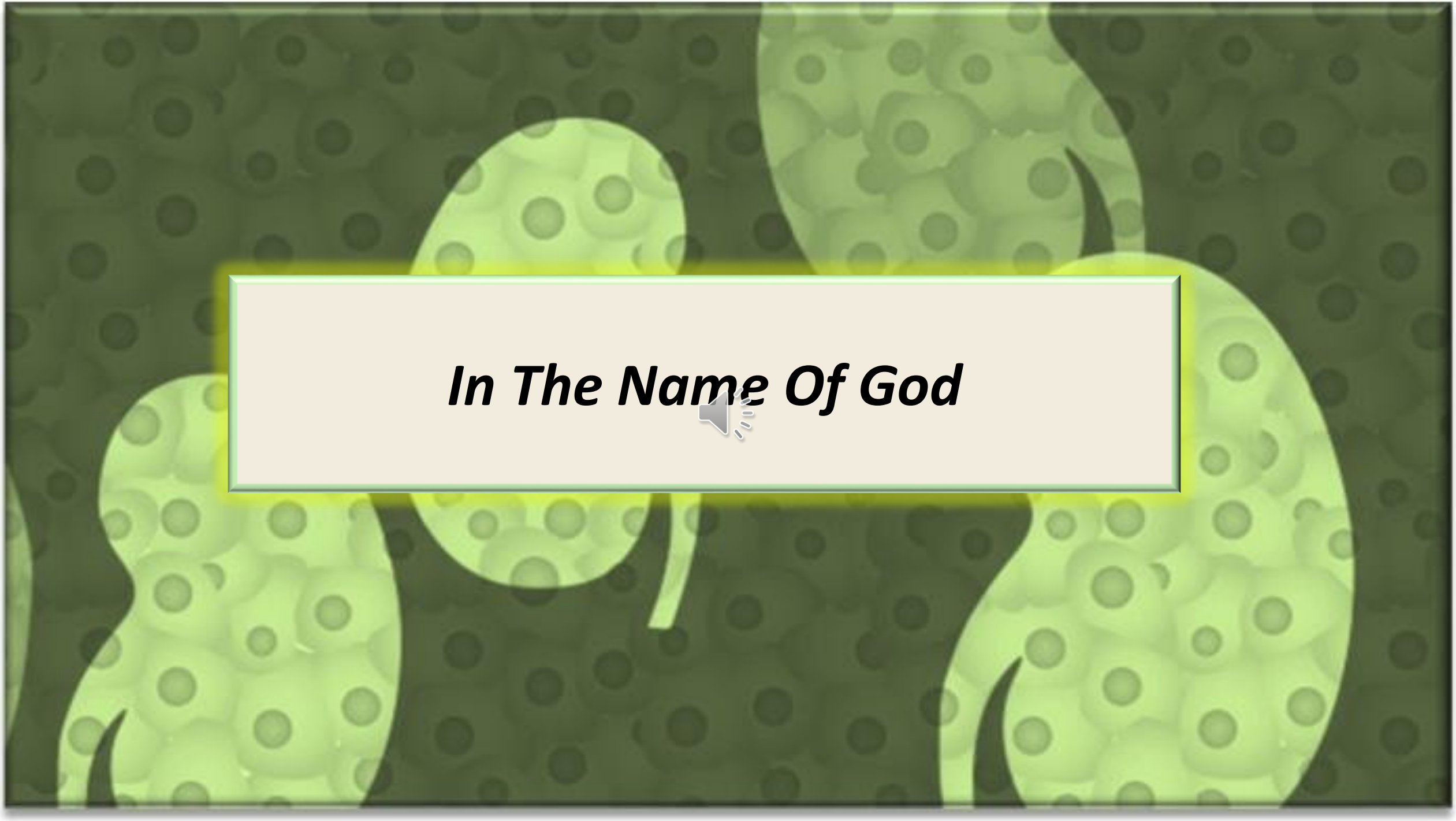
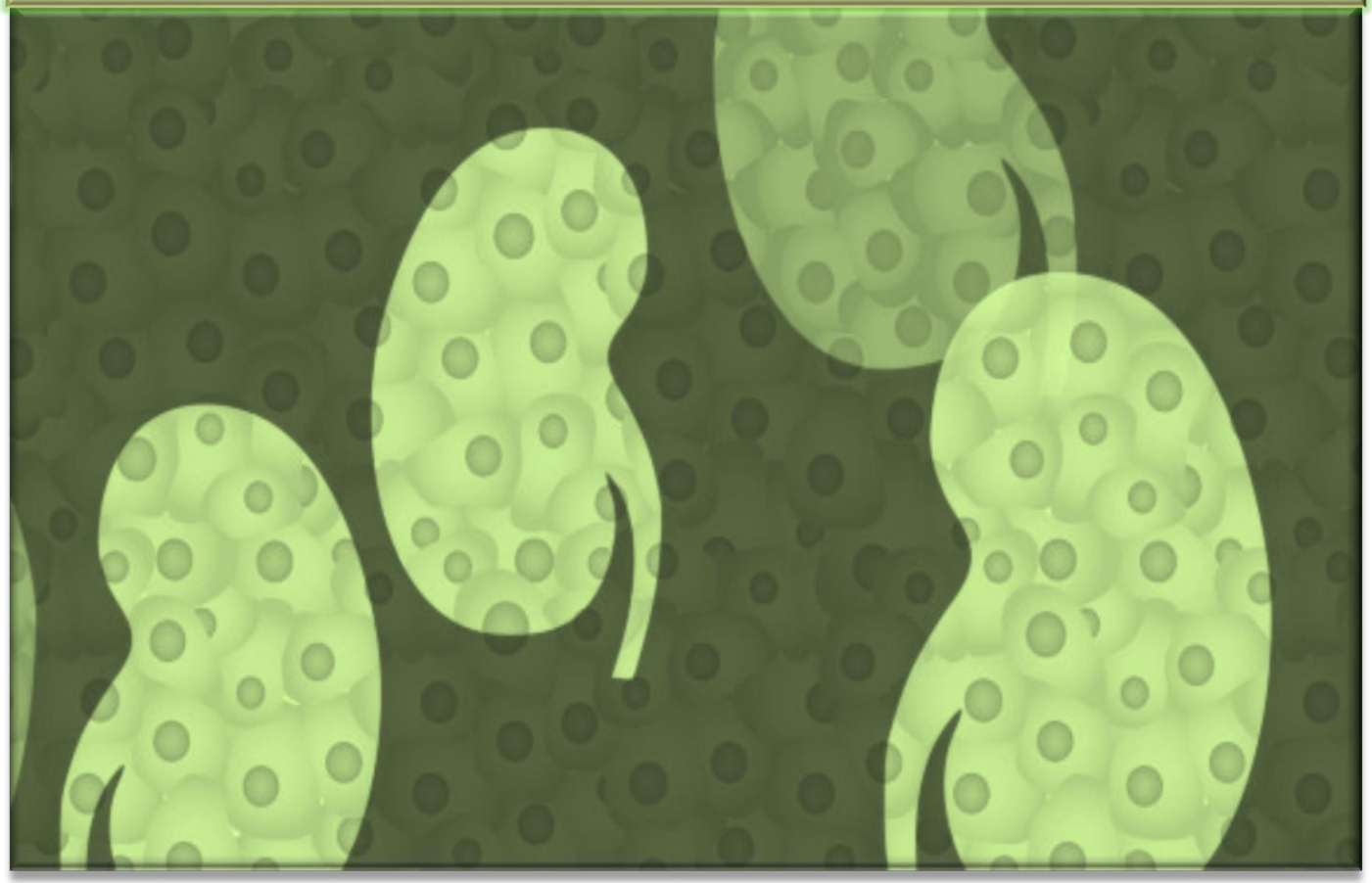

In The Name Of God

Electrolyte and Acid-Base Disorders in Cancer



Dr. Maryam Pourkar Jadid

Nephrologist(Guilan)

INTRODUCTION

Electrolyte disorders are common in cancer patients and can be caused by the cancer itself, cancer treatment, or other factors. These imbalances, particularly in sodium, potassium, calcium, and magnesium, can lead to serious complications and even life-threatening emergencies.

Early recognition and management are crucial for improving patient outcomes.

Pseudo-electrolyte Disorders in Patients with Cancer

Na

Pseudo-hyponatremia

Hyperproteinemia: Paraproteinemia, hypergammaglobulinemia, IVIG

Hyperlipidemia: Malignancy causing biliary obstruction -> high cholesterol & lipoproteins

Hypertriglyceridemia: Cancer therapy: tamoxifen

K

Pseudo-hyperkalemia

Severe thrombocytosis: Myeloproliferative disorders: observed in "serum" sample but not in "plasma" sample

Reverse pseudo-hyperkalemia

Severe leukocytosis: Leukemia, lymphoma: observed in "plasma" sample

Pseudo-hypokalemia

Severe leukocytosis: Leukemia

Ca

Pseudo-hypocalcemia

Gadolinium contrast agent

Pseudo-hypercalcemia

Severe thrombocytosis: Myeloproliferative disorders

Paraproteinemia: Multiple myeloma, Waldenstrom macroglobulinemia (Total Ca is high but ionized Ca is normal)

P

Pseudo-hyperphosphatemia

Paraproteinemia: Multiple myeloma, Waldenstrom macroglobulinemia, monoclonal gammopathy

Liposomal amphotericin B

Other causes: Heparin, t-PA, hyperbilirubinemia, hyperlipidemia

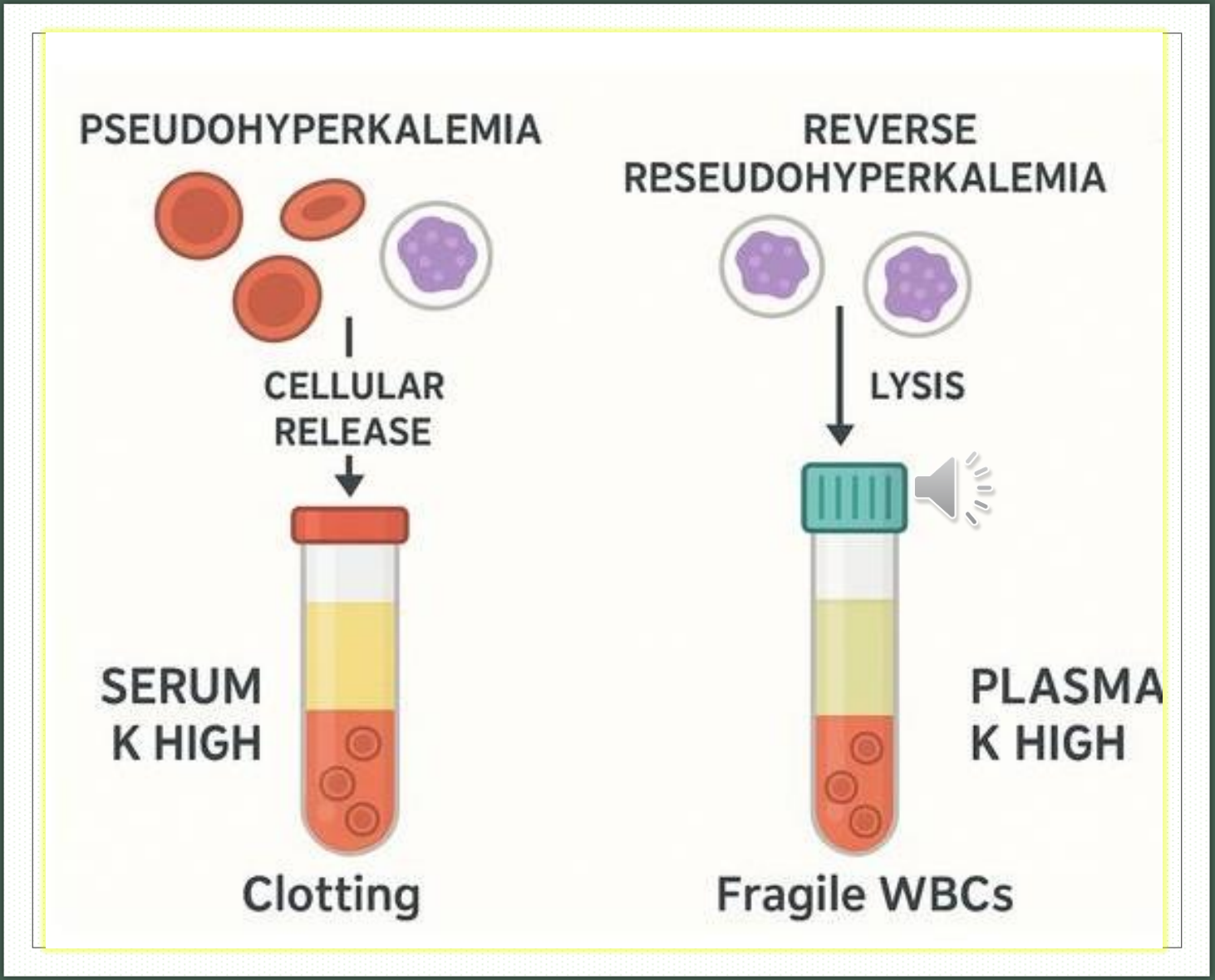
Pseudo-hypophosphatemia

Paraproteinemia: Multiple myeloma

Liposomal amphotericin B

Mannitol

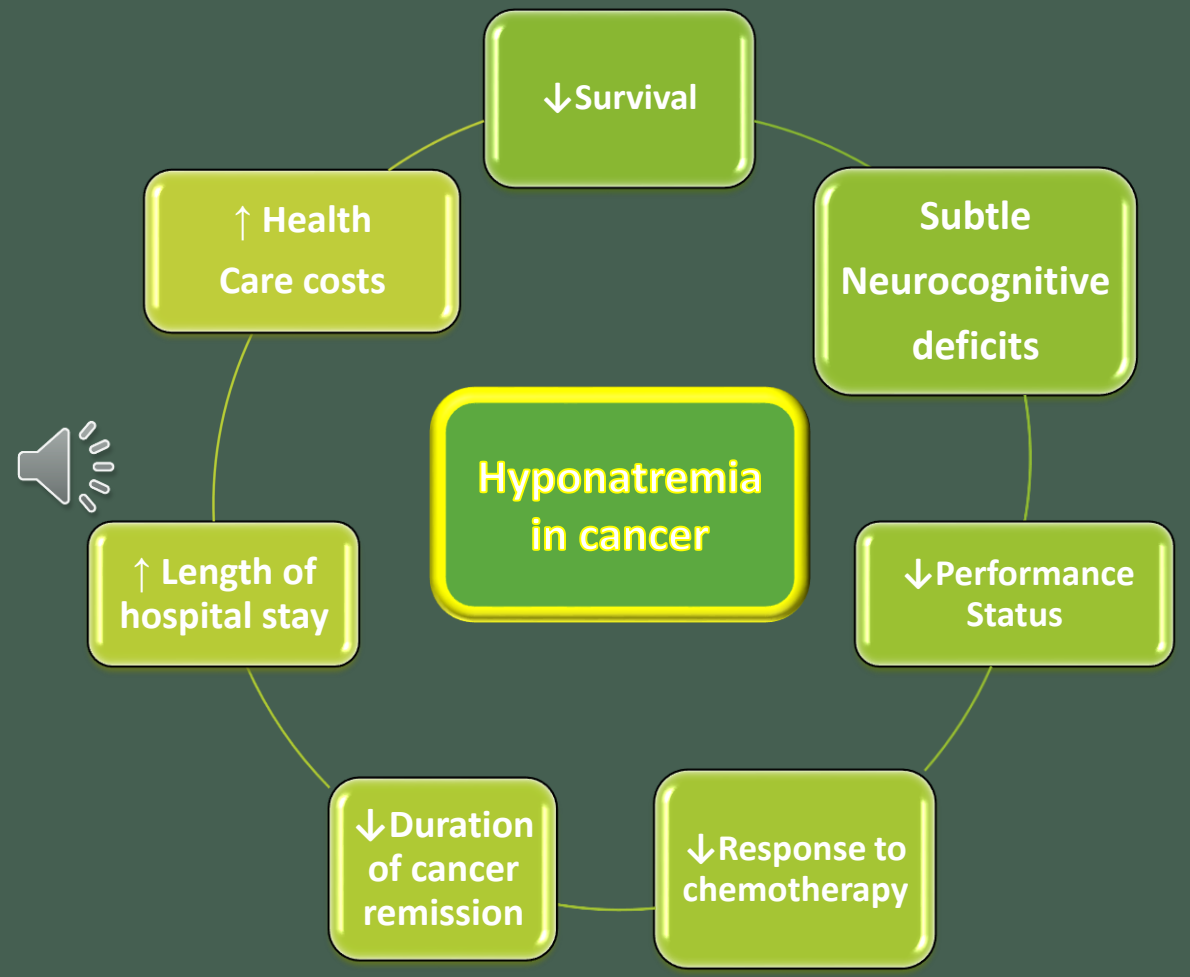
Visual abstract by @InsaraJaffer @aishaikh



Pseudohyperkalemia
vs
Reverse
Pseudohyperkalemia

Hyponatremia impacts cancer survival negatively at all cancer stages.

