

ELECTROLYTE DISTURBANCES IN MEDICINE

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OSMOLALITY AND VOLUME STATUS

↑ (280 - 294)

Normal serum osmolality is usually 282 ± 2 mOsm/ kg H₂O. If no osmolal gap exists from an acid alcohol ingestion, then measured osmolality should be equal to calculated osmolality, which is (roughly):

$$\text{Osm}_{\text{calc}} = 2[\text{Na}^+] + (\text{glucose}/18) + (\text{BUN}/2.8)$$

If glucose and BUN are normal, use $2 \times (\text{Na}^+)$ to quickly see if the patient's osmolality is - 270.

Antidiuretic hormone (ADH) is the common term for arginine vasopressin (AVP). ADH is the primary regulator of renal water excretion; it is a neurohypophysial hormone that acts on the late distal tubule and cortical collecting duct to increase water permeability and mediate the urine concentration.



ADH levels are regulated by several mechanisms. The 2 most important are:

1) *Osmoreceptors in the hypothalamus*

2) *Volume (stretch) receptors in the left atrium (and possibly in the pulmonary veins) and blood vessels*

The strongest stimulant for ADH release is significant volume loss resulting in hypotension; e.g., hemorrhage. This stimulates both the stretch receptors and baroreceptors.

High plasma osmolality is a weaker but more sensitive stimulus for ADH release.

