Hypermagnesemia: Causes, symptoms, and treatment

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Introduction

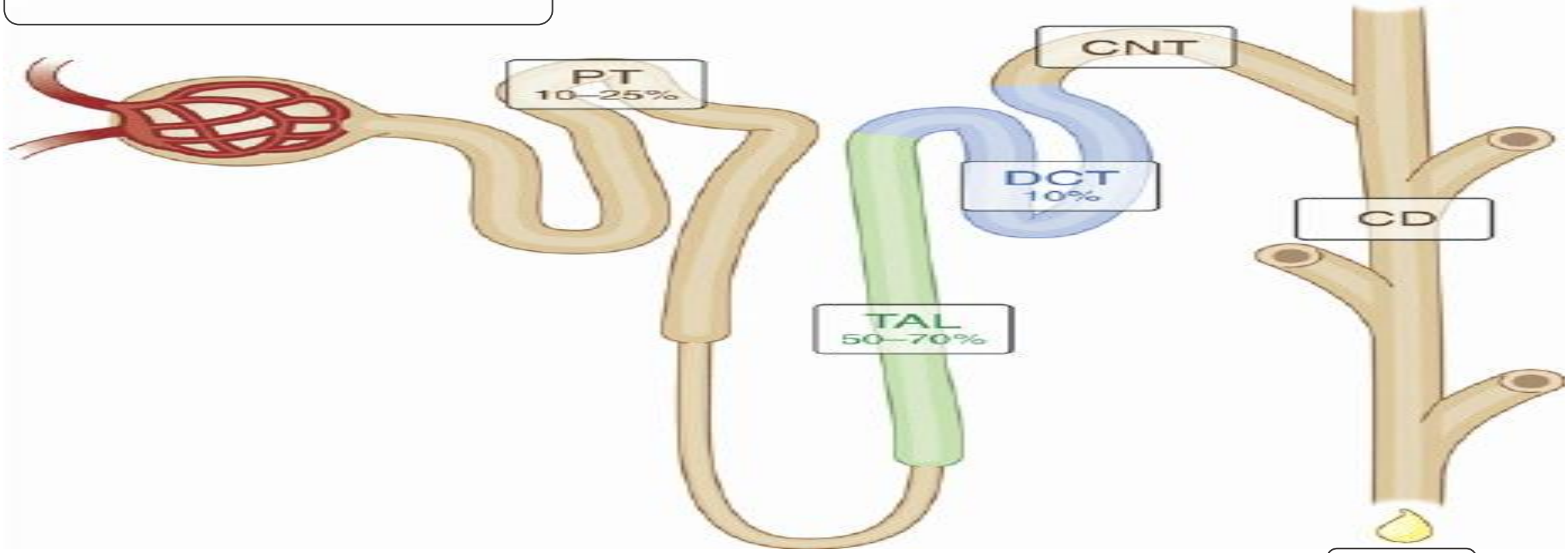
- Magnesium (Mg) is a vital mineral that functions as a cofactor in over 300 enzymatic reactions in the human body. It is essential for adenosine triphosphate (ATP) metabolism, DNA and RNA synthesis, and protein synthesis. Moreover, it plays a critical role in regulating numerous physiological functions, including muscular contraction, blood pressure, insulin metabolism, cardiac excitability, vasomotor tone, nerve transmission, and neuromuscular conduction
- The kidney is crucial in maintaining the normal plasma magnesium concentration in the narrow range.
- Serum Mg level: 1.7-2.4mg/dl (0.7 to 1 mmol/L)
- The normal values may differ between laboratories.