Its development can signal the presence of new comorbidities or toxicity, such as cardiomyopathy and advanced liver disease, or it can be a biomarker of advanced or unresponsive disease.



Causes of Hyponatremia in Patients with Cancer

ETIOLOGY	MECHANISM
Cancer treatment • Chemotherapy (vincristine, cisplatin, vinblastine, cyclophosphamide) • Hypotonic fluids/feeds	Tubular injury
Immune checkpoint treatment • Ipilimumab, nivolumab, pembrolizumab	Adrenalitis, hypophysitis, isolated ACTH deficiency
SIAD	ADH production from cancers, such as small cell lung cancer, hematologic (eg, Hodgkin disease, non-Hodgkin disease, chronic lymphatic leukemia, multiple myeloma); cancers of the head and neck, brain (primary and metastatic), skin (eg, melanoma), gastrointestinal system (esophageal, gastric, pancreatic, colon), gynecologic system, breast, prostate, and bladder; sarcoma thymoma; and adrenal malignancies
Insensible losses	Hypovolemia, aldosterone production
Appropriate ADH secretion	Nausea, vomiting, pain
Opioid derivatives	Increase ADH
Renal tubule dysfunction	Acute tubular injury (AKI, CKD)
Malnutrition	Low solute intake
Polydipsia	Infiltrating craniopharyngioma
Salt wasting	Cisplatin
Pseudohyponatremia	Production of paraproteins

https://doi.org/10.3322%2Fcaac.21636

Etiologies of Syndrome of Inappropriate Antidiuresis

I. SIAD directly associated with malignancy
1. Primary paraneoplastic endocrine effect
   - Small-cell lung cancer
   - Head and neck cancer
   - Other malignancies
2. Malignancy with brain involvement (primary or metastatic)
3. Malignancy with pulmonary involvement (primary or metastatic)

II. SIAD not directly associated with malignancy
1. Antineoplastic drugs

   Increase vasopressin production/release
   - Vinca alkaloids: vincristine, vinblastine
   - Alkylating agents: cyclophosphamide, ifosfamide
   - Platinum compounds: cisplatin, carboplatin
   - Methotrexate
   - Interferon α
   - Interferon γ
   - Imatinib

   Increase water permeability of distal nephron
   - Cyclophosphamide

   Unknown
   - Brivanib
   - Cetuximab
   - Pazopanib
   - BRAF/MEK inhibitors
   - Selinexor
2. Pulmonary infections
3. Pain
4. Nausea

https://doi.org/10.3322%2Fcaac.21636

Diagnosis of Syndrome of Inappropriate Antidiuresis

Plasma serum osmolality <275 mOsmol/kg H_2O

Presence of euvolemia on physical examination (as defined by the absence of signs of hypovolemia or hypervolemia)[a]

Elevated urinary sodium (>20-30 mEq/L or mmol/L)

Inappropriate urinary concentration (Uosm >100 mOsmol/kg H_2O)

Absence of other potential causes of hyponatremia, such as diuretic use, severe hypothyroidism, adrenal insufficiency

https://doi.org/10.3322%2Fcaac.21636

Hyponatremia in cancer
PNa < 135 mEq/l

POsm < 275 mOsm/kg

Hypotonic

UOsm ≥ 100 mOsm/kg

Urine is inappropriately concentrated for hypotonic plasma

Vasopressin-dependent

UNa < 20 mEq/l

↓ EABV

Vasopressin secretion is physiologically appropriate

- Hypovolemia (chemotherapy-induced GI losses, CAR-T– and IL-2–induced capillary leak syndrome, cisplatin-induced RSW)
- Heart failure (anthracyclines, targeted therapies, amyloidosis)
- Liver disease (metastases, chemotherapy, VOD following HSCT)

UNa> 30 mEq/l

↑ or N EABV

Vasopressin secretion is physiologically inappropriate

- SIAD (SCLC, head and neck tumors, brain or lung metastases, chemotherapy, nausea, pain)
- Cortisol deficiency (CTLA4 inhibitors—induced hypophysitis, or adrenalitis; PD-1 inhibitors—induced adrenalitis, hypophysitis, or isolated ACTH deficiency; adrenal metastases)

UOsm < 100 mOsm/kg

Urine is appropriately diluted for hypotonic plasma

Vasopressin-independent

- Primary polydipsia
- Low solute intake (tea and toast diet; beer potomania)
- Renal insufficiency*

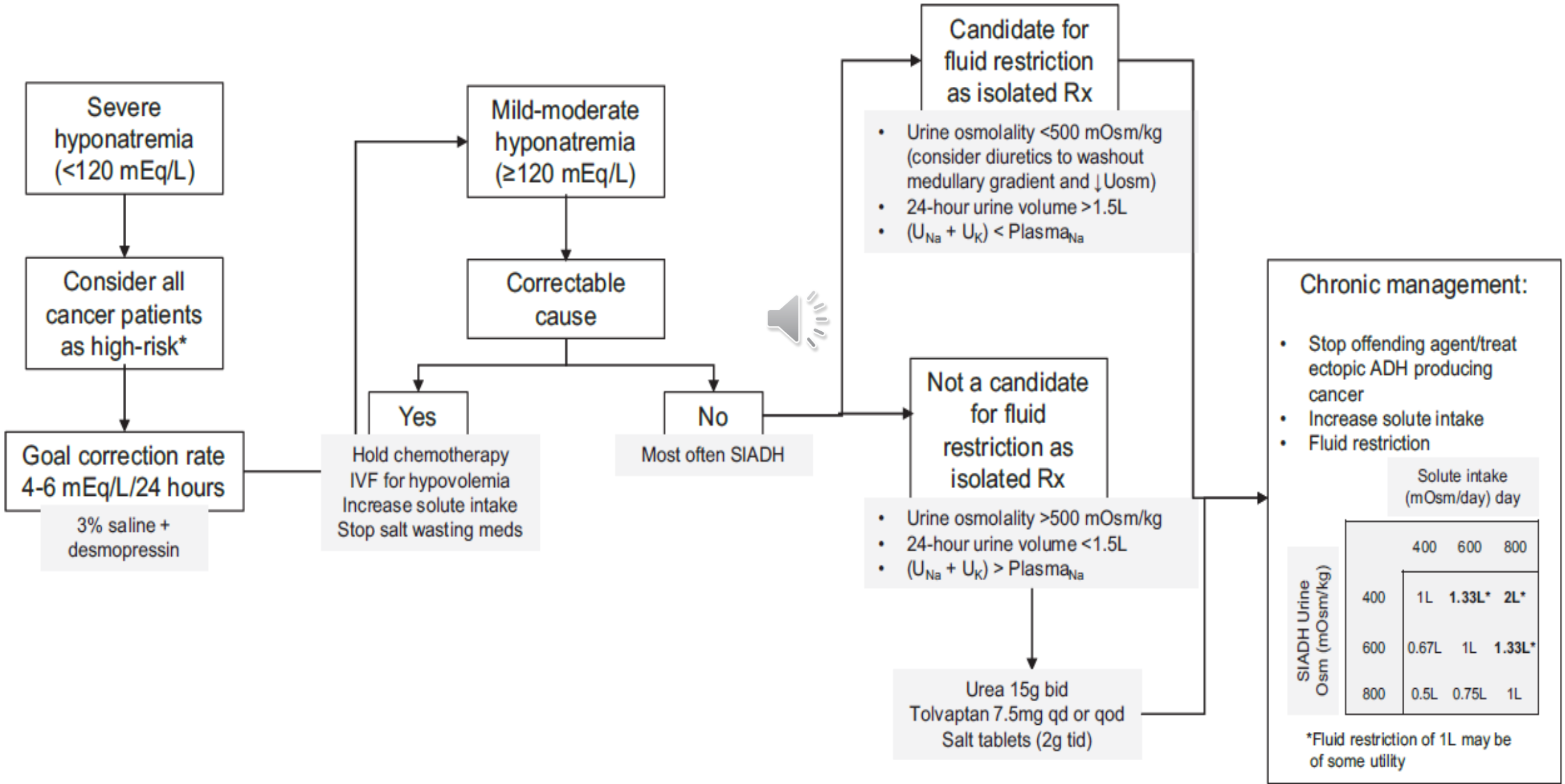
POsm ≥ 275 mOsm/kg

Isotonic
- Pseudohyponatremia (Paraproteinemias, hypertryglyceridemia, lipoprotein X in cholestasis)
- Nonconductive irrigant or hysteroscopy (glycine, sorbitol, and mannitol)
- I.v. Ig

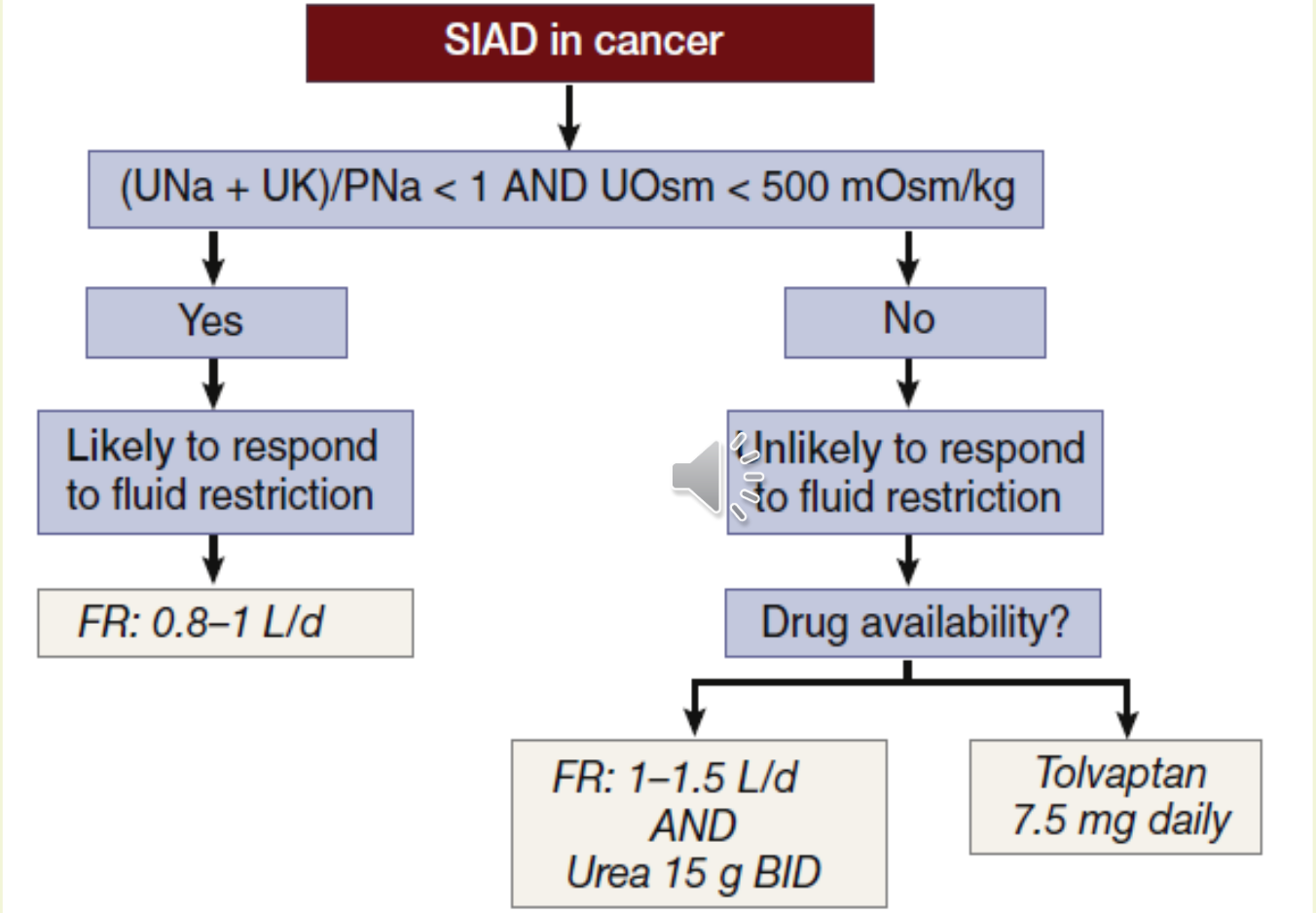
Hypertonic
- Hyperglycemia
- I.v. Ig

Hypotonic
- Concomitant presence of ineffective osmoles (e.g., urea and ethanol)