Baroreceptors Can Be Divided Into Two

a) High pressure Arterial Baroreceptors

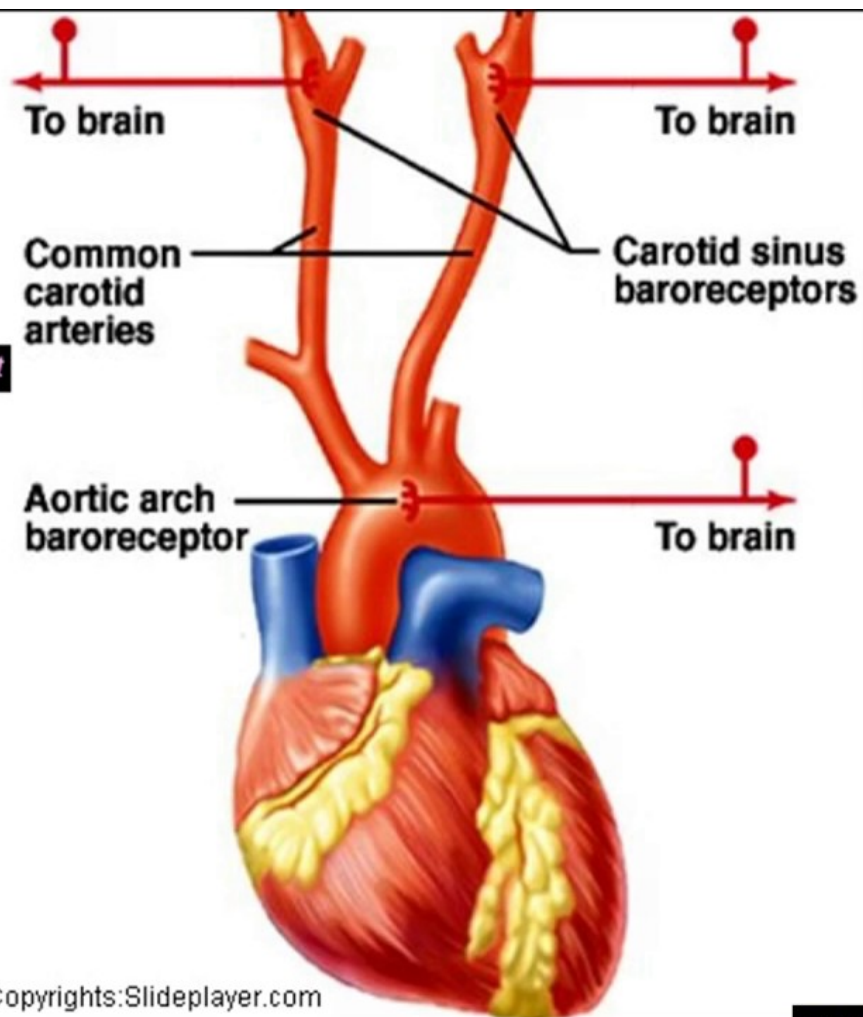
Baroreceptors Found Within Aortic Arch

Enable The Examination of Blood Being

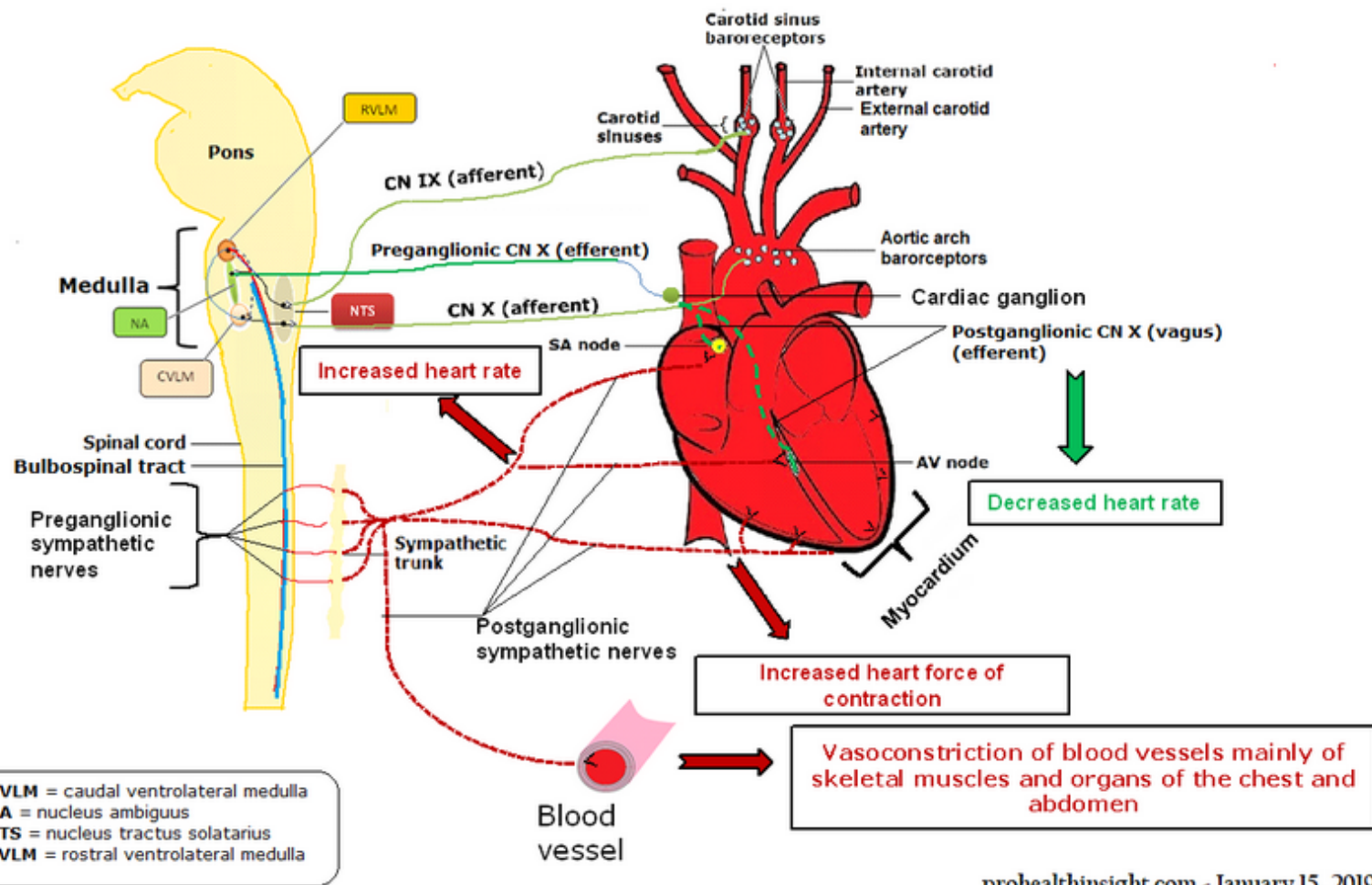
Delivered to All Blood Vessels Via Systemic Circuit