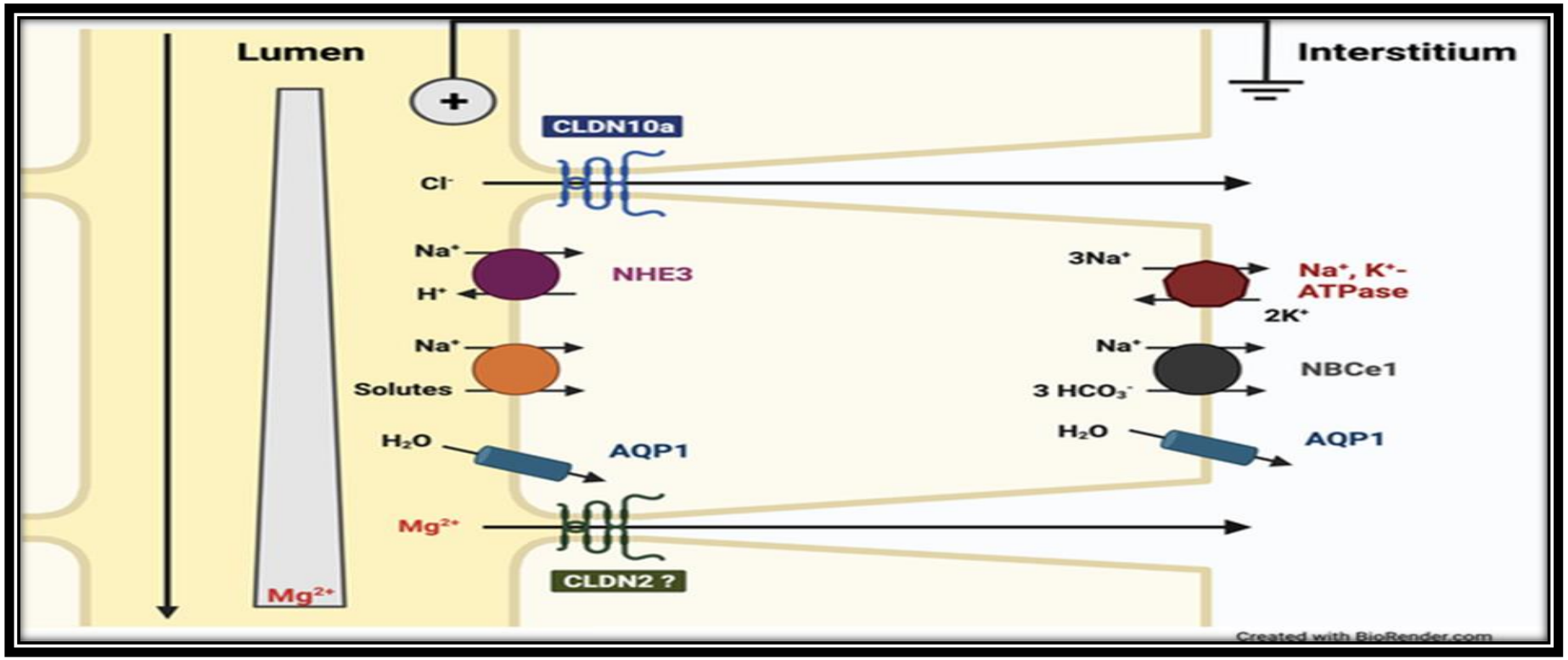
Mg Storage and Renal Regulation

- **Almost all Mg in the body is stored**, with less than 1% found in the serum and red blood cells.
- The main storage location for Mg is in **the bone**, with roughly one-third found on the bone surface, and it is related to the serum Mg concentration.
- In the serum, Mg is found in the following three forms: two-thirds as ionized Mg, one-third as protein-bound Mg, and a minimal amount bound to anions.
- The kidneys play a vital role in maintaining Mg balance in the body, with **90–95% of filtered Mg being reabsorbed** and **only 3–5% excreted** in the urine.

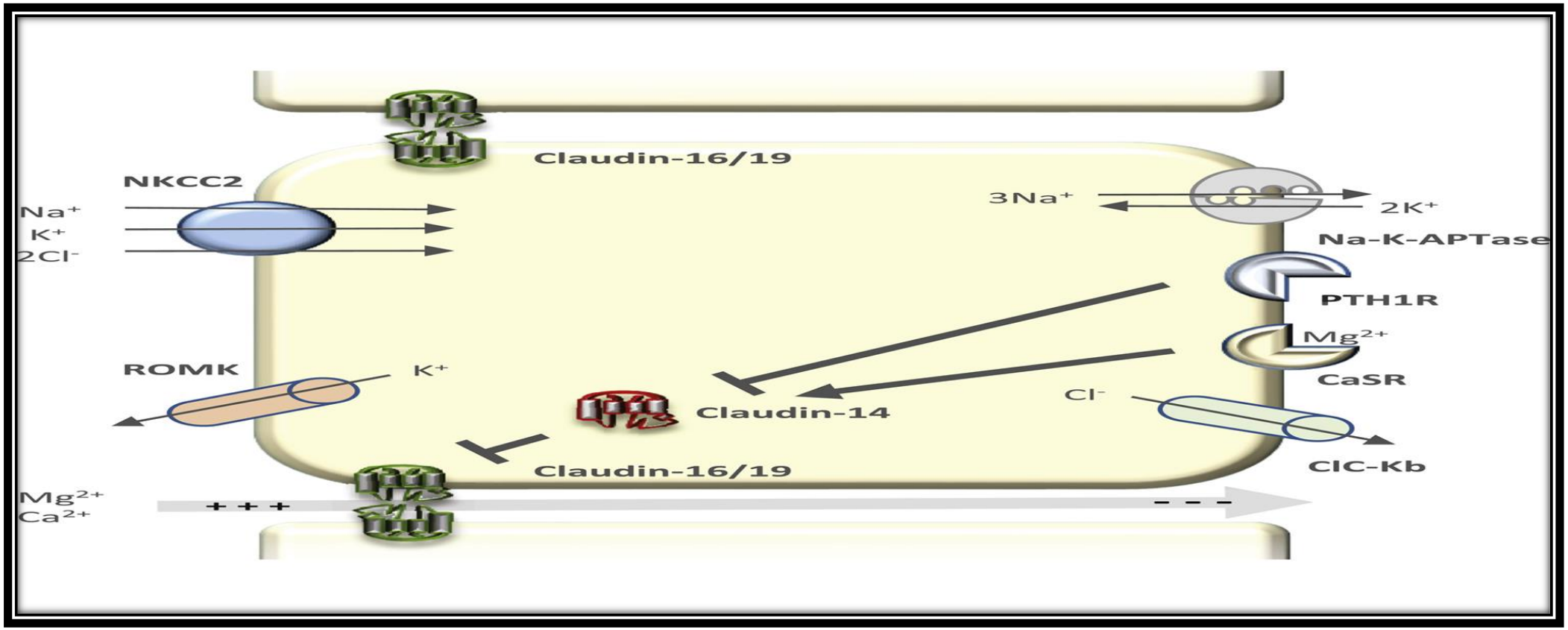
Magnesium reabsorption along the nephron