A Stepwise approach to the management of hyponatremia in a patient with cancer



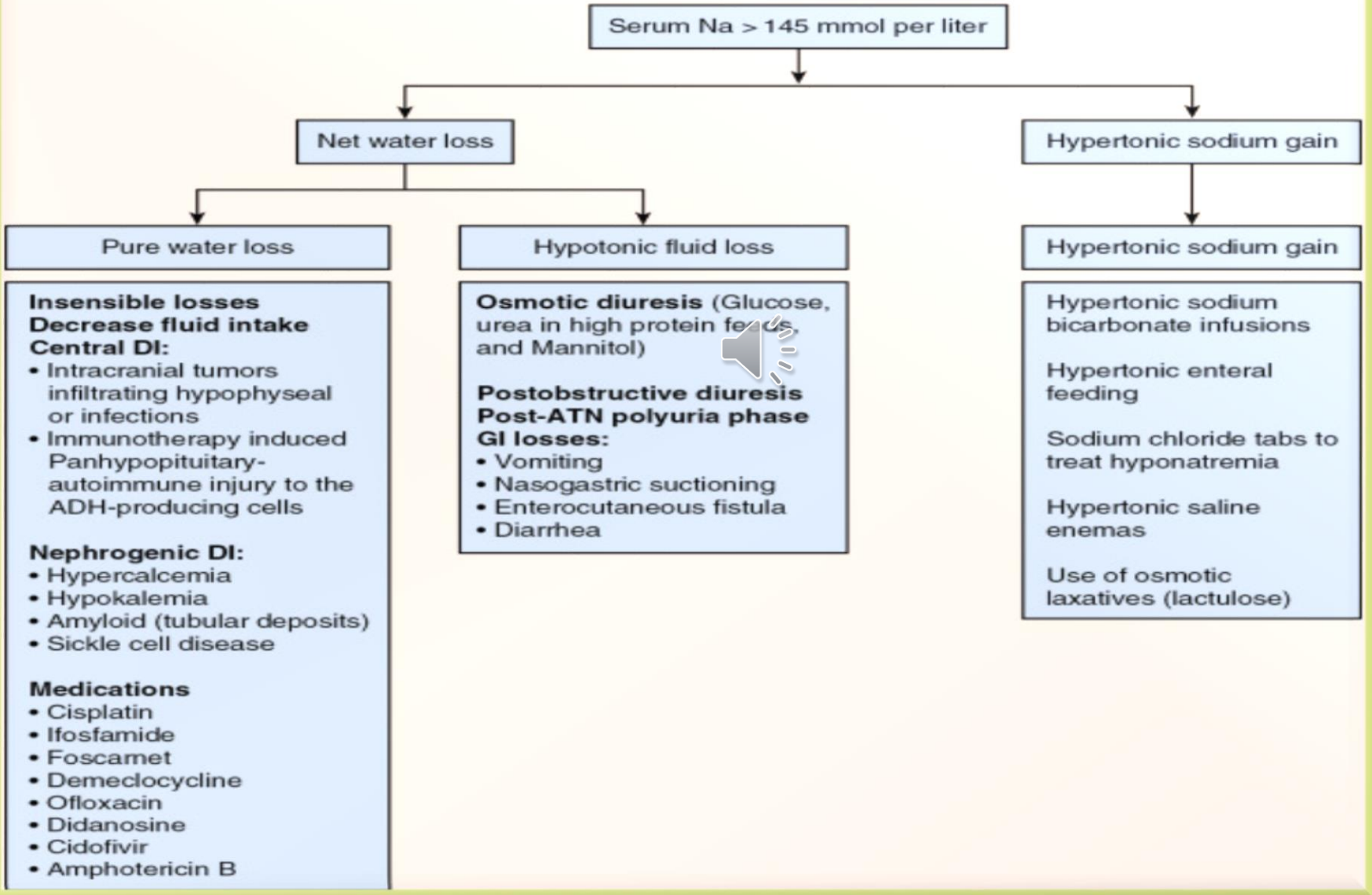
Therapeutic approach to SIAD in cancer patients



DOI :10.1016/j.kint.2020.05.015

HYPERNATREMIA IN CANCER

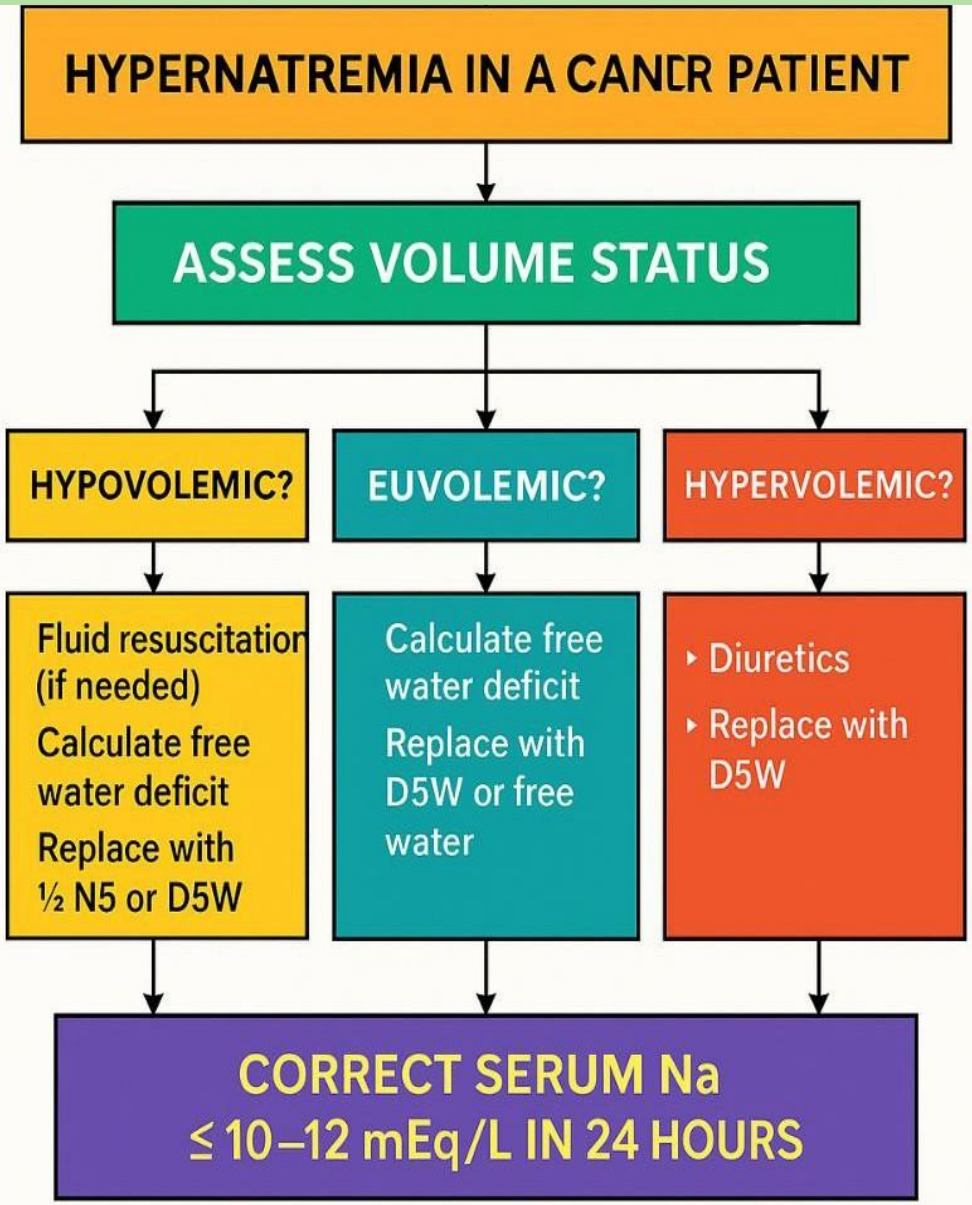
Algorithm for diagnosis of hypernatremia in cancer patients



Causes and Treatment of Hypernatremia

ETIOLOGY	TREATMENT
Insensible loses/inadequate intake of free water[a]	Repletion with isotonic saline, followed by oral water, or 0.45% NS, or 5% dextrose to reduce hyperosmolality
Hypervolemia from isotonic fluid administration	Oral water, or 0.45% NS, or 5% dextrose; loop diuretics
Central diabetes insipidus[b]	Oral water, or 0.45% NS, or 5% dextrose; desmopressin or vasopressin
Nephrogenic diabetes insipidus	Diuretics, NSAIDs[c]

$$\text{Water deficit} = \text{Current TBW} \times \left(\frac{\text{Serum [Na]}}{140} - 1\right)$$



HYPOKALEMIA IN CANCER

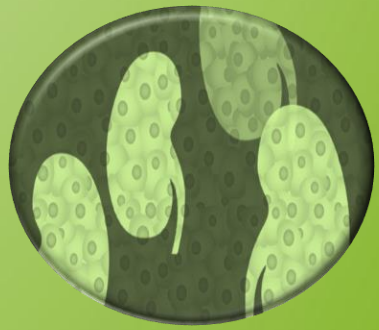
Etiologies of Hypokalemia in the Patient With Cancer

Inadequate potassium intake
- Poor nutrition, anorexia

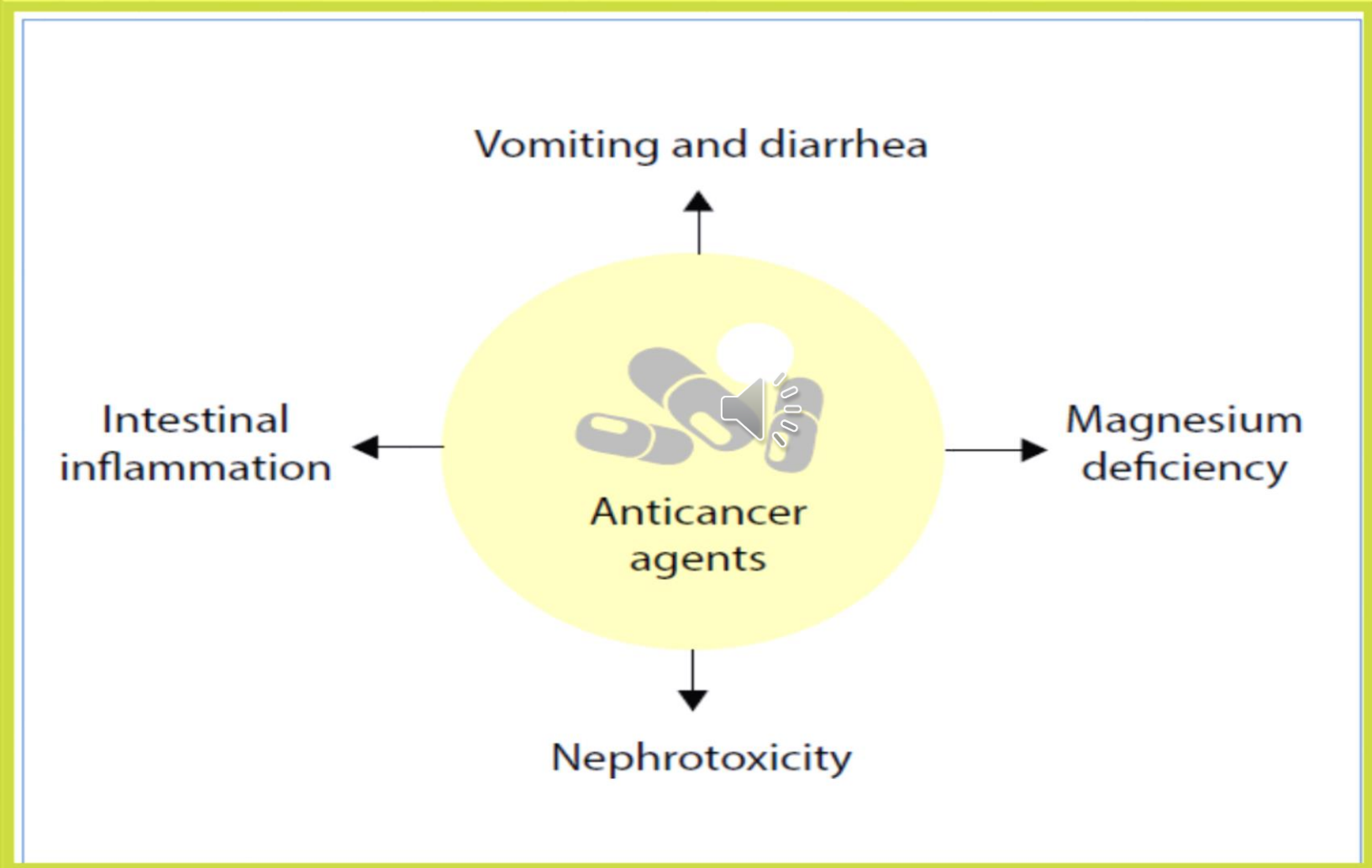
Excessive gastrointestinal losses
- Vomiting (chemotherapy-induced)
- Diarrhea (chemotherapy-induced, tumor-associated, postsurgical resection)
- Posturetosigmoid diversion

Kidney losses- Diuretics
- Hypercalcemia
- Hypomagnesemia
- Postobstructive diuresis
- Drugs
  - Amphotericin B
  - Aminoglycosides
  - Cisplatin
  - Ifosfamide
  - Glucocorticoids
- Lysozymuria with acute leukemia
- Mineralocorticoid excess
  - Primary hyperaldosteronism (adrenal adenoma or carcinoma)
  - Renin-producing tumors
  - Ectopic adenocorticotropin syndrome

Intracellular shifts
- Pseudohypokalemia
- Use of growth factors and vitamin B12 therapy

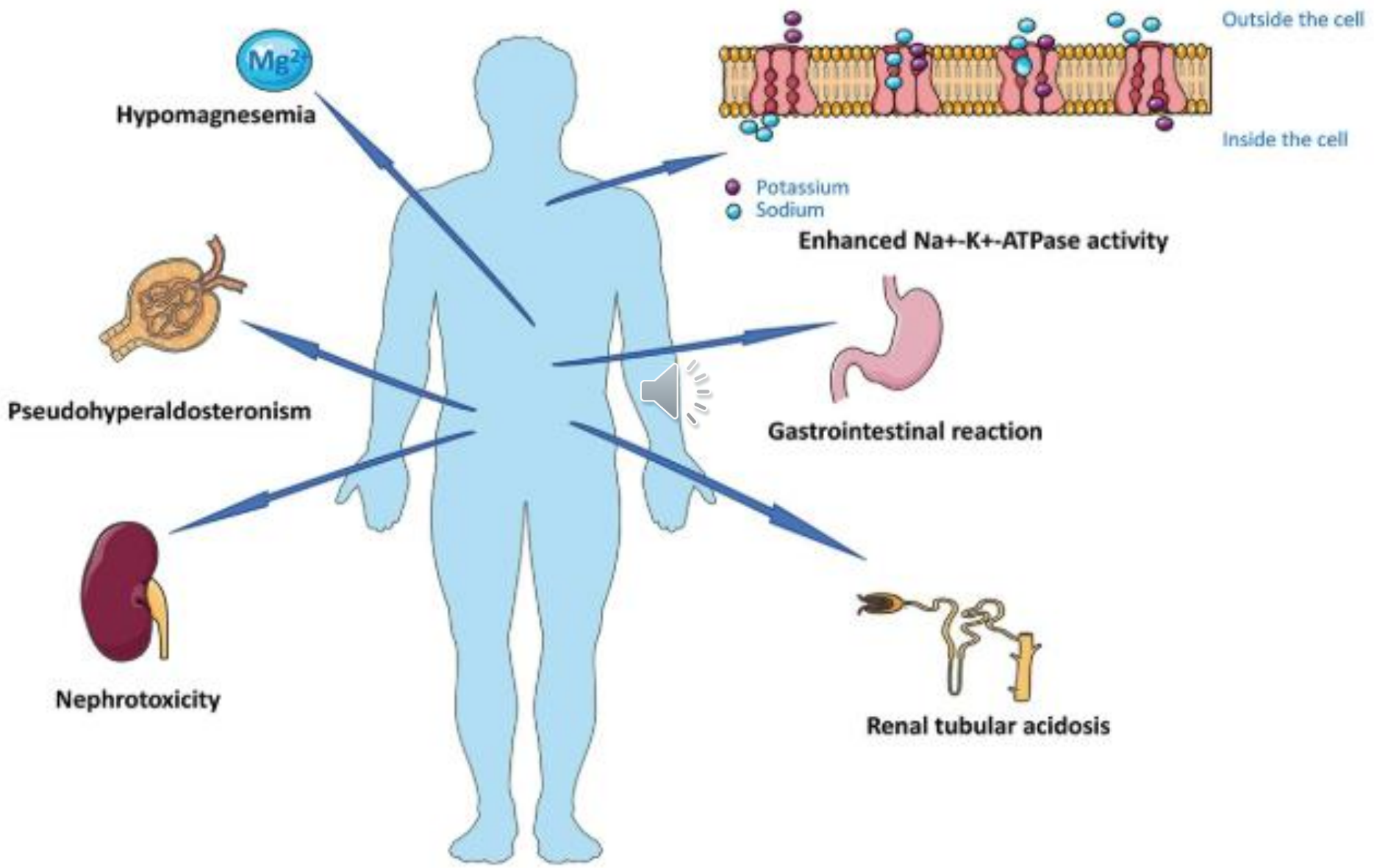


Mechanisms of hypokalemia induction by Anticancer TX.