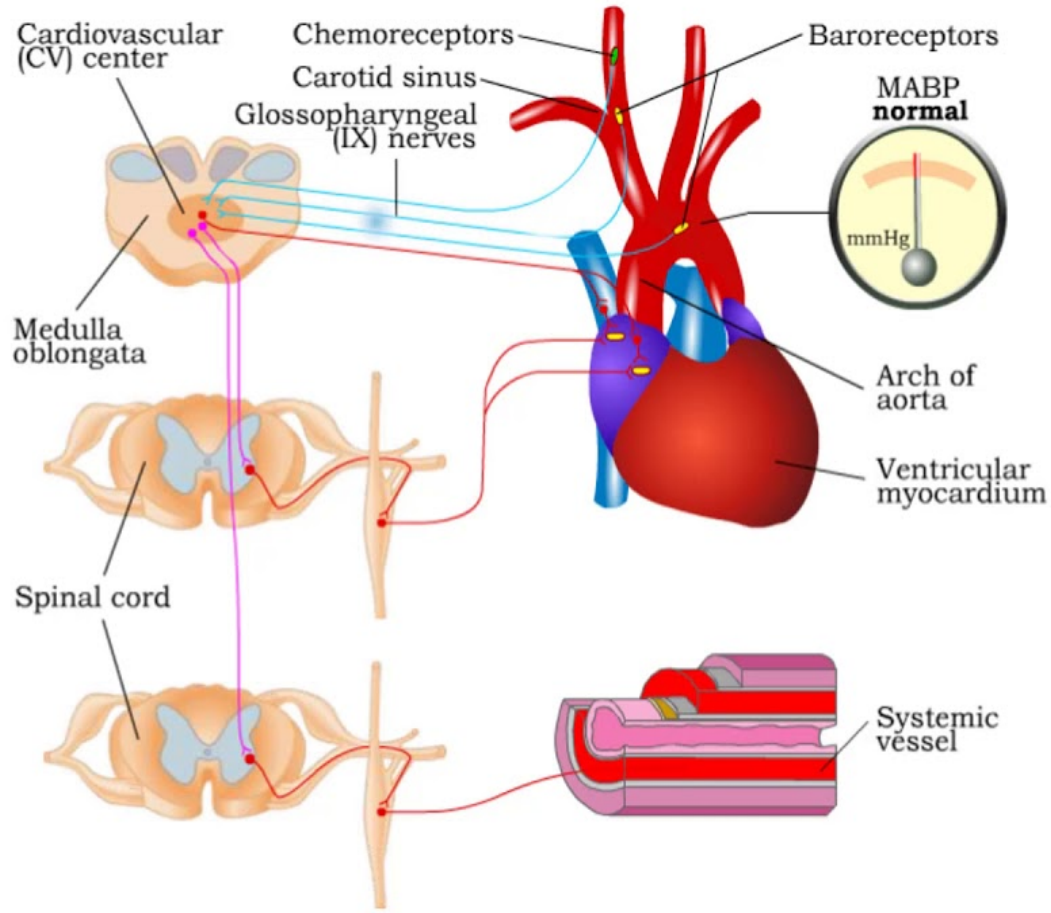
Baroreceptors Within The Carotid Artries

Monitor Blood Pressure of Blood Being



Arterial Baroreceptor Reflex Pathways





Neural regulation of blood pressure - baroreceptor reflexes

- Carotid sinus reflex helps maintain normal blood pressure in brain.
- Baroreceptors are stimulated by the changes in the stretch of the carotid sinus wall; nerve impulses propagate from the baroreceptors over glossopharyngeal nerves to the CV center in the medulla oblongata.
- Aortic reflex maintains general systolic blood pressure.