70-80% of serum Mg is filterable

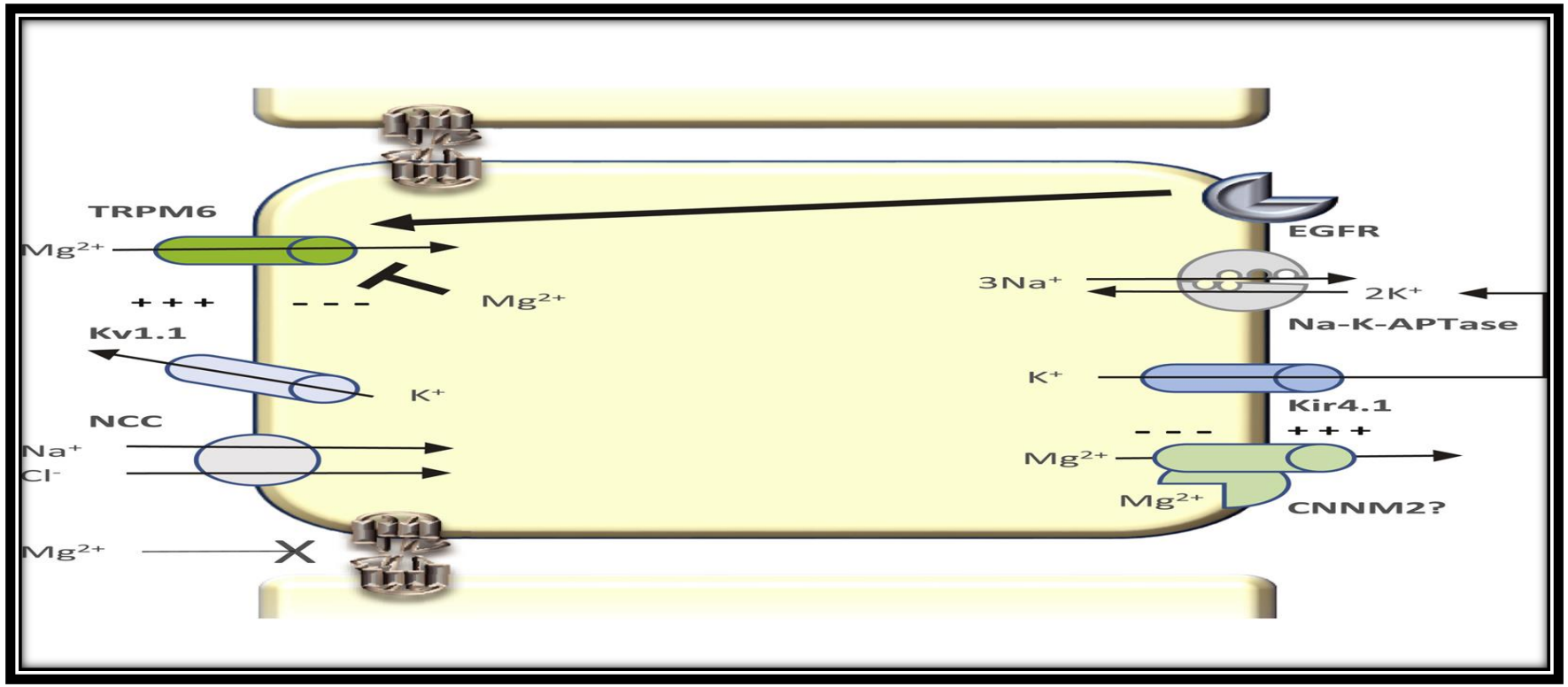




- **In the proximal tubule:** Mg^{2+} reabsorption takes place mainly along the paracellular pathway. Paracellular permeability to Mg^{2+} is due to the expression of CLDNs at the tight junction. CLDN2 may be involved in that permeability. A transepithelial chemical difference generated by water reabsorption is the main driving force for Mg^{2+} reabsorption. Water reabsorption is linked to the transepithelial reabsorption of sodium (Na^+) and anions. Water reabsorption occurs either transcellularly via aquaporin 1 (AQP1), which is expressed at both the apical and basolateral membranes, or paracellularly. Na^+ is reabsorbed actively, largely via the apical Na^+/H^+ exchanger subtype 3 (NHE3) and to a lesser extent by various apical Na^+ cotransporters of glucose, phosphate, amino acids, and other molecules. $HCO3^-$ ions are produced by the dissociation of H2CO3 in the cell and exit the cell via the $Na^+/(HCO3^-)3$ cotransporter (NBCe1). It should be noted that in the mid and late proximal tubule, a small lumen-positive transepithelial potential difference contributes to Mg reabsorption. The expression of CLDN10a at the tight junction increases the paracellular permeability to anions such as Cl^-.