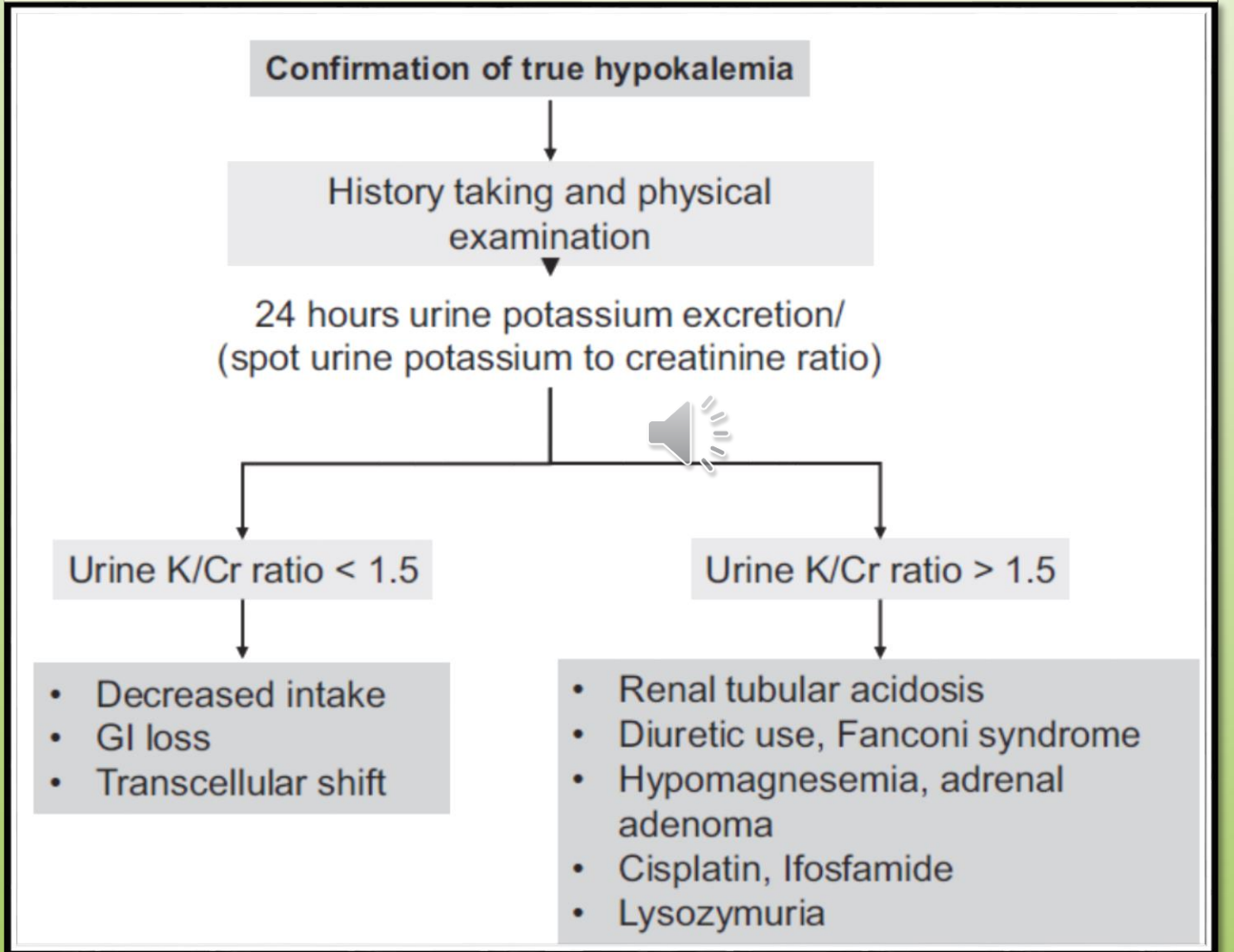
DOI:10.5603/ocp.96314

Common causes of drug-induced hypokalemia.

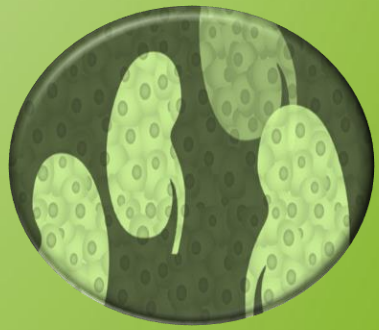


https://doi.org/10.1080/14740338.2025.2468861

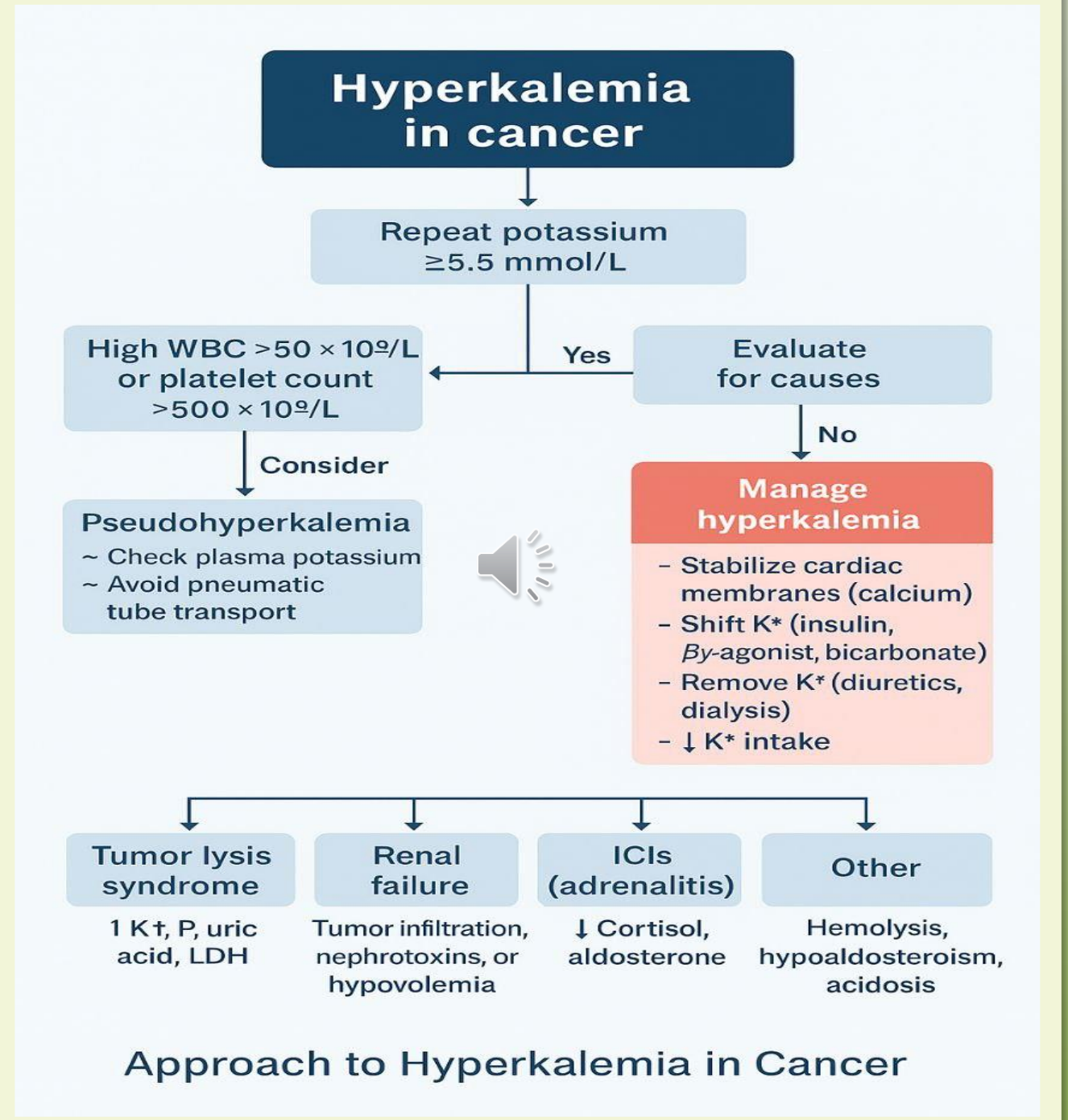
Diagnostic algorithm for Hypokalemia



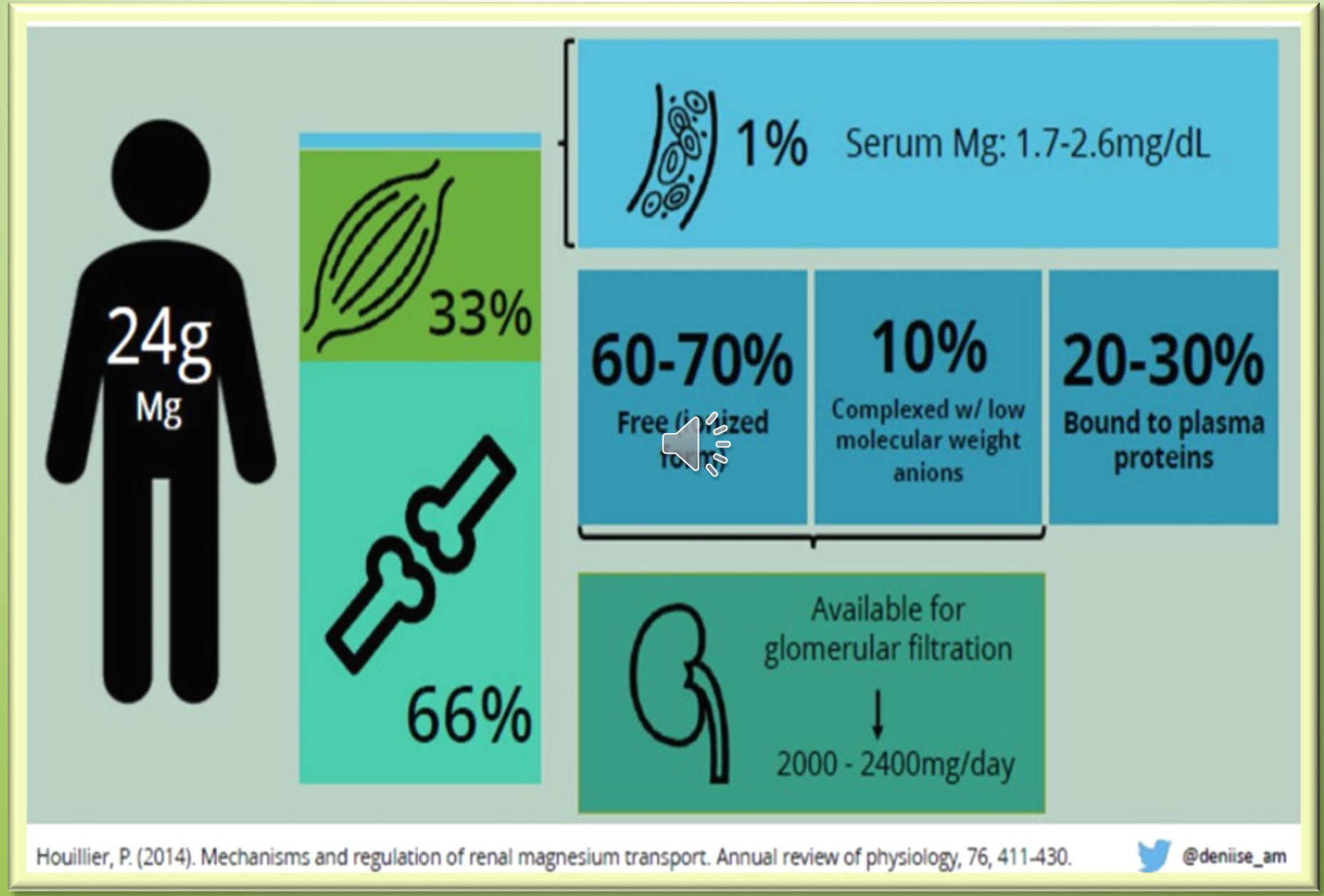
Adv Chronic Kidney Dis. 2022;29(2):171-179