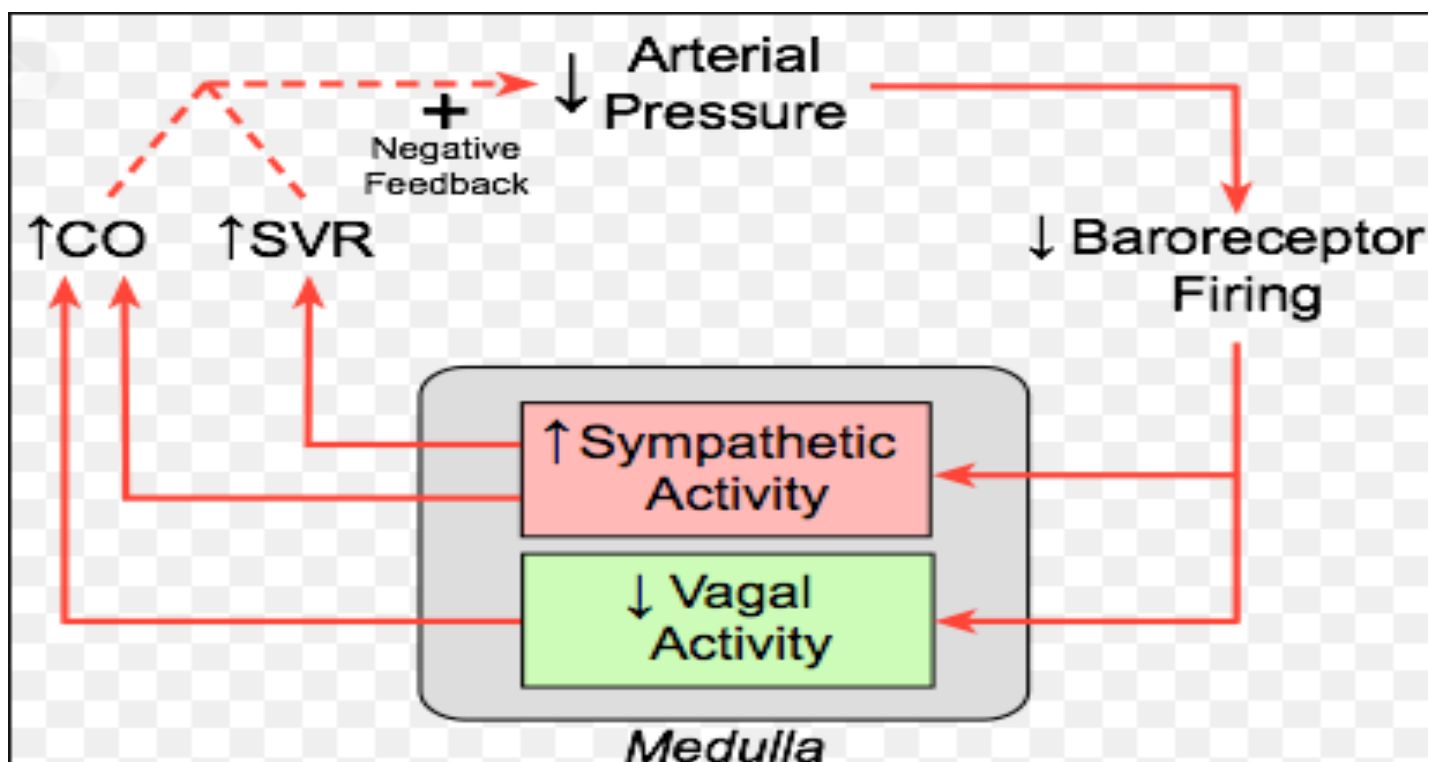