- **Magnesium transport in TAL:** Magnesium transport in the cortical TAL primarily occurs through the paracellular shunt pathway, driven by a highly positive lumen potential. The lumen potential produced is a result of active sodium transport by NKCC2 at the apical membrane and consequent apical backflux of potassium via ROMK and basolateral chloride reabsorption via Clc-Kb.
- **Paracellular magnesium permeability** is **increased by claudin-16 and claudin-19** and **decreased by claudin-14**.
- **Major pathways** in the regulation of TAL magnesium transport occur through activation of basolateral receptors **CaSR** or **PTH1R**.
- **Claudin-14 expression** is decreased by activation of PTH1R and increased by activation of CaSR, thus altering magnesium permeability and reabsorption in the TAL.



- **Magnesium transport in DCT:** Magnesium transport in the DCT is an **active transcellular** process. Polarization of the apical membrane by the voltage-gated potassium channel Kv1.1 provides the driving force for magnesium to enter the cell via the magnesium **channel TRPM6**. The molecular mediator of magnesium extrusion at the basolateral membrane remains unknown.

- EGFR activation also leads to **increased active TRPM6** at the apical membrane.

Hypermagnesemia

- Hypermagnesemia :**Serum Mg> 2.7 mg/dL (2.2 mEq/L, 1.1mmol/L).**
- Hypermagnesemia is uncommon in patients with preserved kidney function because the capacity of the kidneys to excrete magnesium is high.
- Thus, for hypermagnesemia to occur 2 conditions must be satisfied: impaired renal function or increased magnesium intake
- Among hospitalized patients, the reported rates of hypermagnesemia range from <1% to 9.3%.
- Patient groups at risk include patients with AKI/ESKD/CKD and pregnant women with eclampsia who receive high doses of magnesium sulfate

Hypermagnesemia

- Hypermagnesemia has been associated with poor health outcomes among hospitalized patients, including increased **in-hospital mortality** and **1-year mortality** among hospitalized patients .
- Hypermagnesemia strongly predicts the in-hospital mortality rate of **acute myocardial infarction, development of arrhythmia, myocardial depression**, and **vasodilation**.
- Moreover, hypermagnesemia appears to be an indicator of disease severity among patients hospitalized with SARS-CoV-2, and hypermagnesemia was associated with **prolonged hospitalization, higher rates of ICU admission, greater need for mechanical ventilation, and mortality**

Hypermagnesemia

- When it occurs, the elevation in the plasma magnesium concentration is usually **mild (Mg <3.6 mg/dL**, or 1.5 mmol/L) and the patient is **asymptomatic.**
- However, clinical symptoms may be seen when the plasma magnesium concentration exceeds (Mg >4.8 mg/dL or 2 mmol/L).

Determinants of renal Mg reabsorption

- **Hormonal**

❖ **PTH:** affects the Mg reabsorption in the kidneys by acting **on PTH-receptor in the basolateral membrane of the cortical TAL and DCT.** When PTH acts at high concentration, it **augments the sodium-chloride** reabsorption. Subsequently, it enhances the trans-epithelial voltage, resulting in the **paracellular reabsorption of Mg.**

✓ PTH also enhances the Mg reabsorption in the DCT in an otherwise not yet clearly understood mechanism. Although PTH activates renal Mg absorption, its effect on serum Mg concentration is not fully understood.

✓ **Normal serum Mg** concentration **can be found** in patients with primary hyperparathyroidism and hypoparathyroidism.

❖ **calcitonin** also influences the reabsorption of Mg in both the TAL and DCT.

❖ **The epidermal growth factor** is a hormone, which directly regulates the **action of the TPRM6 channel** in the DCT, and patients receiving anti-EGF receptor monoclonal antibodies such as cetuximab or panitumumab were at increased risk of hypomagnesemia with an overall incidence of 17% versus 3% in non-treated patients

❖ **Transcription factor hepatocyte nuclear factor 1 homeobox B (HNF1β)** also contributes to Mg reabsorption by stimulating the **expression of FXYD2 protein**. Hence, renal Mg wasting syndrome is found in patients with a pathological variant in the FXYD2 gene.

