously every 5 to 7 days) may be used in patients with severe renal failure.

- Other therapies for hypercalcemia, such as chelation with ethylenediaminetetraacetic acid (EDTA) and intravenous phosphate, have adverse side effect profiles and are no longer recommended.

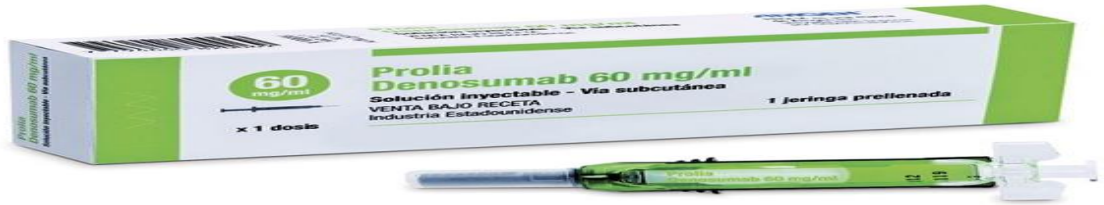
Glucocorticoids

- Glucocorticoids are useful therapy for hypercalcemia from a specific subset of causes.
- They are most effective in hematologic malignancies (multiple myeloma, Hodgkin's disease) and disorders of vitamin D metabolism (granulomatous disease, vitamin D toxicity)

Hemodialysis

- In severely hypercalcemic patients who are comatose, have ECG changes, have severe renal failure, or cannot receive aggressive hydration, hemodialysis with a low- or no-calcium dialysate is an effective treatment.
- Continuous renal replacement therapy can also be used to treat severe hypercalcemia.
- The effect of dialysis is transitory, and it must be followed by other measures.

Denosumab



- Denosumab is a fully human monoclonal antibody that binds to RANKL and inhibits osteoclast maturation, activation, and function .
- It is FDA approved for preventing skeletal-related events in patients with solid malignancy, as well preventing bone fractures in postmenopausal women with osteoporosis.
- . Denosumab is well tolerated, with arthralgias as the most common side effect
- Because RANKL is expressed on B and T cells, there was some concern that denosumab would increase the risk for serious infections.
- Denosumab is not cleared through renal mechanisms and does not require dosing adjustments for renal impairment .