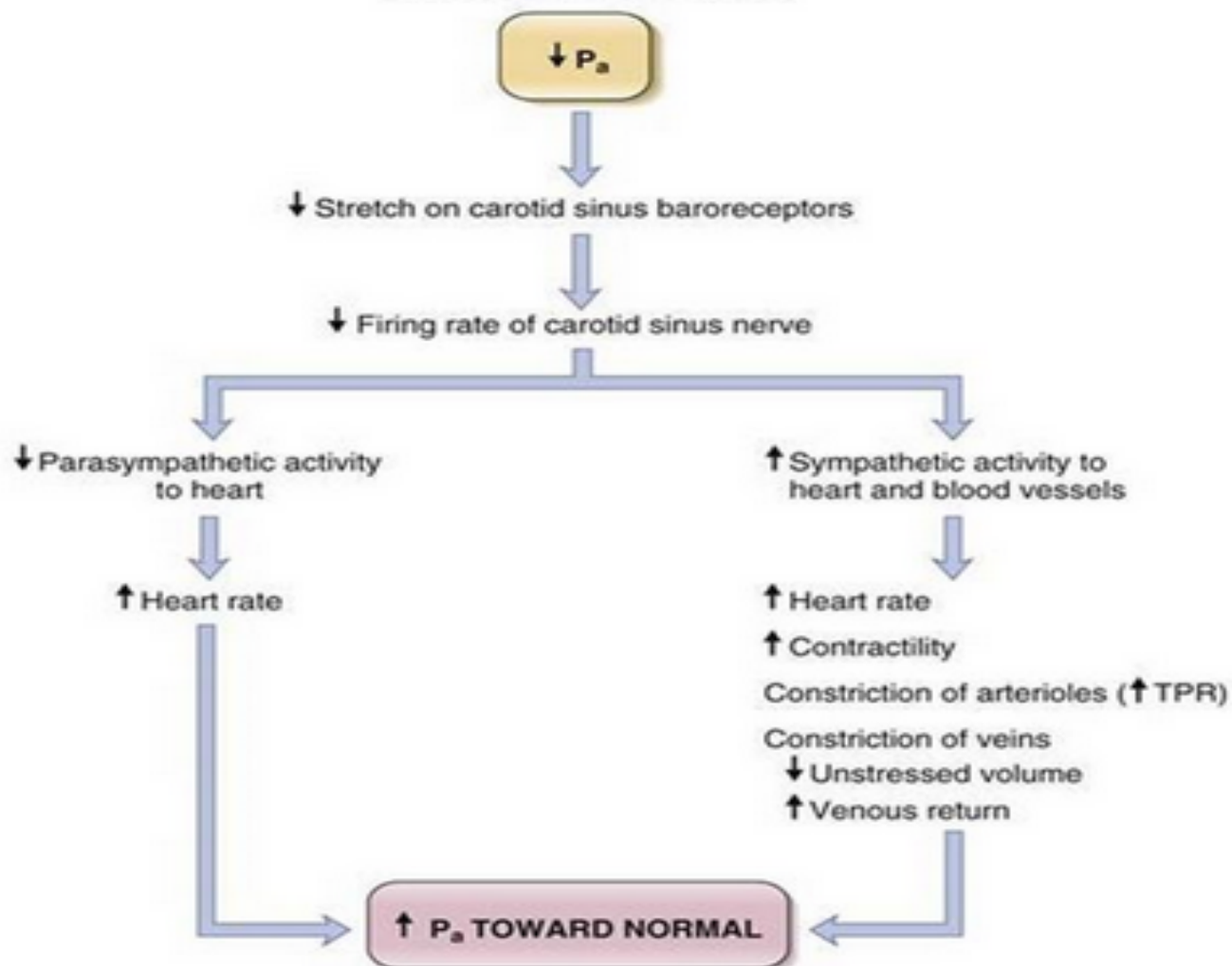