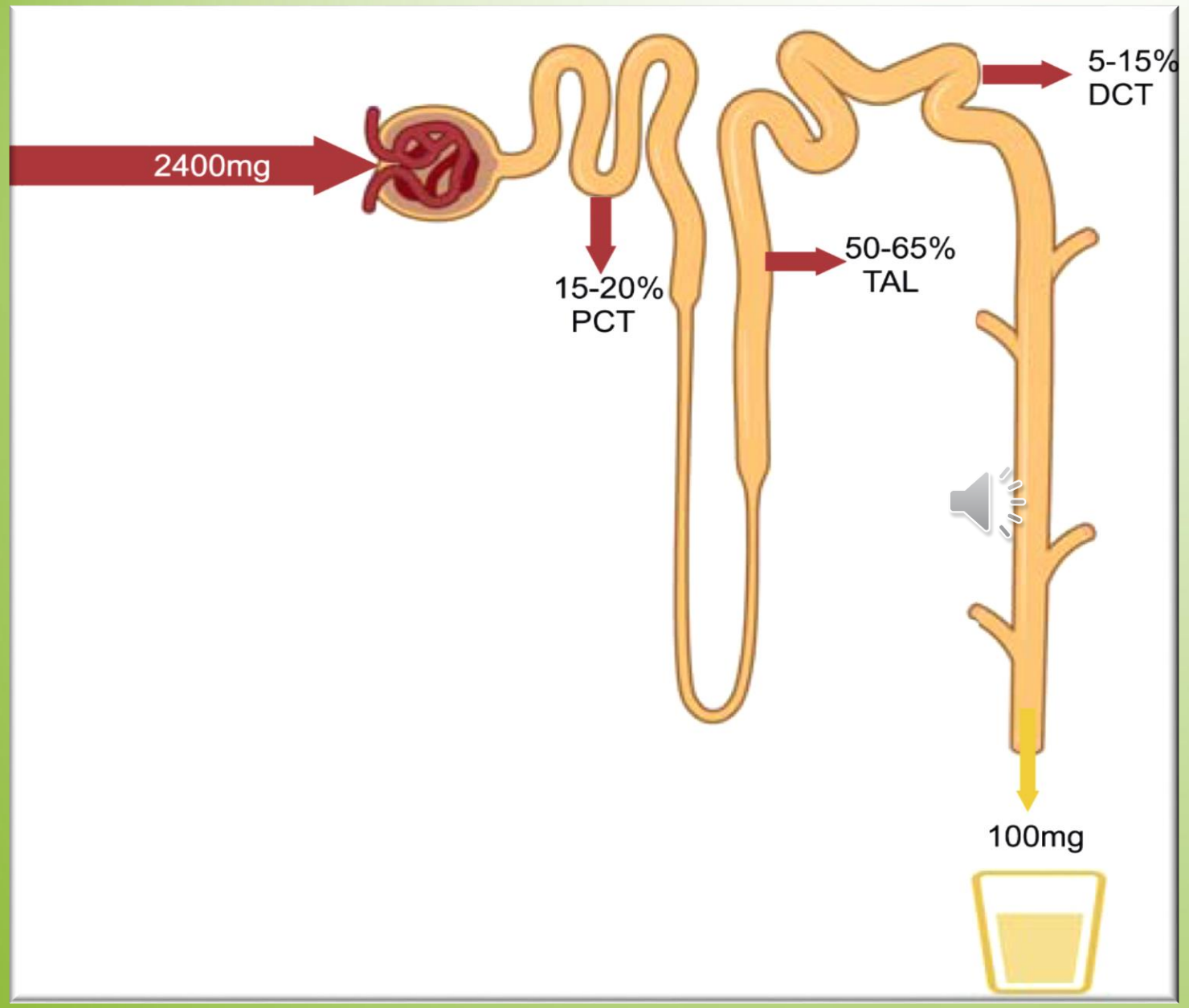


HYPERKALEMIA IN CANCER


Hyperkalemia in cancer
Repeat potassium ≥5.5 mmol/L
Yes
Evaluate for causes
No
High WBC >50 × 10⁹/L or platelet count >500 × 10⁹/L
Consider
Pseudohyperkalemia
~ Check plasma potassium
~ Avoid pneumatic tube transport
Manage hyperkalemia
– Stabilize cardiac membranes (calcium)
– Shift K⁺ (insulin, β-agonist, bicarbonate)
– Remove K⁺ (diuretics, dialysis)
– ↓ K⁺ intake
Tumor lysis syndrome
↑ K⁺, P, uric acid, LDH
Renal failure
Tumor infiltration, nephrotoxins, or hypovolemia
ICIs (adrenalitis)
↓ Cortisol, aldosterone
Other
Hemolysis, hypoaldosteroism, acidosis
Approach to Hyperkalemia in Cancer

HYPOMAGNESEMIA IN CANCER

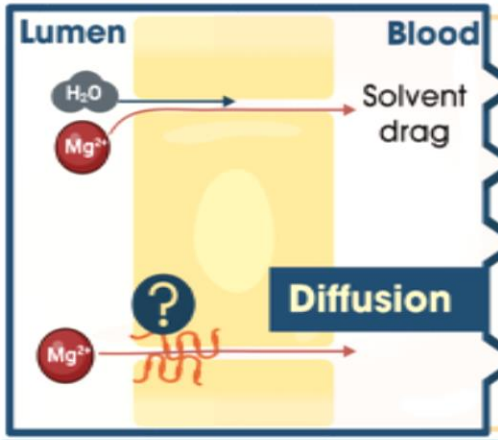

24g
Mg
33%
66%
1%
Serum Mg: 1.7-2.6mg/dL
60-70%
Free (ionized
10%
Complexed w/ low molecular weight anions
20-30%
Bound to plasma proteins
Available for glomerular filtration
2000 - 2400mg/day
Houillier, P. (2014). Mechanisms and regulation of renal magnesium transport. Annual review of physiology, 76, 411-430.
@deniise_am



Magnesium reabsorption along the renal tubule. The kidney filters 2.4g of magnesium daily.

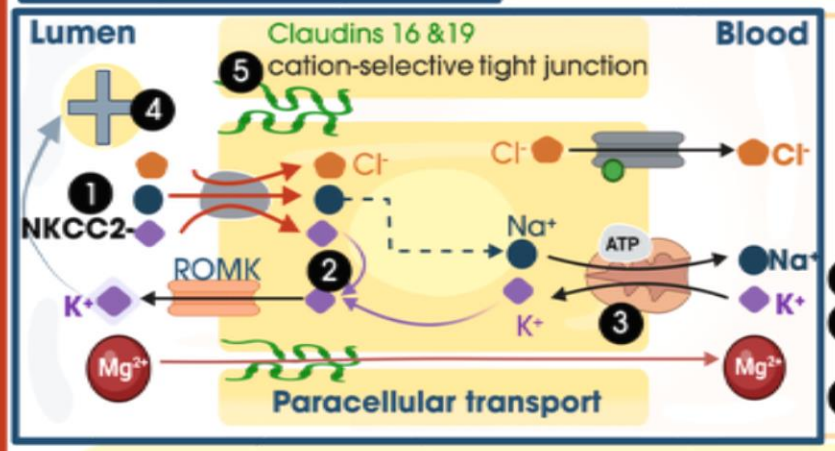
The bulk of reabsorption occurs along the paracellular route in the proximal tubule and the thick ascending limb of the loop of Henle. The distal convoluted tubule is responsible for the fine-tuning of magnesium reabsorption, with a final fractional excretion of about 4%.

Magnesium Handling along the Nephron



Proximal Convoluted Tubule

- 10-20% reabsorbed
- Paracellular → through tight junctions
- Not completely understood



Thick Ascending Limb (Loop of Henle)

70% reabsorbed

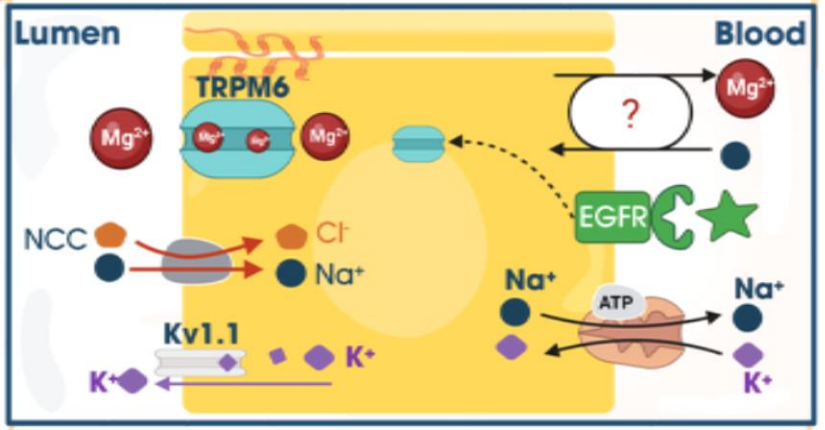
- **Apical side**
  1. Na^+-K^+-2Cl-(NKCC2)
  2. ROMK
- **Basolateral side**
  3. Na^+/K^+-ATPase

4 → transepithelial +voltage

5 → Paracellular transport

Distal Convolute Tubule

transcellular
10% reabsorbed



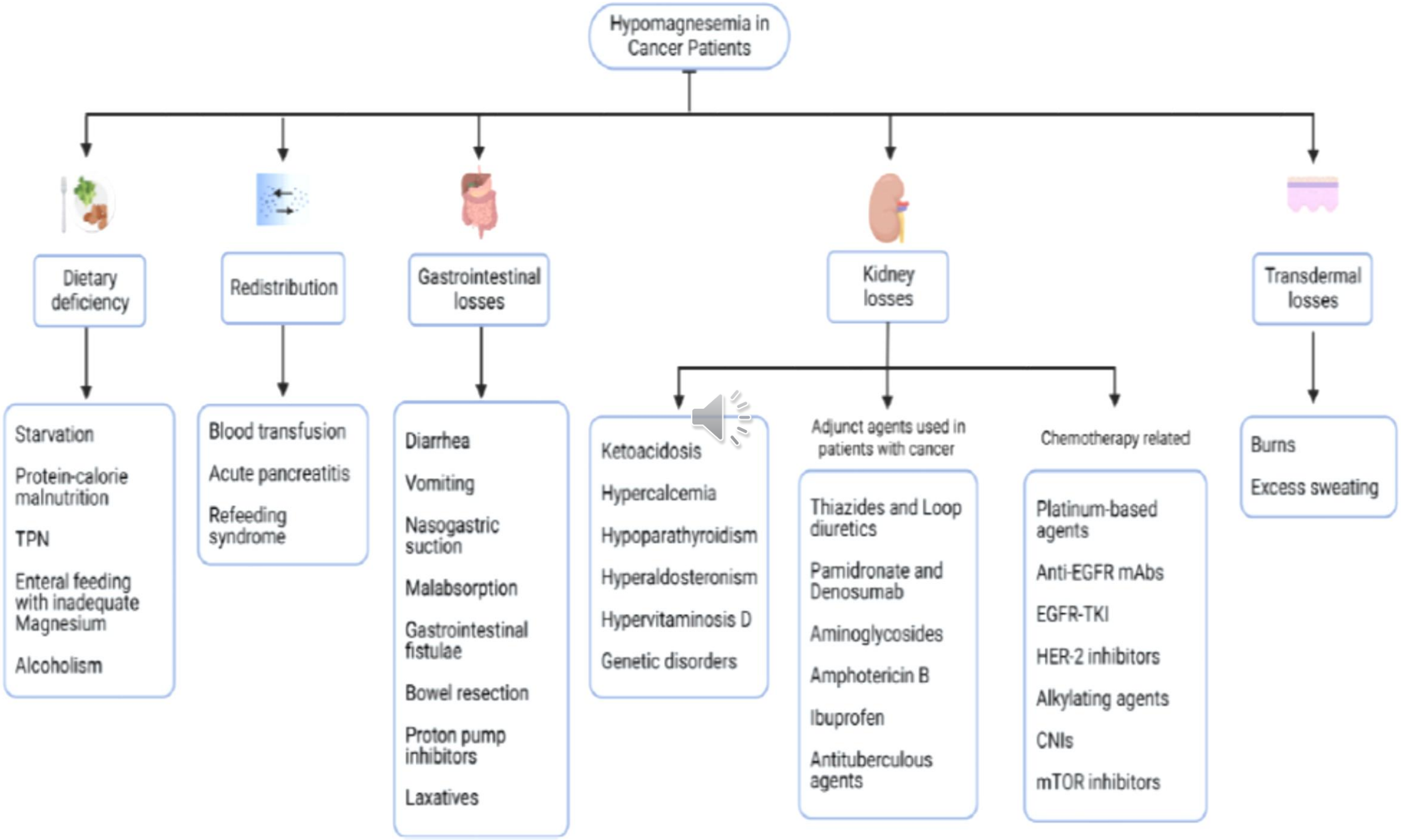
- **EGF +EGF Rc** → trigger intracellular signaling → cascade stimulate transient receptor potential melastin member 6
- TRPM6 mediate transcellular Mg^{2+} entry
- **Voltage-gated K^+ channel (Kv1.1)** mediates transcellular Mg^{2+} entry → tubular lumen.
- **K^+ = driving force of Mg^{2+} reabsorption**

EGF- epithelial growth factor

Conclusion: Magnesium reabsorption takes place in proximal convoluted tube (10-20%), loop of Henle (70%), and distal convoluted tube (10%). In PCT & LoH it is reabsorbed passively, by diffusion. Claudins, form tight junctions and play a part, but it is not completely understood. In DCT it takes place fine tuning reabsorption, through transcellular transport.

- de Baaij JH, et al. Clin Kidney J. 2012, PMID 26069817
- Blaine J, et al. Clin J Am Soc Nephrol. 2015, PMID 25287933
- Tomacruz, D et al. 2021. Kidney News, 13(8), 20-22

VA by @NephroSeeker



https://doi.org/10.1016/j.semnephrol.2023.151347

$$\text{FE Mg} = \frac{\text{urine Mg x plasma Cr}}{(0.7 \text{ x plasma Mg}) \text{x urine Cr}} \text{ x } 100$$

HYPOMAGNESEMIA
(serum Mg < 1.6mg/dl)

Assess FeMg/24-hour Mg

RENAL Mg WASTING
FeMg >4%
24-hour Mg >30mg

NON-RENAL Mg LOSS
FeMg <2%
24-hour Mg <10mg

PT/TAL:
Osmotic diuretics
Loop diuretics
Aminoglycosides
Bartter syndrome

DCT:
Thiazide diuretics
CNI
mTORi
EGFRi
Gitelman syndrome

MISCELLANEOUS:
Platinum based chemotherapy
Amphotericin
Pentamidine
Diabetes mellitus

GI:
PPI
Resin binders
Diarrhea
Malabsorption syndrome
Short bowel syndrome
High output stoma
Alcohol use disorder

Transcellular shift:
Refeeding syndrome

Drug Class or Name
Loop diuretics
Pamidronate
RANKL mAb (denosumab)
Ibuprofen
Aminoglycosides (amikacin, gentamicin, tobramycin, neomycin, streptomycin)
Antituberculous agents (viomycin, capreomycin)
Amphotericin B