Determinants of renal Mg reabsorption

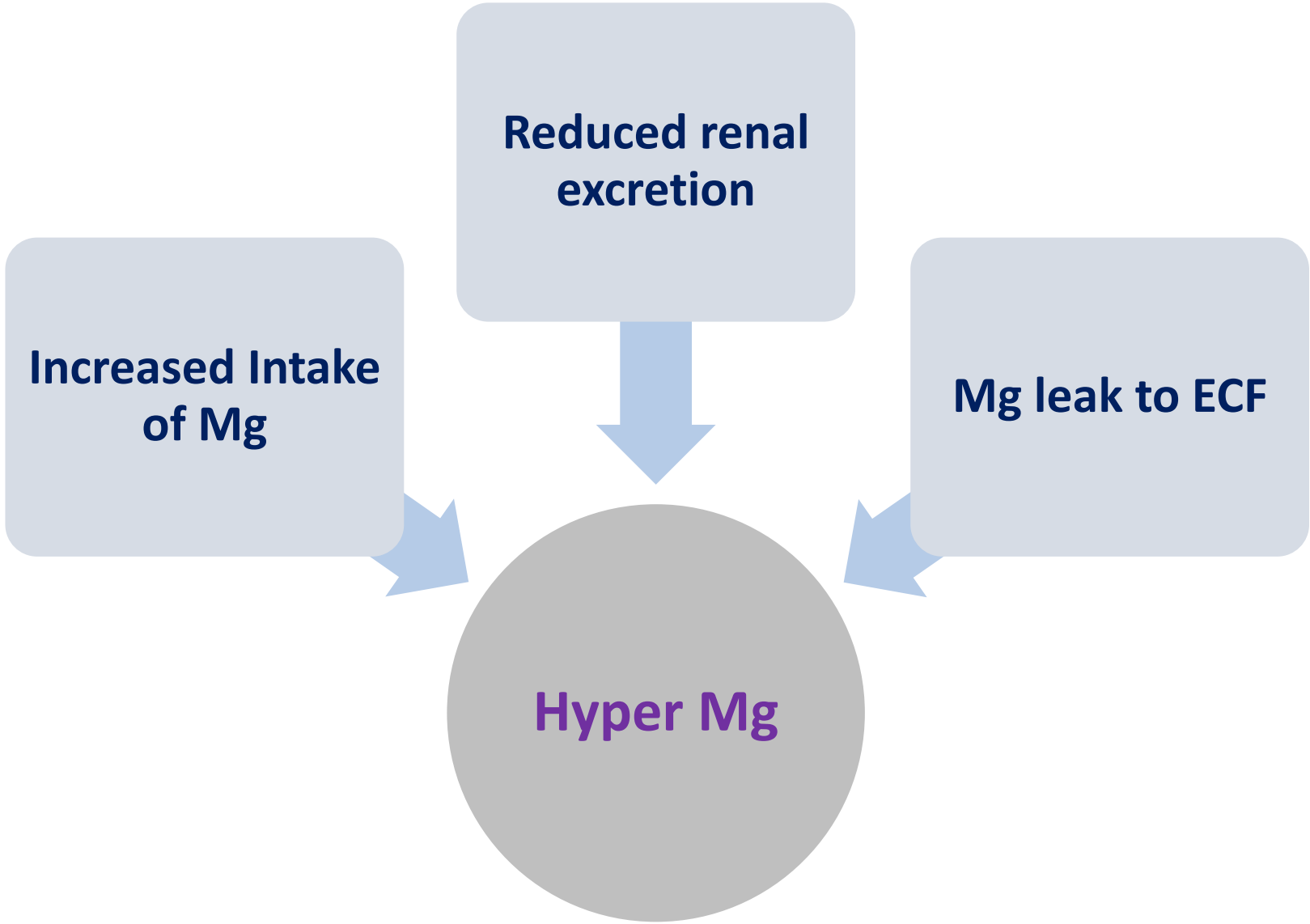
- **Non-Hormonal:** Several non-hormonal factors influence Mg absorption in the kidneys.

❖Specifically, an elevation in luminal Mg concentration triggers Mg reabsorption by the kidneys, while an increase in peritubular Mg concentration has the converse effect, leading to a decrease in Mg reabsorption.

❖The calcium-sensing receptor (CaSR), present in the basolateral membrane of the TAL, plays a crucial role in this effect. The CaSR senses changes in extracellular calcium concentration and regulates the transport of other ions, including Mg. This mechanism elucidates the reduced Mg excretion observed in instances of Mg depletion in the human body.

❖Furthermore, serum acid-base status has been shown to impact Mg excretion by the kidneys. For example, chronic metabolic acidosis has been linked to renal Mg wasting, while acute metabolic alkalosis has been associated with reduced renal Mg excretion.

❖Mg reabsorption in distal tubule is correlated to bicarbonate delivery.