Figure 3. A sudden decrease in arterial pressure decreases baroreceptor firing, which activates sympathetic neurons and inactivates vagal neurons in the medulla. The resulting increases in CO and SVR act as a negative feedback mechanism to attenuate the fall in arterial pressure.

BARORECEPTOR REFLEX



input

Imposed decrease in
arterial blood pressure



Sensed by arterial baroreceptors
as decreased stretch



Decreased baroreceptor
afferent nerve activity



processing

Signal processed by medullary
cardiovascular control pathways



output

Increased sympathetic activity

- Increased heart rate
- Increased force of heart contraction
- Arteriolar vasoconstriction

Decreased parasympathetic activity

- Increased heart rate



Increased arterial blood pressure

Volume status of the patient with a sodium abnormality is critical in determining the treatment. In general, if the patient is edematous, there is volume overload. If the patient has the clinical signs of volume loss, there is a volume deficit. If there is neither of these, the patient is considered euvolemic.

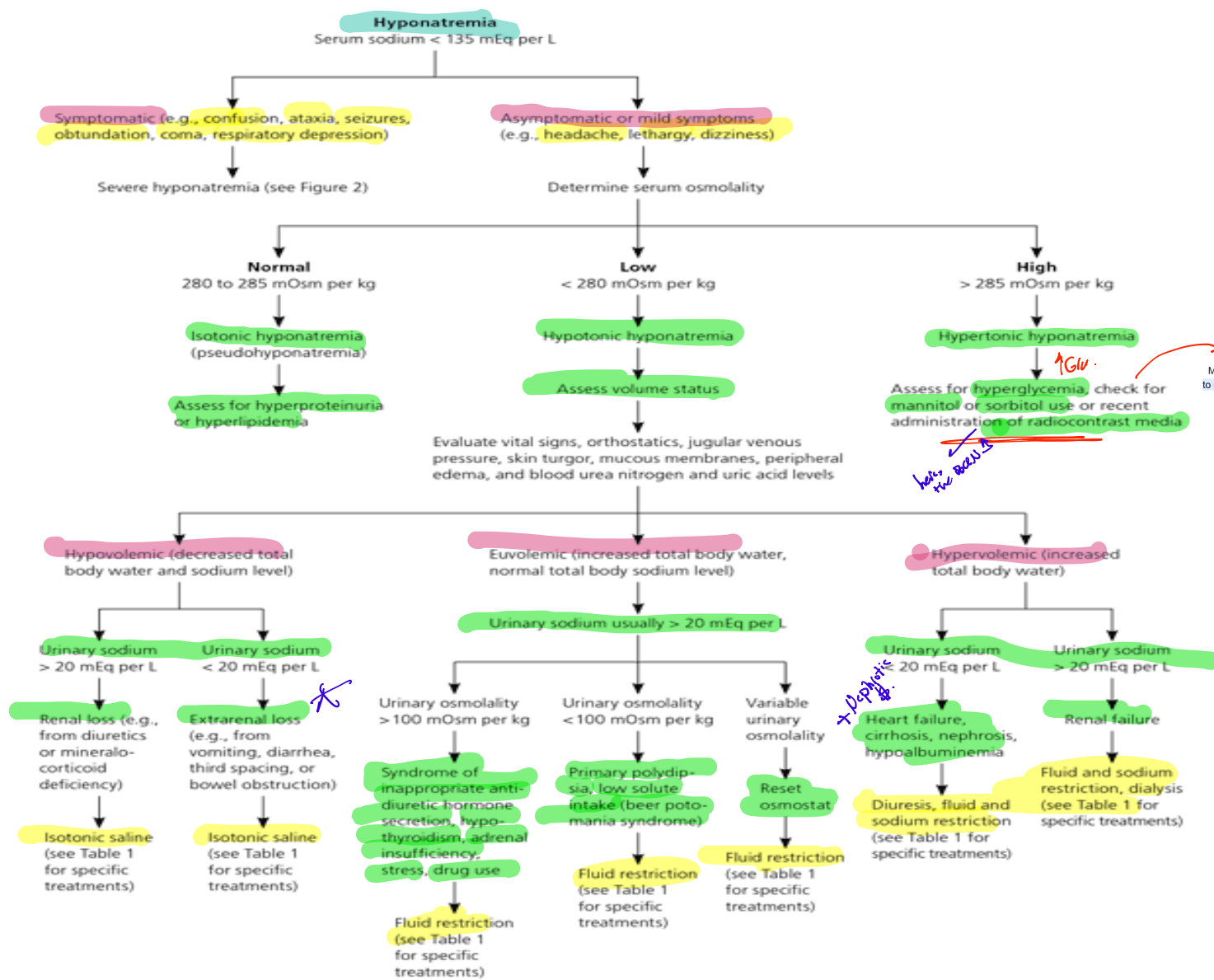
Remember these clinical clues to hypovolemia: tachycardia, narrowed pulse pressure, orthostatic hypotension, and resting tachycardia with hypotension. Central venous pressure is low.