DOI: 10.34067/KID.0005622020

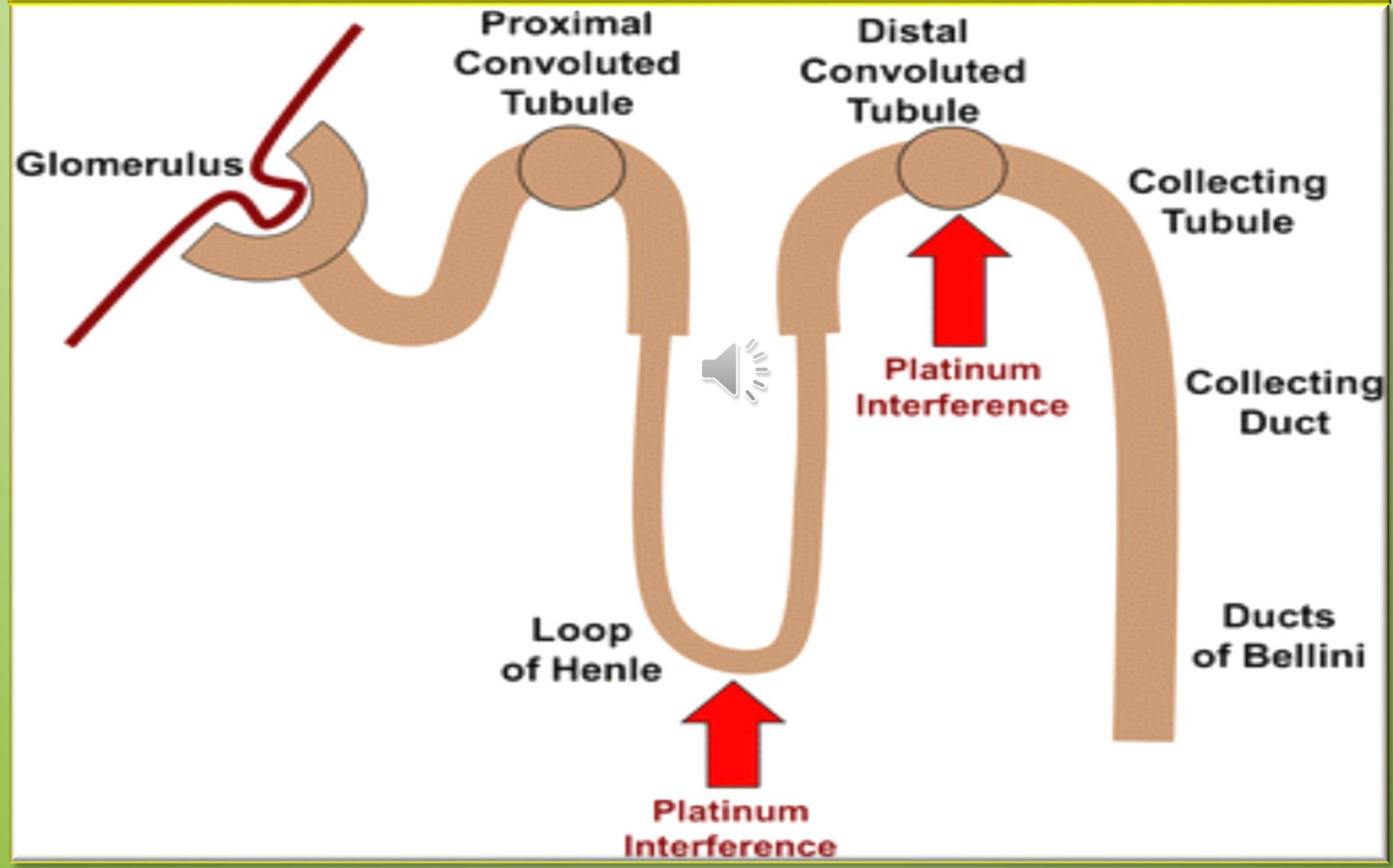
Drug-induced hypomagnesemia in a patient with cancer: adjunct agents used in patients with cancer

Drug Class	Examples
Anti-EGFR mAbs	Cetuximab, panitumumab, zalutumumab
EGFR tyrosine kinase inhibitors	Afatinib, erlotinib, gefitinib
Platinum-based agents	Cisplatin, carboplatin, oxaliplatin
HER-2 inhibitors	Trastuzumab, pertuzumab
Calcineurin inhibitors	Cyclosporine, tacrolimus
Immunotherapy	IL-2
mTOR inhibitors	Rapamycin
Topoisomerase inhibitors	Amsacrine
Anthracyclines	Pegylated liposomal doxorubicin
Alkylating agents	Ifosfamide

DOI: 10.34067/KID.0005622020

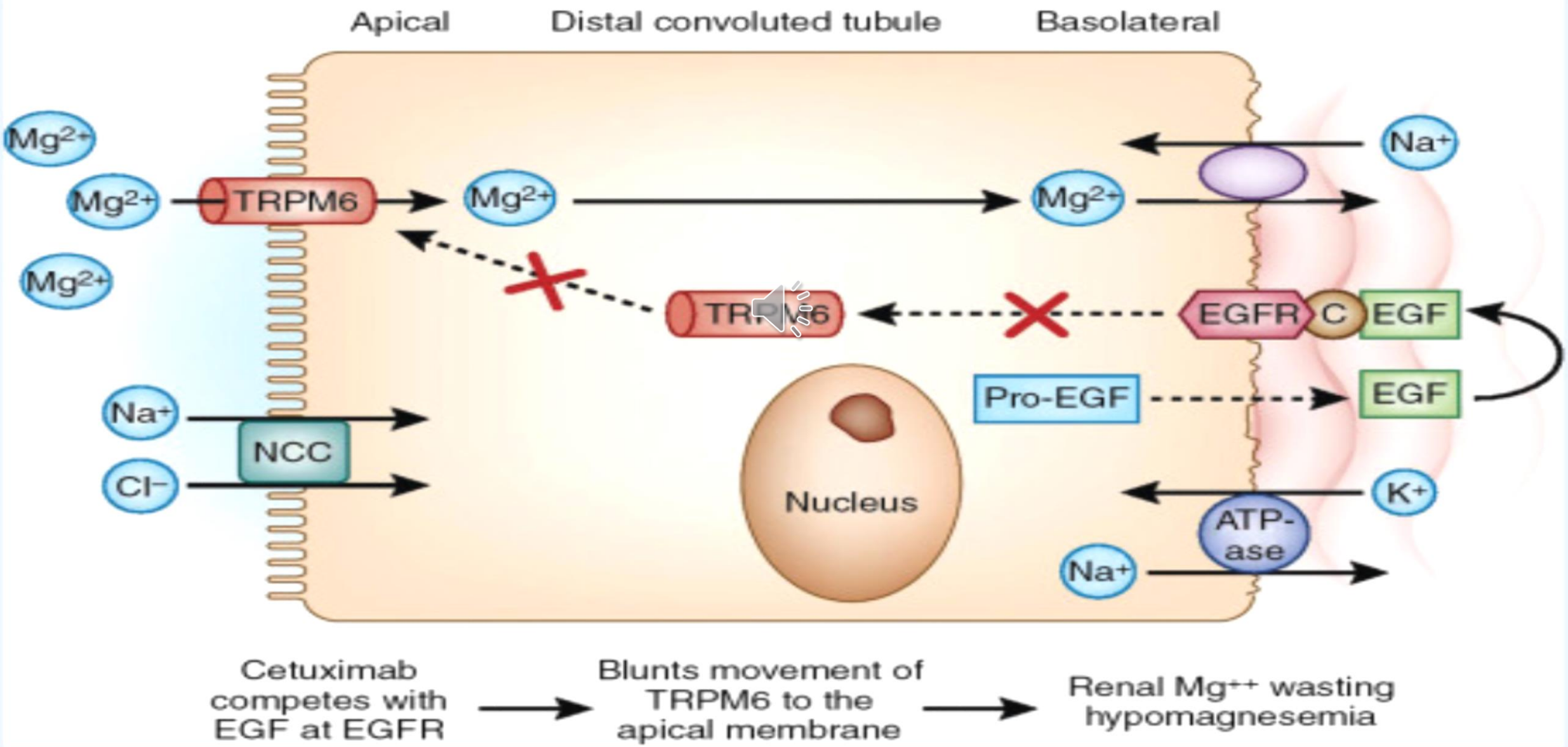
Drug-induced hypomagnesemia in a patient with cancer: antineoplastic agents

Nephron structure and sites of platinum interference with magnesium absorption



DOI:https://doi.org/10.1007/s00280-017-3392-8

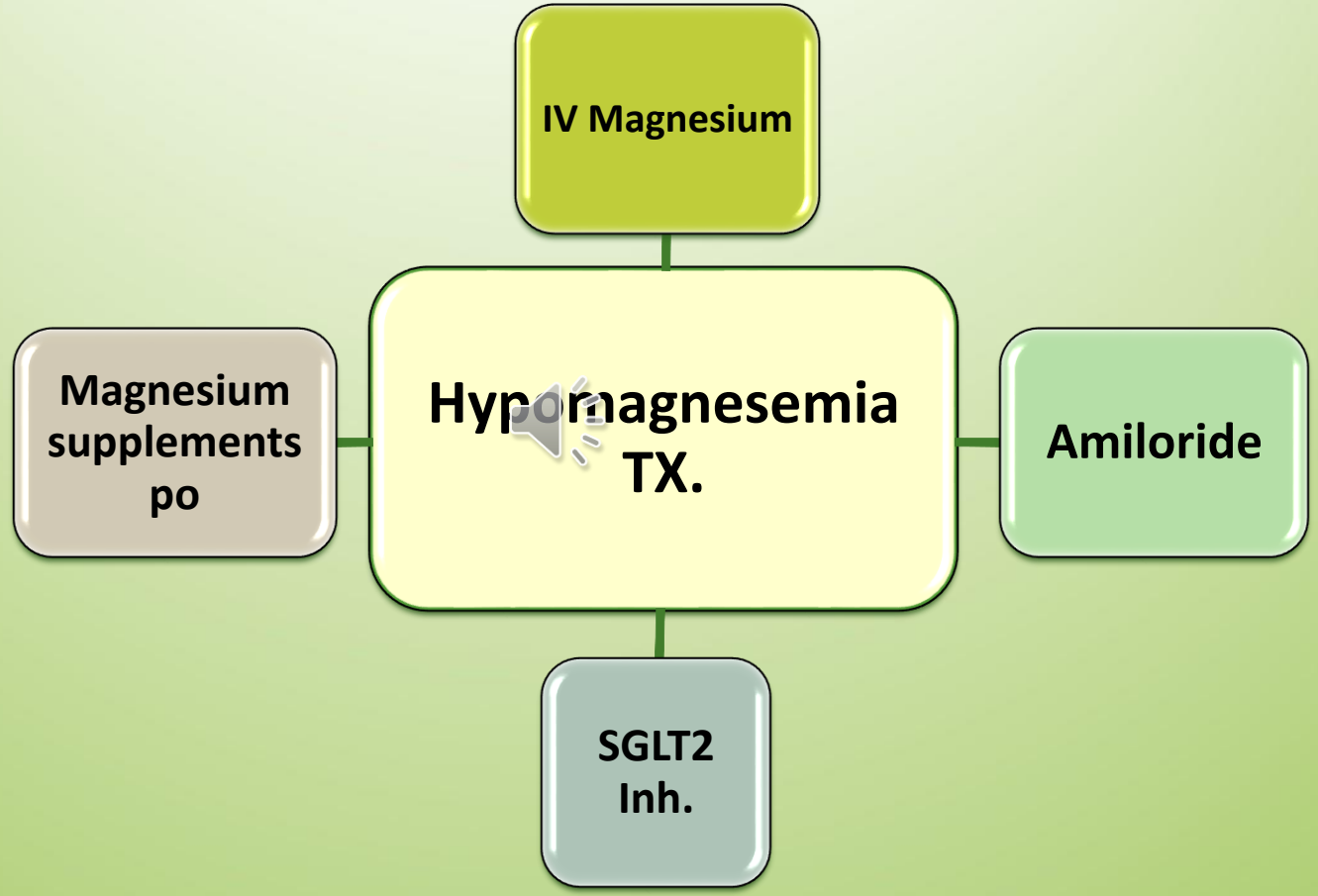
CETUXIMAB


Apical
Distal convoluted tubule
Basolateral
Mg2+
Mg2+
Mg2+
TRPM6
Mg2+
Mg2+
Na+
EGFR
C
EGF
EGF
Pro-EGF
Na+
NCC
Cl−
Nucleus
K+
ATP-ase
Na+
Cetuximab competes with EGF at EGFR
Blunts movement of TRPM6 to the apical membrane
Renal Mg++ wasting hypomagnesemia

Grades of Hypomagnesemia

Grade	Serum Magnesium (mg/dl)	Clinical Significance
1	1.2–1.7	Mild or no symptoms, fatigue
2	0.9–1.2	Muscle weakness, fasciculations
3	0.7–0.9	Neurologic deficits, atrial fibrillation
4	<0.7	Psychosis, seizures, tetany, nystagmus, lethal arrhythmia

DOI: 10.34067/KID.0005622020


IV Magnesium
Magnesium supplements po
Hypomagnesemia TX.
Amiloride
SGLT2 Inh.