Reduced renal excretion
Increased Intake of Mg
Mg leak to ECF
Hyper Mg

Reduced renal excretion

- Patients with either AKI or CKD are at increased risk of hypermagnesemia due to the importance of the renal system for Mg excretion
- Several endocrinological conditions might cause marked **rises in serum Mg concentrations**, such as hyperparathyroidism, adrenal insufficiency, and hypothyroidism, by increasing Mg renal reabsorption.
- Hyperparathyroidism and calcium metabolism disturbance can result in **hypermagnesemia** through an increased calcium-induced Mg absorption in the tubule.
- In hypothyroidism, it is suggested that Mg excretion is impaired due to a **drop in renal blood flow and glomerular filtration rate** .Increased sodium-potassium ATPase activity in settings of hypothyroidism has been reported, which results in a high electromechemical gradient leading to reabsorption of Mg.
- Adrenal insufficiency: can result in **hypermagnesemia**, may be due to volume depletion

Reduced renal excretion

- Familial hypocalciuric hypercalcemia (FHH) is a rare autosomal dominant condition that occurs due to a **variant in CaSR gene**. The CaSR presents in all the kidney segments and prominently in the basolateral side of TAL, controlling the sodium chloride and divalent cation, such as Mg and calcium, transportation both transcellularly and paracellularly by enhancing various channels such as NKCC2 and ROMK. Loss of CaSR function **as a result of CaSR gene variations, the aforementioned channels (NKCC2 and ROMK) get over-activated and create a positive activity in the lumen, which encourages the action of the paracellin**, which induces the reabsorption of the Mg and calcium transcellularly and paracellularly
- Finally, certain drugs that act on **renal endothelial vessels** and **the angiotensin system** might cause hypermagnesemia, such as lithium, angiotensin-converting enzyme inhibitors, and non-steroidal anti-inflammatory drugs

HELIX syndrome

- **HELIX syndrome** – Mild **hypermagnesemia** has been described as part of a familial syndrome associated with **hypohidrosis**, **electrolyte imbalance (hypocalciuria and hypokalemic metabolic alkalosis), lacrimal gland dysfunction, ictiosis** and **xerostomia.**
- It is caused by **mutations in CLDN10**, which encodes the tight junction protein, claudin-10. This likely functions as a paracellular sodium channel in the thick ascending limb of Henle. **Loss of claudin-10 function** reduces paracellular sodium reabsorption, enhancing the transepithelial voltage driving divalent cation (magnesium and calcium) reabsorption

Increased Intake of Mg

- Hypermagnesemia might develop in **individuals despite normal renal functions**, especially in elderly patients with **certain bowel conditions that enhance the absorption or reduce gut motility,** including inflammatory bowel diseases, gastritis, colitis and constipation.
- Similarly, anticholinergics medications or laxatives might result in high serum Mg concentrations, primarily in settings of pre-existing bowel pathology. Medications containing Mg can elevate serum Mg concentrations if taken continuously, particularly when renal function is impaired.
- The study indicated a correlation between hypermagnesemia and CKD grade 4 and higher dosages of magnesium oxide. Moreover, elevated serum Mg concentration was associated with **magnesium oxide dosage exceeding 1000 mg/day, CKD grade 4, and the concurrent use of stimulant laxatives**

Increased Intake of Mg

- Milk alkali syndrome :**hypercalcemia, hyperphosphatemia, hypermagnesemia, and azotemia secondary to calcium carbonate-containing alkali therapy**.
- In patients undergoing dialysis, **increased dialysate Mg** can also cause symptomatic hypermagnesemia.
- A case report demonstrated hypermagnesemia in a patient with post-urethral irrigation with hemiacidrin, which is utilized in the nephrolithiasis process.
- Excessive infusion of Mg sulfate during the management of eclampsia is a well-known cause of hypermagnesemia, which can be fatal Hypermagnesemia resulting solely from dietary intake is not reported thus far, as the kidneys effectively eliminate excess magnesium through urine.
- Patients with CKD are more susceptible to developing hypermagnesemia due to impaired renal excretion. Hence, educating these patients **about minimizing their consumption of magnesium-rich foods, such as seeds, nuts (such as almonds and cashews), black beans, brown rice, bananas, and broccoli, is crucial**.

Table 1. Causes of hypermagnesemia.

Category	Sub-Category	Causes	Mechanisms
Reduced Renal Excretion	Kidney Disease	Acute kidney injury Chronic kidney disease	Reduced ability of the kidneys to excrete Mg
	Endocrinological Conditions	Hyperparathyroidism Adrenal insufficiency Hypothyroidism	Abnormalities in calcium metabolism or renal blood flow/filtration rate
	Certain Drugs	Lithium, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs	Alteration of renal endothelial vessels and angiotensin system
Increased Intake of Mg	Bowel Conditions	Elderly patients with bowel conditions	Enhanced absorption or reduced gut motility
	Medications	Anticholinergics, laxatives, and medications containing Mg	Increased intake or absorption of Mg
	Other Causes	Milk alkali syndrome, increased dialysate Mg, post-urethral irrigation with hemiacidrin, excessive infusion of Mg sulfate	Various mechanisms
Mg Leak to Extracellular Fluid	Hemolysis	Tumor lysis syndrome	Movement of Mg from intracellular to extracellular space
	Metabolic Acidosis	Diabetic ketoacidosis	Movement of Mg from intracellular to extracellular space
	Other Causes	Chronic low-grade metabolic acidosis	Various mechanisms