ECF Volume Excess: Hypervolemia

Cardiovascular Changes	Respiratory Changes	Skin Changes	Neurologic Changes	Other Changes
○ ↑ Pulse: full and bounding ○ Full peripheral pulses ○ Distended neck veins ○ ↑ BP	○ ↑ respiratory rate ○ Shallow respirations ○ ↑ dyspnea with exertion or in the supine position ○ Pulmonary congestion and pulmonary edema ○ SOB ○ Irritative cough ○ Moist crackles	○ Edematous may feel cool ○ Skin may feel taut and hard ○ Edema-eyelids, facial, dependent (sacrum), pitting, peripheral extremities 	○ Altered LOC ○ Visual disturbances ○ Skeletal muscle weakness ○ Paresthesia ○ Cerebral edema ○ Headache ○ Confusion ○ Lethargy ○ Diminished reflexes ○ Seizures, coma	○ Urine: polyuria, nocturia ○ Lab data ↓Hematocrit, BUN GI Changes ○ Increased motility ○ Enlarged liver

Image 4: Signs and symptoms of Hypervolemia

HYPONATREMIA



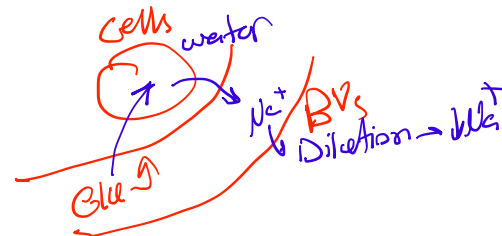
HYPONATREMIA

Isoosmolar and Hyperosmolar

Low serum Na^+ is the most common electrolyte abnormality.

- **Isoosmolar hyponatremia:** An artifactual decrease in the serum Na^+ associated with older lab instruments that miscalculated sodium in settings of **high protein** (e.g., **myeloma**) or **lipids**. The current standard in laboratory practice is to use ion-specific electrodes, thus eradicating this problem.
- **Hyperosmolar:** **Both glucose and mannitol** cause an osmotic shift of water out of cells, which dilutes plasma Na^+ . (**elevated BUN**)

Remember: For each 100 increase in glucose over 100 mg/dL, the sodium concentration decreases by 1.6.



Hypoosmolar

By far, the largest low- Na^+ subgroup is the hypoosmolar group. Note that the terms hypo osmolar and hypotonic are interchangeable.

The low osmolality causes water movement into cells, leading to intracellular swelling, which may result in neuromuscular excitability, seizures, and coma-usually when the Na^+ falls acutely (< 120). If the sodium level decreases slowly, the cells re-equilibrate and do not swell enough to cause these symptoms. The hypoosmolar group is further subdivided by volume status: low, high, and normal.