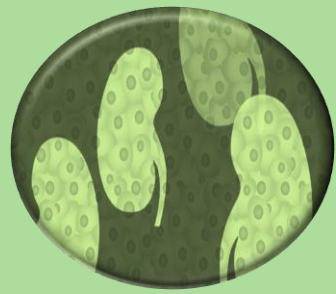
HYPOCALCEMIA IN CANCER

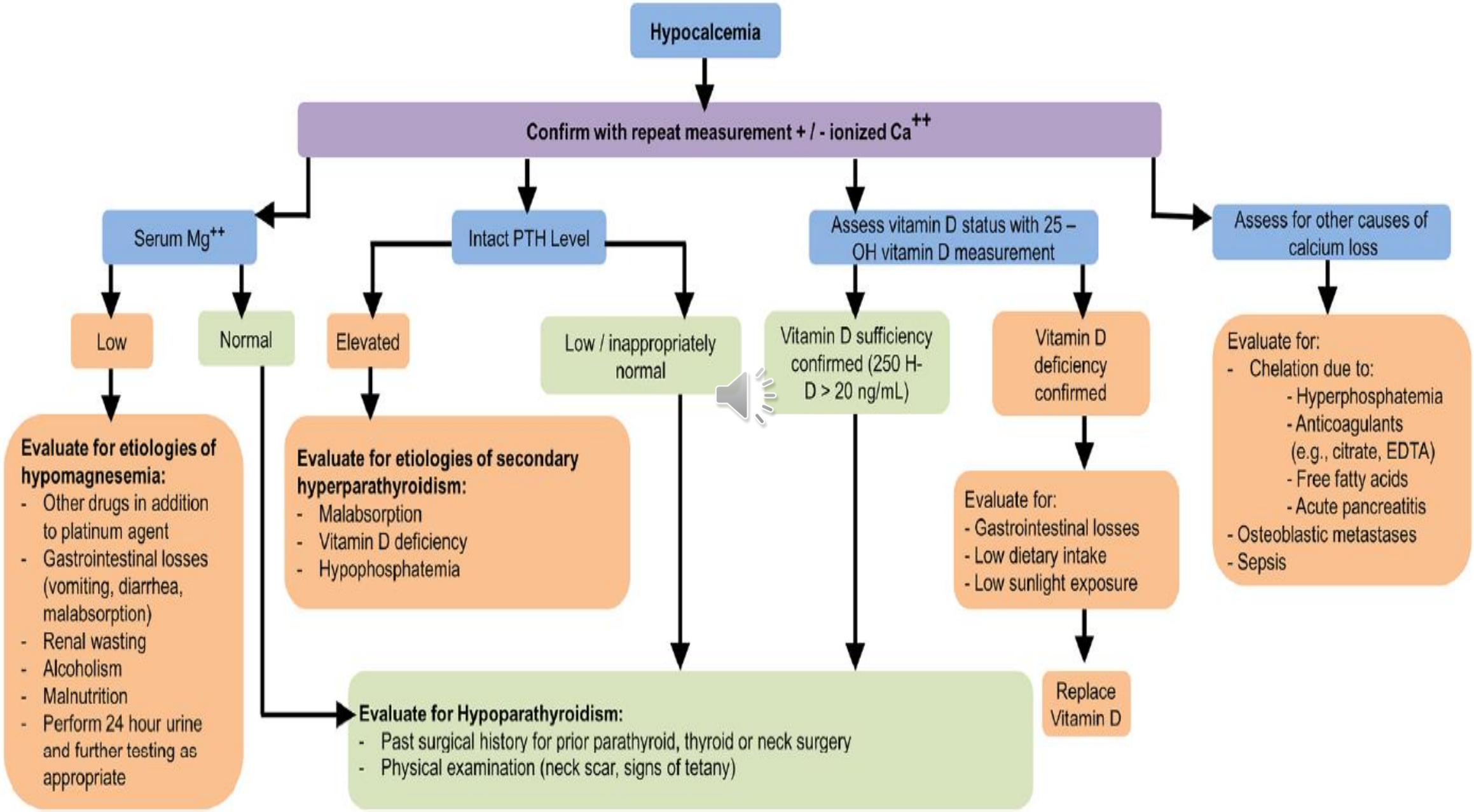
TLS

Hypocalcemia in cancer-specific causes

Osteoblastic metastases

Anti-neoplastic Drugs





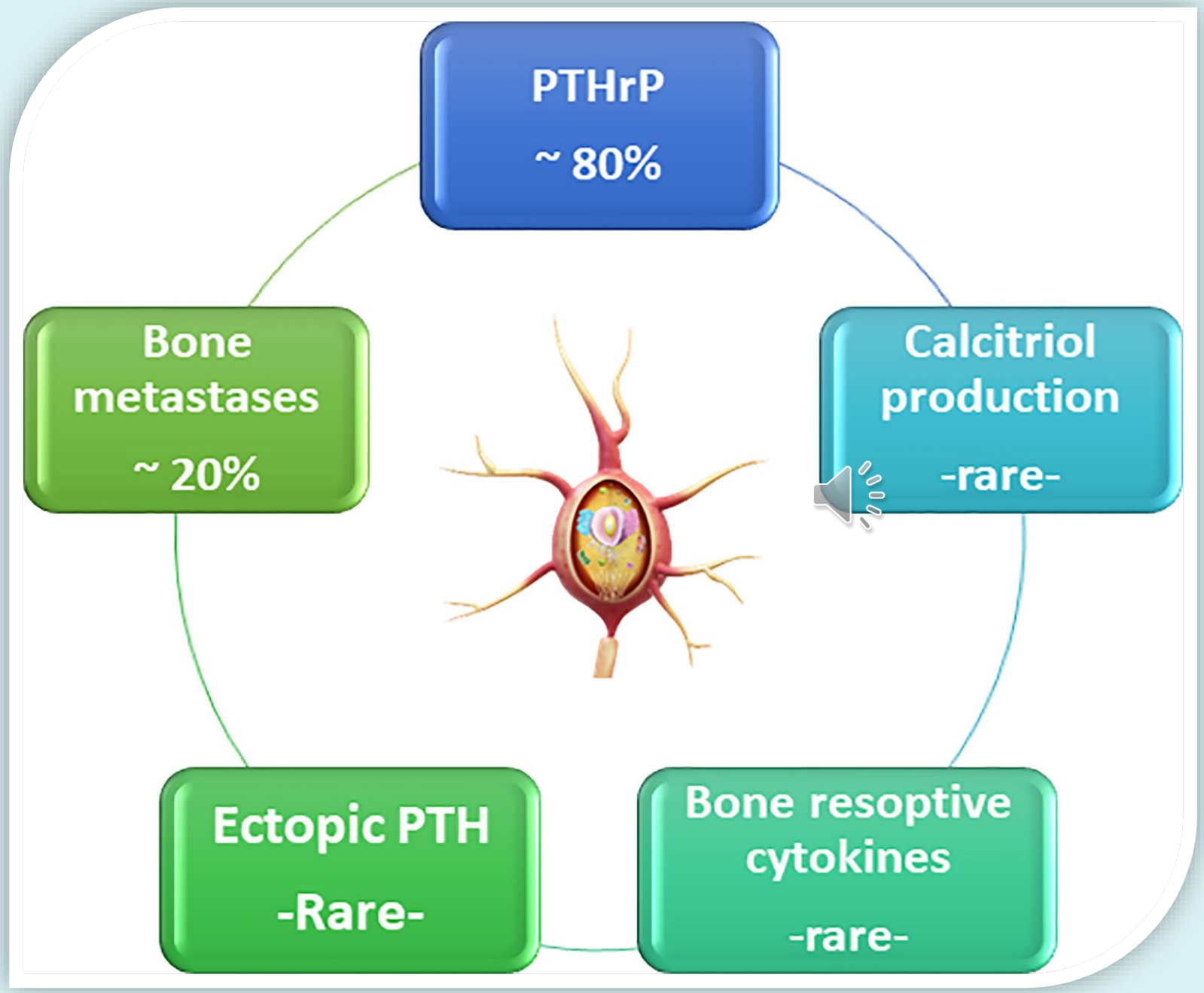
10.1007/s00280-017-3392-8.

Cancer Therapies Associated With Hypocalcemia

Cancer Therapy	Proposed Mechanism
Dinaciclib, alvocidib, venetoclax, obinutuzumab, chimeric antigen receptor (CAR-T) cell therapy[37,56]	Tumor lysis syndrome (calcium precipitation in soft tissues secondary to acute hyperphosphatemia)
Cisplatin, carboplatin[13,37,57]	Hypomagnesemia-induced reduction in parathyroid hormone (PTH) secretion, end-organ resistance to the effects of PTH Direct inhibitory effect on bone resorption and decreased 1-alpha-hydroxylation (cisplatin)
Cetuximab, panitumumab[32,37,58]	Hypomagnesemia-induced reduction in PTH secretion, end-organ resistance to the effects of PTH
Imatinib[37,59-61]	Direct effect on the c-KIT tyrosine kinase receptors of renal tubular cells, osteoclast inhibition, and osteoblast activation with bone sequestration of calcium
Nilotinib[37,62]	Immune-mediated destruction of the parathyroid glands, drug interference with calcium-sensing receptors
Combination 5-fluorouracil with 5-formyl tetrahydrofolic acid (leucovorin)[37,63]	Reduced vitamin D absorption from the intestine due to mucositis, inhibition of vitamin D 1- and 25-hydroxylation
Estramustine[37,64]	Severe vitamin D deficiency
Denosumab[65]	Osteoclast inhibition

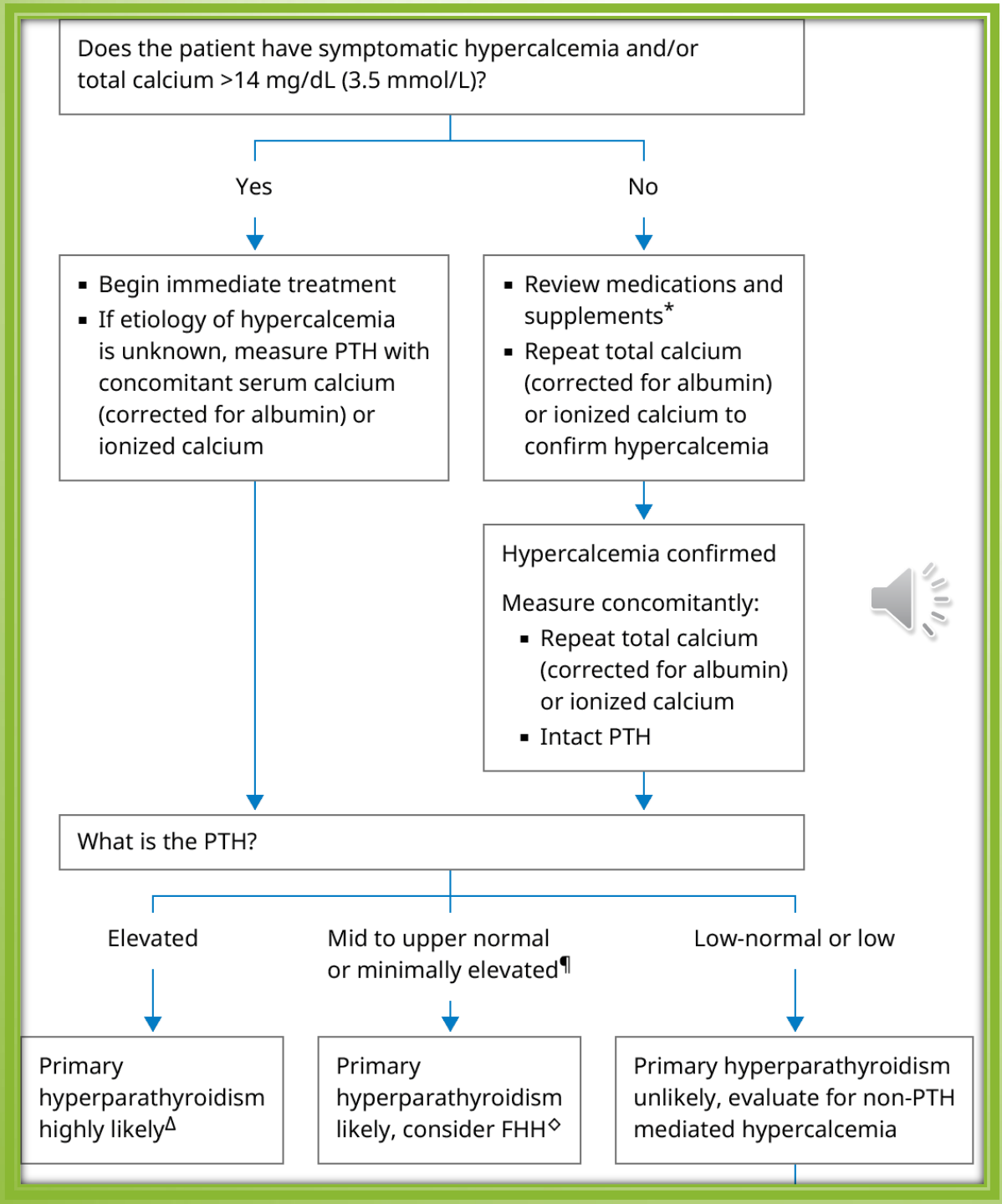
Doi: 10.1053/j.ackd.2021.09.005.

HYPERCALCEMIA IN CANCER

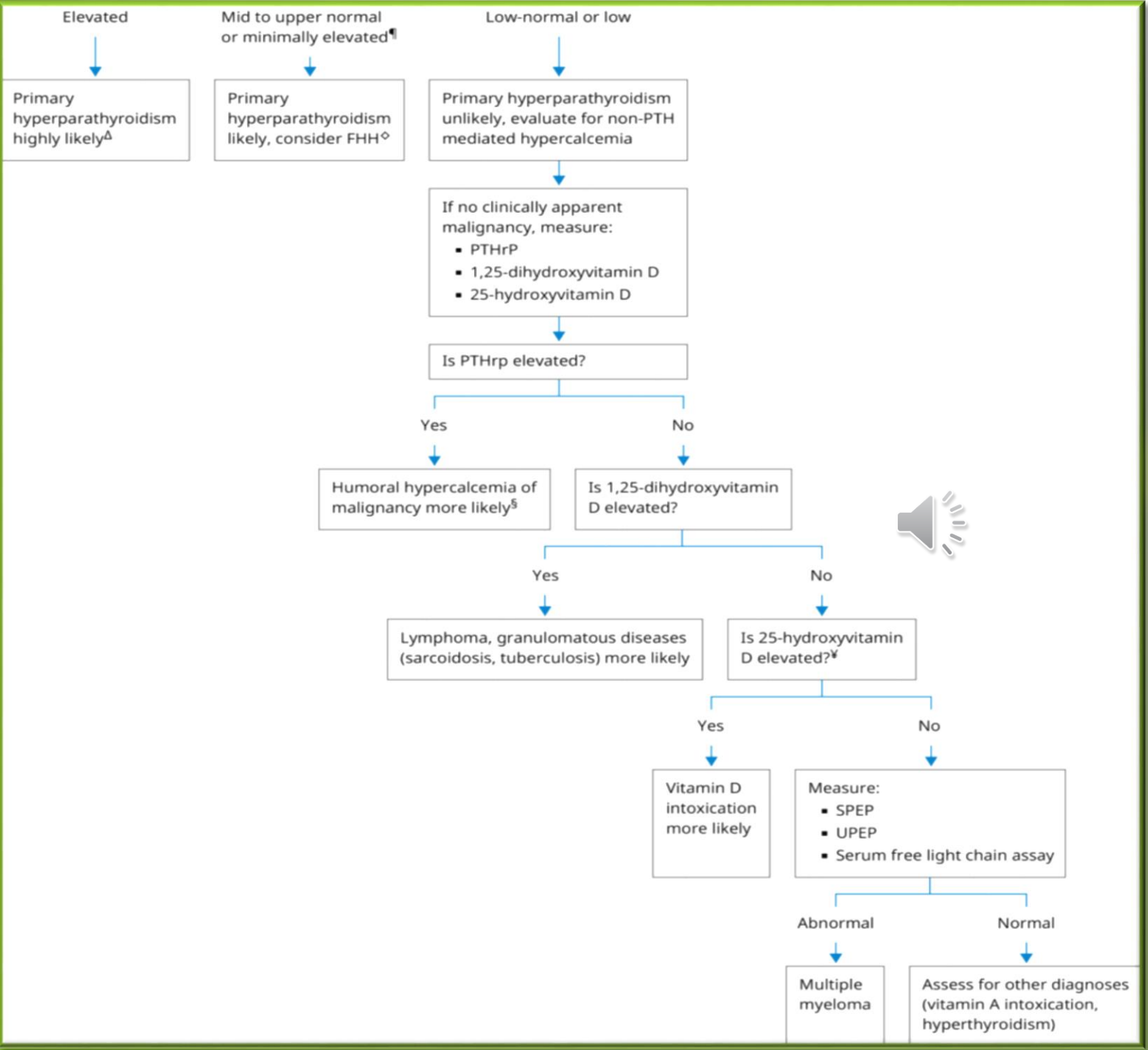


DOI 10.3389/fendo.2023.1039490

The Etiologies of Malignant-Associated Hypercalcemia



Diagnostic algorithm to Hypercalcemia(1) Uptodate



Diagnostic algorithm to Hypercalcemia(2) Uptodate

Treatment options for hypercalcemia of malignancy.

Agent	Regimen	Mechanism of action	Onset	Duration	Side Effects
0.9% saline	2-4 l/day or 200-500 ml/h	Enhance renal excretion of Ca^{2+}	Immediate	1-3 days (depends on cardiovascular and renal status)	Volume overload
Zoledronic acid or Pamidronate	4 mg IV over 15 to 30 minutes in a solution of 50-100 ml NS or D5W 60 to 90 mg IV over 4 to 24 hours	Inhibits osteoclastic bone resorption	48 hours	Every 3-4 weeks May be additional	Renal toxicity, acute-phase reactions, gastrointestinal toxicity, hypocalcemia and osteonecrosis of the jaw
Denosumab	120 mg SQ	İnhibits the binding of RANKL with its receptor RANK and decreases OC activity	7-10 days	Every 4 weeks and additional on days 8 and 15 for first month	Allergic reactions, hypocalcemia, osteonecrosis
Calcitonin	4 units/kg SQ repeated every 6-12 hours	Increases renal calcium excretion reduce bone resorption by interfering with OC function	4-6 hours	24 to 48 hours	Pain at the injection site and cutaneous flushing, anaphylactic reactions
Glucocorticoids	200-400 mg/day of hydrocortisone 10-20 mg/day of prednisone	Inhibit $1,25(OH)_2$ D synthesis and thus calcium absorption from the intestine	7 days	3-10 days (unclear)	Myopathy, immunosuppression, elevated blood glucose
Gallium Nitrate	100 to 200 mg/m2 IV over 24 hours for 5 days	inhibits osteoclast activity	4 days	2 weeks	Nephrotoxicity, bone marrow supression

Ca^{2+} calcium ions; SQ subcutaneously; D5W 5% dextrose in water; NS normal saline; OC osteoclastic; RANK receptor activator of nuclear factor kappa-B ligand.