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Symptoms of hypermagnesiumia

- Neuromuscular effects
- Cardiovascular effects
- Hypocalcemia
- Other symptoms

Neuromuscular effects

- **Neuromuscular toxicity** is the most consistently observed complication of hypermagnesemia.
- Increased magnesium **decreases impulse transmission** across the **neuromuscular junction**, producing a **curare-like effect**.
- The initial clinical manifestation of this problem is **diminished deep tendon reflexes**, which are usually first noted when the plasma magnesium concentration reaches **4.8 to 7.2 mg/dL.**
- More **severe hypermagnesemia** can result in **somnolence; loss of deep tendon reflexes**; and **muscle paralysis**, potentially leading to **flaccid quadriplegia** and, since **smooth muscle function** is also **impaired, decreased respiration** and eventual **apnea**.
- Parasympathetic blockade inducing **fixed and dilated pupils**, thereby **mimicking a central brainstem herniation syndrome**, can also be seen in this setting

Cardiovascular effects

- **Magnesium** is an effective calcium channel blocker both **extracellularly** and **intracellularly;** in addition, intracellular magnesium profoundly **blocks several cardiac potassium channels.**
- These changes can combine to **impair cardiovascular function. Hypotension, conduction defects, and bradycardia** begin to appear at a plasma magnesium concentration above 4.8 to 6 mg/dL.
- **ECG changes** : prolongation of the PR interval, an increase in QRS duration, and an increase in QT interval. Complete heart block and cardiac arrest

Hypocalcemia

- **Moderate hypermagnesemia** can inhibit the **secretion of parathyroid hormone (PTH),** leading to a **reduction in the plasma calcium** concentration.
- This effect has been described **after magnesium infusion** in normal subjects and in **pregnant women** with eclampsia. **The fall in the plasma calcium concentration is usually transient and produces no symptoms**; in some cases, however, ECG abnormalities associated with hypocalcemia can be seen.
- **In the long term**, **hypermagnesemia** can contribute to **osteomalacic renal osteodystrophy** and **adynamic bone disease**, especially in patients with kidney disease

Other symptoms

- Hypermagnesemia may be associated with **nonspecific** early symptoms such as **nausea, vomiting**, and **flushing**.
- In addition, **hyperkalemia** has been described in **three pregnant** women following parenteral magnesium administration. The mechanism responsible for the hyperkalemia is unclear, but **decreased urinary potassium excretion** due to magnesium-induced blockade of renal potassium channels may be involved.
- Hypermagnesemia can also cause and/or exacerbate **pruritus** in dialysis patients, which is possibly due to altered nerve conduction velocity.

Clinical Manifestations of hypermagnesemia

Hypermagnesemia

CNS

Headache
Dizziness
Drowsiness
Confusion
Respiratory depression

CVS

Vasodilatation
Facial flushing
Hypotension
Bradycardia
AV block
Asystole

GI system

Nausea
Vomiting
Constipation
Ileus

Weakness
Loss of reflexes
Paralysis

MSK system

Urinary Bladder

Urinary retention

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Clinical Assessment of Hypermagnesemia

- ✓Obtaining a detailed medication history, as certain drugs have been associated with hypermagnesemia
- ✓ Obtaining the patient's medical history, particularly for constipation or infammatory bowel disease,
- ✓ Laboratory tests: serum Mg, Ca, Ph, K concentration, assessing renal function with tests such as GFR, creatinine, BUN, glucose, urine specifc gravity, ABG, TFT, PTH
- ✓Closely monitored for cardiac abnormalities
- ✓ECG

Treatment of hypermagnesiumia

- Most cases of symptomatic hypermagnesemia **can be prevented** by anticipation.
- **Patients with kidney failure** should not receive magnesium-containing medications.
- **Patients receiving parenteral magnesium for any reason** should be monitored **at least daily, and perhaps more frequently**, depending upon the amount of magnesium infused and the dosing schedule.
- The approach to therapy depends upon the **kidney function, magnesium concentration, and clinical symptoms**

Treatment of hypermagnesiumia

- **In normal or near-normal kidney function:**

✓If kidney function is normal, **cessation of magnesium therapy** will allow prompt restoration of normal magnesium levels. In addition, **loop (or even thiazide) diuretics** can be used to increase renal excretion of magnesium.

Treatment of hypermagnesiumia

- **Moderate kidney impairment: CKD with eGFR between 15 - 45 mL/min/1.73 m2 , mild AKI**,

✓In most such cases, initial treatment consists of **cessation of magnesium-containing medications** and **therapy with intravenous isotonic fluids (eg, normal saline)** plus a **loop diuretic (eg, furosemide)**.

✓**Higher diuretic doses** may be required in these patients since they have reduced GFR.

✓If these measures fail to improve the serum magnesium concentration, **dialysis** may be required, especially if there are **severe neurologic manifestations** (eg, paralysis, somnolence, coma) or **cardiovascular manifestations** (eg, bradycardia, electrocardiographic abnormalities, hypotension).