Denosumab

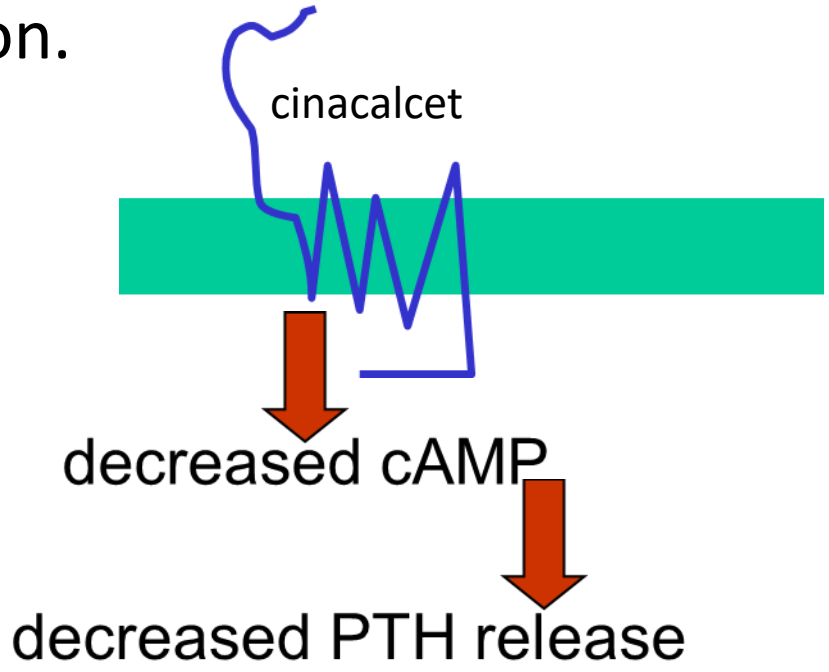


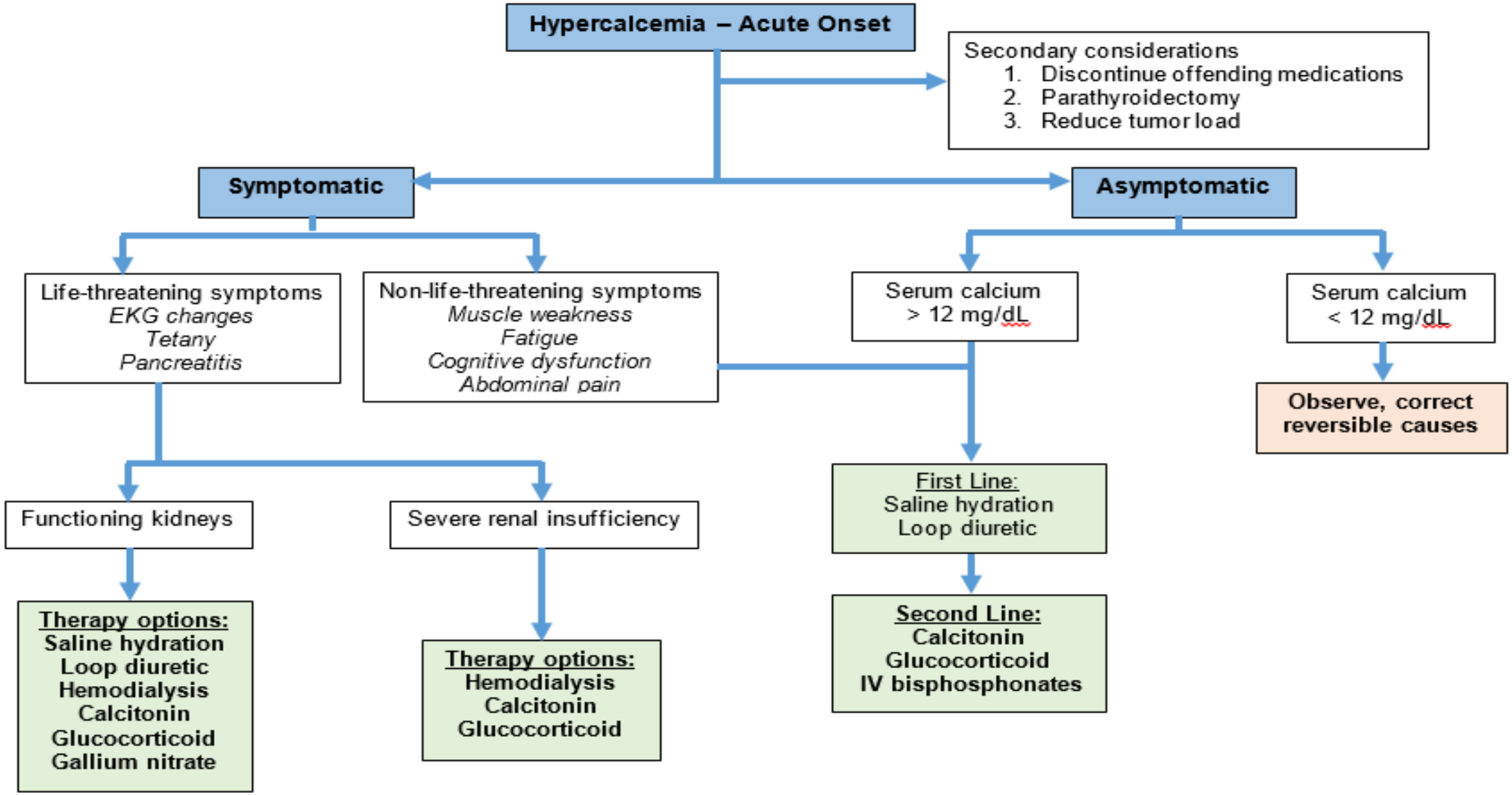
- These patients had solid malignancies or myeloma and elevated corrected serum calcium levels (12.5 mg/dl) despite recent IV bisphosphonate therapy.
- Patients received denosumab, 120 mg subcutaneously, every 4 weeks, with additional loading doses of 120 mg on days 8 and 15 of the first month
- The primary end point was reaching a response defined as a corrected serum calcium level ≤11.5 mg/dl within the first 10 days after denosumab dosing

cinacalcet



- cinacalcet, an allosteric activator of CaSR, is approved for use in patients with inoperable parathyroid cancer to control hypercalcemia.
- In case of persistent hypercalcemia of malignancy, the administration of calcimimetic cinacalcet could be an additional effective therapeutic option.