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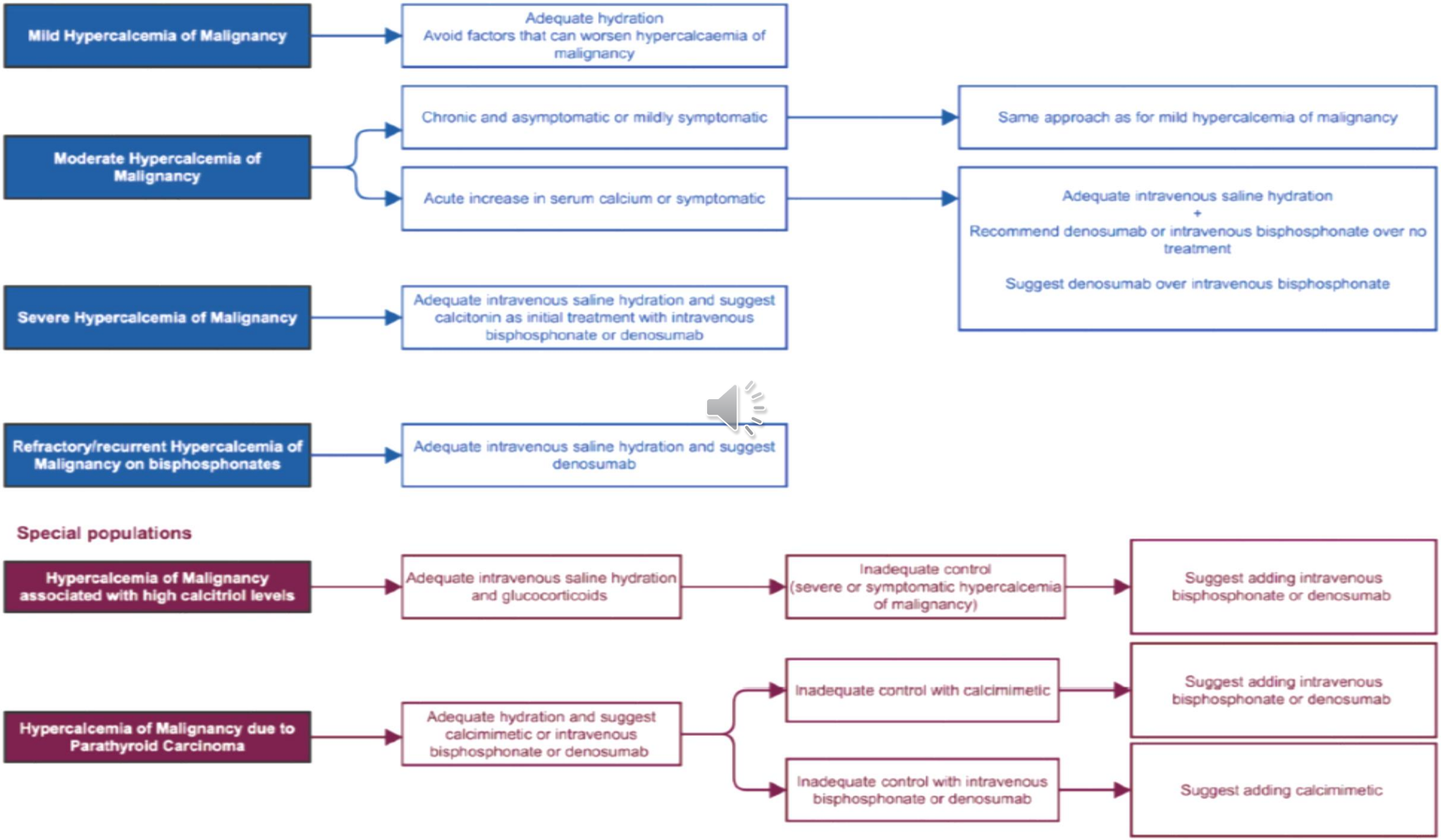

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HYPERPHOSPHATEMIA IN CANCER

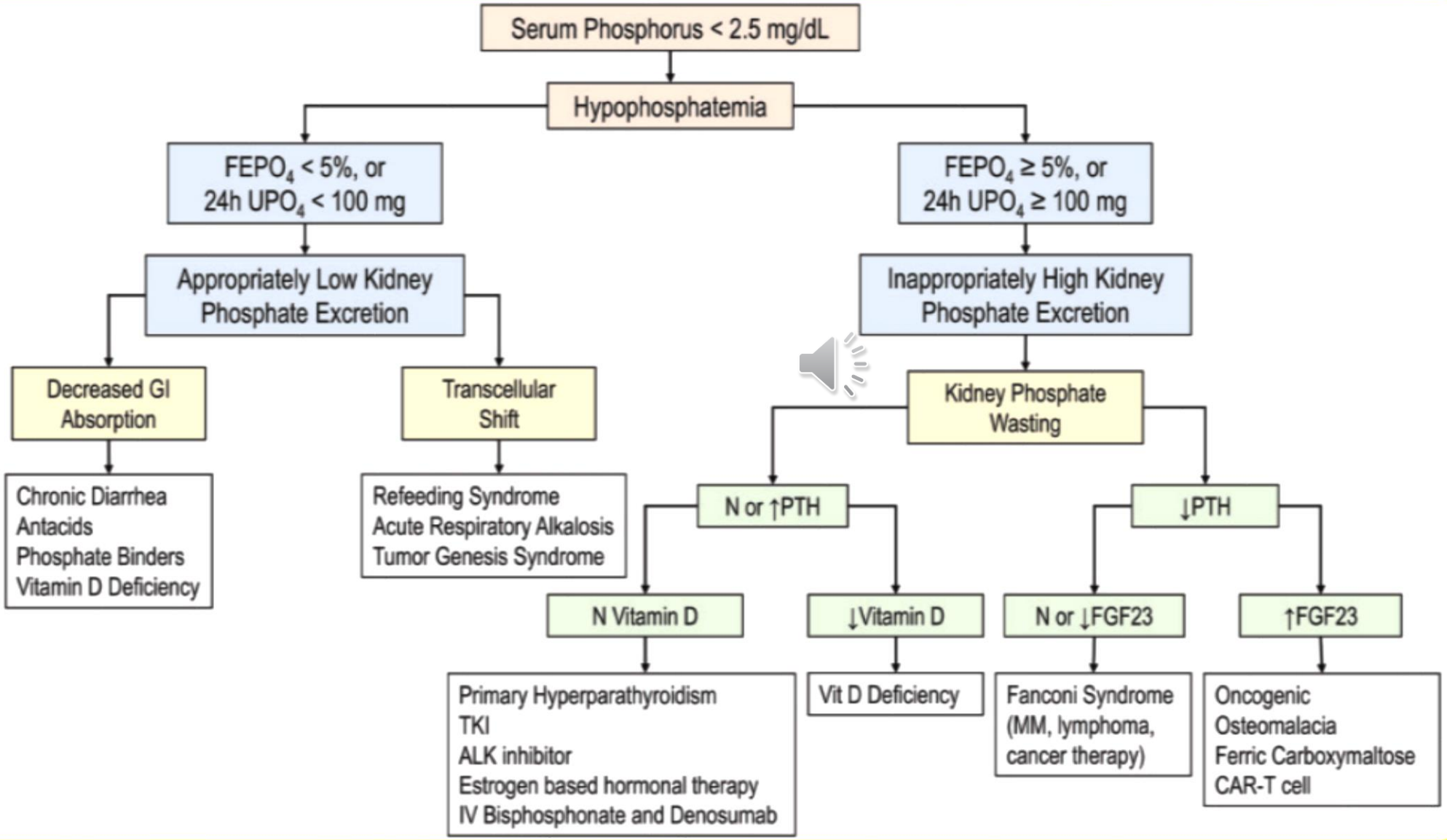
Hyperphosphatemia in Cancer

1 Decreased kidney function
   a. Acute or chronic kidney disease
2 Increase tubular reabsorption of phosphate a. Hypoparathyroidism
   b. Bisphosphonates
   c. Cinacalcet
   d. Familial tumoral calcinosis
   e. Fibroblast growth factor receptor inhibitors (erdafitinib, infigratinib, pemigatinib)
3 Phosphate loads
   a Endogenous
      i. Tumor lysis syndrome
      ii. Rhabdomyolysis
   b. Exogenous
      i. Phosphate-containing laxatives
      ii. Vitamin D toxicity
4 Cellular shifts
   a. Lactic or ketoacidosis

https://doi.org/10.1053/j.ackd.2021.09.005

HYPOPHOSPHATEMIA IN CANCER

Hypophosphatemia in Cancer



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Cancer therapies associated with hypophosphatemia

Nitrogen mustard alkylating agent Ifosfamide
Platinum based antineoplastic Cisplatin
Antimetabolite agent Azacitidine
Nitrosourea alkylating agent Streptozocin
Different classes Suramin, amrubicin, pamidronate, nivolumab, ipilimumab, imatinib, vemurafenib, capecitabine in combination with irinotecan and bevacizumab
TKI Imatinib Sunitinib Sorafenib Regorafenib Nilotinib Dasatinib
ALK inhibitor Ceritinib
mTOR inhibitor Temsirolimus Everolimus Ridaforolimus
Estrogen-based hormonal therapy Estramustine and high-dose diethylstilbestrol diphosphate
ICPI Pembrolizumab, Ipilimumab and Nivolumab
CAR T cell axicabtagene ciloleucel tisagenlecleucel

Supportive therapies associated with hypophosphatemia

TPN
IV iron/FCM
RANKL inhibitor Denosumab
Bisphosphonates Zoledronic acid Pamidronate
CRRT

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Acid-Base Disorders in Cancer

Initial Labs & Calculations

- ABG, Serum electrolytes, Albumin
- Anion Gap (AG) = Na^{+} – (Cl^{-} + HCO_3^{-})
- Corrected AG = AG + 2,5 × (4,0 – Albumin)

Metabolic Acidosis (↓pH, ↓HCO_3^{-})

- **AG High (>12)**
  - Lactic acidosis
    - Type A: Sepsis/shock
    - Type B: Malignancy, drugs
  - Uremia
  - Tumor lysis syndrome
  - Ketoacidosis
  - Drugs/toxins
- **AG Normal (Hyperchloremic)**
  - Type 1 RTA
  - Type 2 RTA
  - GI bicarbonate loss
  - Ureteroenteric diwersion

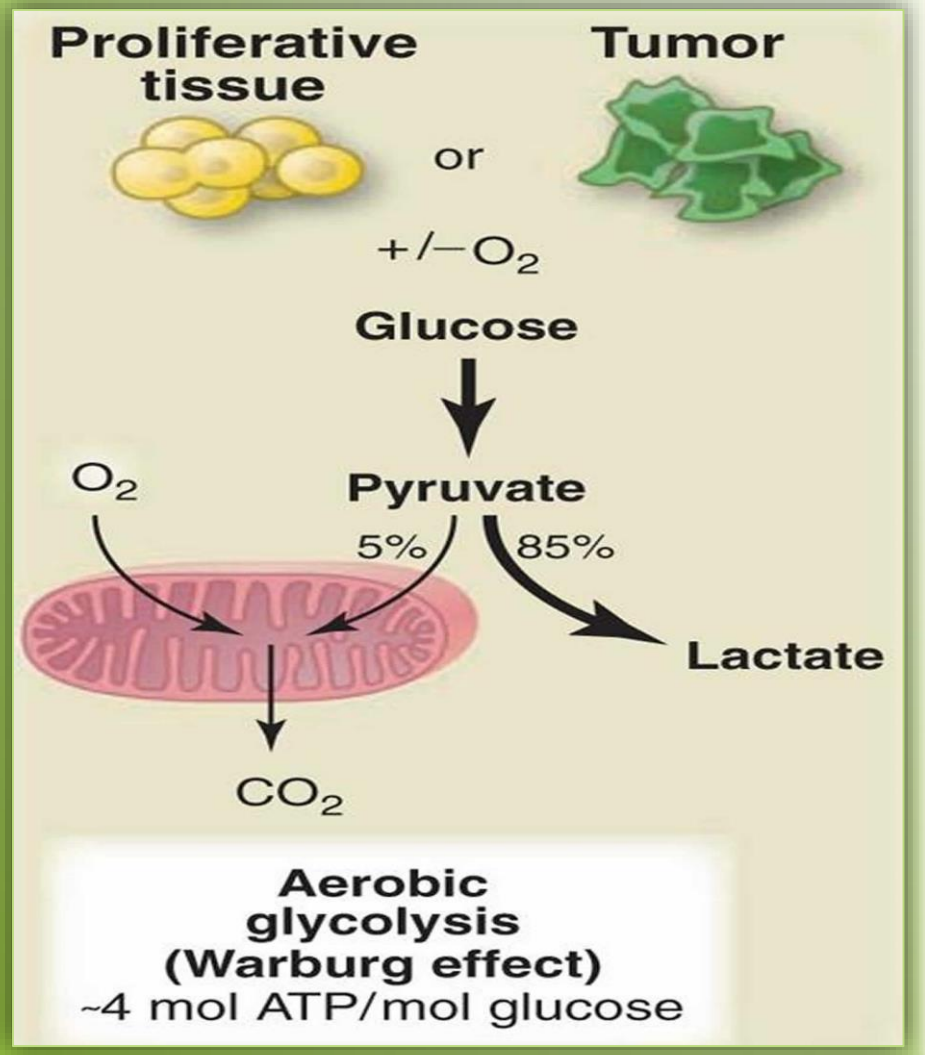
Metabolic Alkalosis

- Volume depletion
- Mineralocorticoid excess
- Chemotherapy-induced vomiting

Respiratory Disorders

- Respiratory alkalosis
- Respiratory acidosis

Warburg Effect



Warburg Effect and Type B Lactic Acidosis in Cancer

The **Warburg effect** refers to the preference of cancer cells for aerobic glycolysis, converting glucose to lactate even in the presence of oxygen. Its metabolic reprogramming insupports tumor growth but leads to type B lactic acidosis - a rare, high anion gap acidosis without hypoxia. Mechanisms einclude increasec lactate production, impaired hepatic clearance, and thiamine deficiency. Management requires urgent in oncologic therapy.* supportive care, and correction of metabolic cofactors.

THANK YOU FOR YOUR ATTENTION