Treatment of hypermagnesiumia

- **Severe kidney impairment:**

❖in patients who have **advanced CKD** (**eGFR less than 15 mL/min/1.73 m2** or who are **on chronic dialysis)** and **moderate to severe AKI, dialysis** is often required .

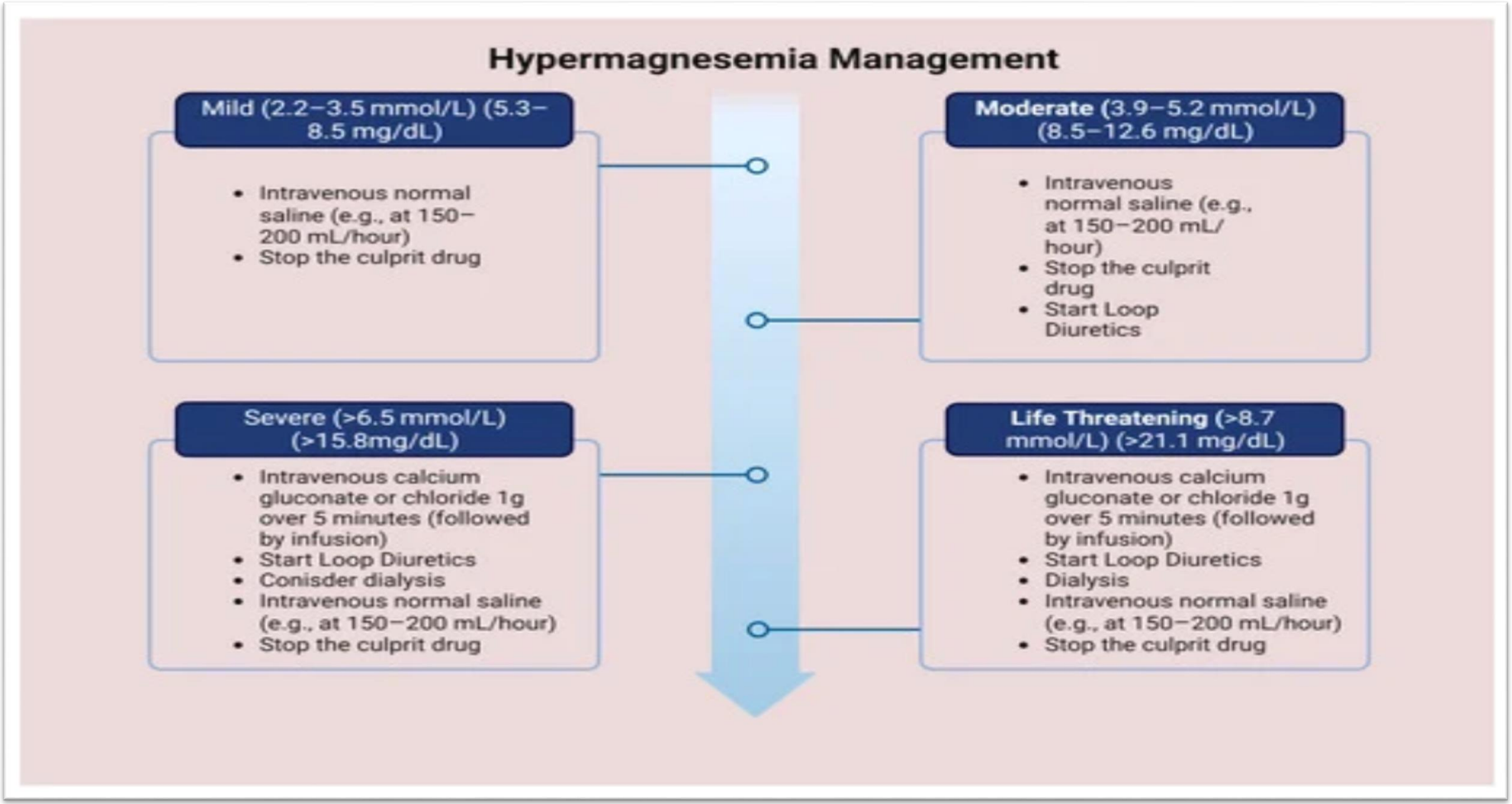
❖**Hemodialysis, with its higher flow rates**, works more **rapidly** than peritoneal dialysis, lowering magnesium levels to a nontoxic range within two to four hours.

❖**Exchange transfusion** has been effective in **neonatal hypermagnesemia**.

❖ Since preparation for hemodialysis often takes one hour or longer, patients with symptomatic hypermagnesemia **should be given intravenous calcium as a magnesium antagonist to reverse the neuromuscular and cardiac effects of hypermagnesemia**.

❖The usual dose is **100 to 200 mg of elemental calcium over 5 to 10 minutes**.

❖**Unless the patient is anuric**, medical management with intravenous fluids and loop diuretics should also be initiated, especially in severe or symptomatic cases, while preparing for dialysis.



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