Hypercalcemia – Acute Onset
Secondary considerations
1. Discontinue offending medications
2. Parathyroidectomy
3. Reduce tumor load
Symptomatic
Asymptomatic
Life-threatening symptoms
EKG changes
Tetany
Pancreatitis
Non-life-threatening symptoms
Muscle weakness
Fatigue
Cognitive dysfunction
Abdominal pain
Serum calcium
> 12 mg/dL
Serum calcium
< 12 mg/dL
Observe, correct reversible causes
Functioning kidneys
Severe renal insufficiency
First Line:
Saline hydration
Loop diuretic
Therapy options:
Saline hydration
Loop diuretic
Hemodialysis
Calcitonin
Glucocorticoid
Gallium nitrate
Therapy options:
Hemodialysis
Calcitonin
Glucocorticoid
Second Line:
Calcitonin
Glucocorticoid
IV bisphosphonates

Treatment approach for hypercalcemia of malignancy

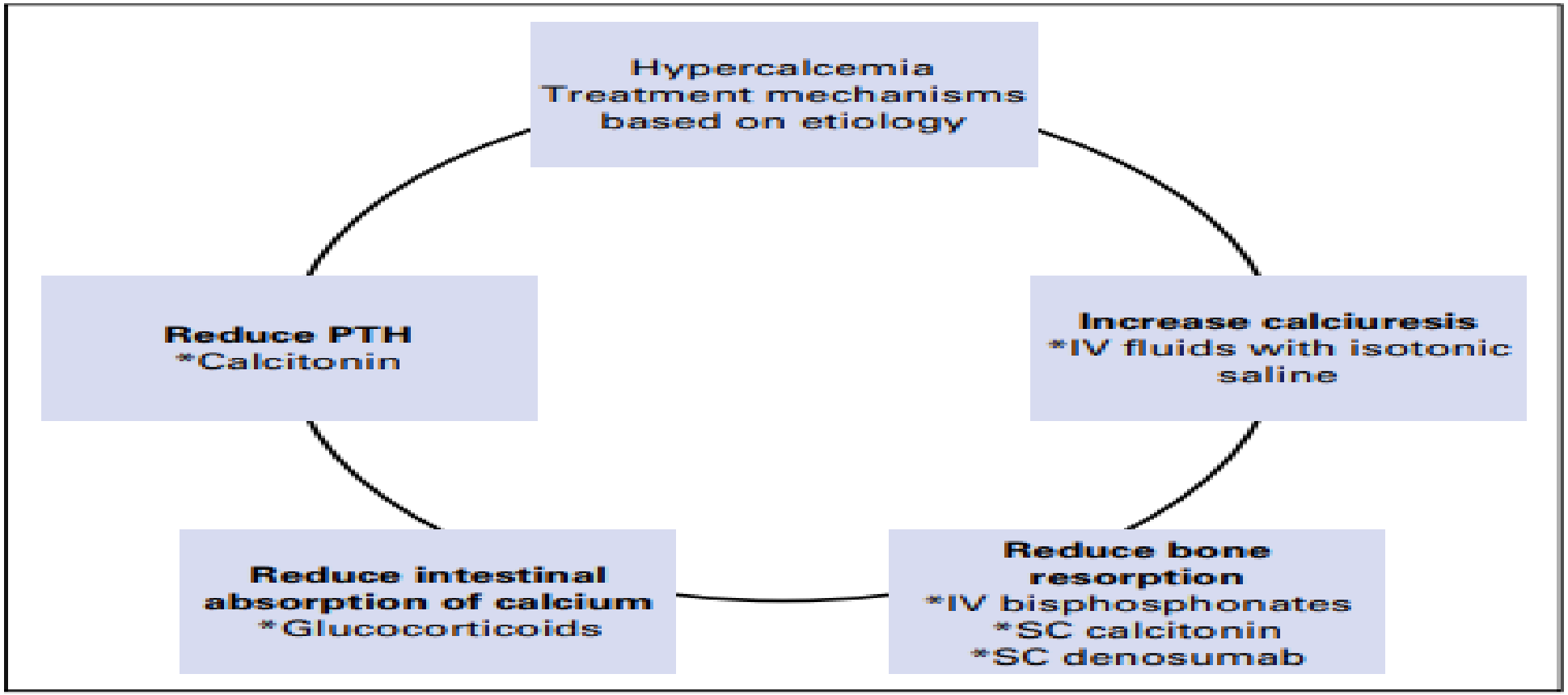
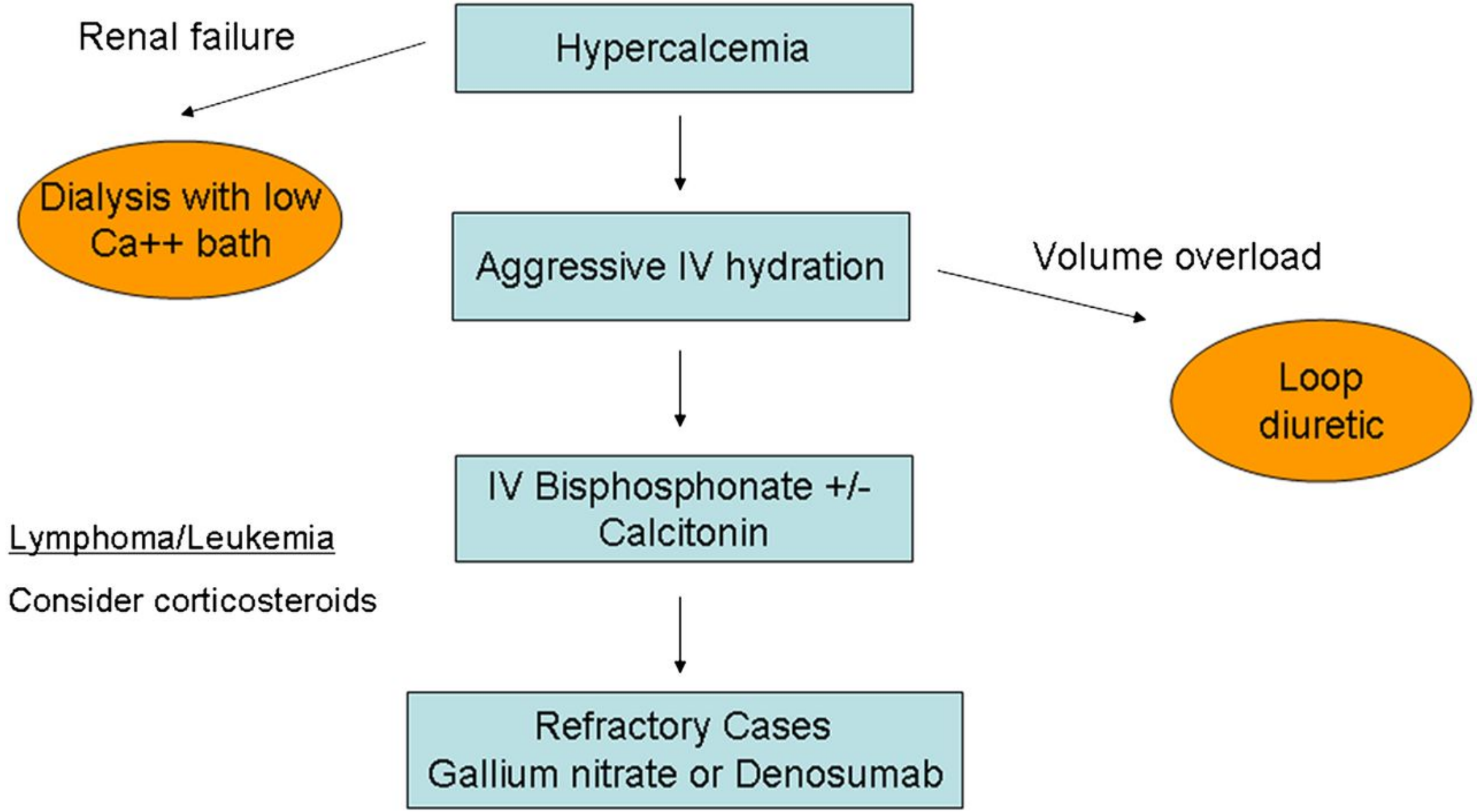


FIG 1. A treatment approach for hypercalcemia of malignancy. *Treatment mechanism. IV, intravenous; PTH, parathyroid hormone; SC, subcutaneous.


Renal failure
Hypercalcemia
Dialysis with low Ca++ bath
Aggressive IV hydration
Volume overload
Loop diuretic
IV Bisphosphonate +/- Calcitonin
Lymphoma/Leukemia
Consider corticosteroids
Refractory Cases
Gallium nitrate or Denosumab

Key Teaching Points

- The most common cause of severe hypercalcemia in hospitalized patients is malignancy
- Malignancy-associated hypercalcemia portends a worse prognosis because the underlying cancer usually is advanced
- Diagnosis relies on a structured approach using measurement of parathyroid hormone (PTH), PTH-related peptide, 1,25-dihydroxyvitamin D, and urine calcium /creatinine ratios
- Emergent treatment includes aggressive volume expansion along with intravenous bisphosphonates
- Newer therapies that target bone resorption pathways , such as denosumab, hold promise

Thank you