Always think of the serum sodium concentration as the ratio of total body sodium to water, with increased total body water content as the key disorder in most cases of hyponatremia. Therefore, hypotonic hyponatremia is a water problem. Whenever the serum sodium is low, it means the patient has more water relative to total body sodium either from loss of sodium, true water excess, or total body sodium excess that is exceeded by water excess.

In the patient with hypotonic low Na^+ , the first thing to do is assess the volume status, which is done clinically.

Volume status essentially reflects total body sodium content.

Low Osmolality ... Low Volume (Hypovolemia)

Low-volume patients have lost both water and Na^+ , but more Na^+ than water.

This has several causes:

- Diuretics
- GI losses (vomiting and diarrhea)
- Third spacing of fluid
- Adrenal insufficiency (Addison disease)

In primary adrenal insufficiency, both cortisol and aldosterone are deficient. The low aldosterone causes renal Na^+ wasting and decreased K^+ and H^+ excretion, resulting in hypovolemia (sometimes with hypotension), hyperkalemia, and metabolic acidosis. The low cortisol stimulates ADH production, resulting in hyponatremia.



Low Osmolality ... High Volume (Hypervolemia)

High-volume hyponatremic patients usually retain water and Na^+ , but more water than Na^+ . These patients have dependent edema and JVD.

Causes of low osmolality, high-volume status include:

- Edema-forming states: heart failure, cirrhosis, and nephrotic syndrome*
- Kidney failure: acute or chronic*

Thiazide diuretics are an FDA-approved class of drugs that inhibit the reabsorption of 3% to 5% of luminal sodium in the distal convoluted tubule of the nephron. By doing so, thiazide diuretics promote natriuresis and diuresis.

Normal treatment is restriction of water and Na^+ .

Lithium and demeclocycline can improve hyponatremia by inducing tubular resistance to ADH, but should not be used routinely because they can lead to chronic kidney disease. Also, avoid chronic, oral thiazide diuretics because they impair urinary-diluting ability, which can worsen hyponatremia. Loop diuretics can be very effective in patients with high-volume hyponatremia.

It's easy to precipitate acute kidney injury with rapid diuresis of a high-volume cirrhotic patient. Cirrhotics tend to have a low GFR, even with a normal serum creatinine.

They have decreased muscle mass, so a decrease in their GFR is not necessarily reflected in their serum creatinine concentration.

Low Osmolality ... Normal Volume (Euvolemia)

SIADH

Normal-volume patients usually have SIADH or are taking drugs that either mimic ADH or cause ADH release.

Know that pain and chronic nausea are potent natural stimulators of ADH release.

Normal-volume hyponatremia also can be caused by psychogenic polydipsia (but in a patient with normal renal function and solute intake, it takes over 15 L/day of water intake to produce hyponatremia), hypothyroidism, and isolated glucocorticoid deficiency.

Causes of SIADH include the following:

- CNS disease (e.g., meningitis)
- Lung disease (e.g., pneumonia)
- Neoplasms (especially small cell lung cancer)
- Drugs

Most common drugs associated with SIADH:

- *NSAIDs*
- *SSRIs*
- *Carbamazepine and oxcarbazepine*
- *Psychotropic drugs: haloperidol, amitriptyline*
- *IV cyclophosphamide*
- *Vincristine/Ninblastine*
- *Cisplatin*
- *Chlorpropamide (now rarely used)*
- *Ecstasy (methylenedioxymethamphetamine)*

Drugs (Enhance ADH release or effect)

Anti-diabetic drugs

Chlorpropamide

Anti epileptic drugs

Carbamazepine, oxcarbazepine

Sodium valproate

Selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline)

Anti cancer drugs

Vincristine, vinblastine, vinorelbine

Cisplatin, thiothixene

Melphalan, ifosfamide, methotrexate

Cyclophosphamide- intravenous

Antipsychotic drugs

Thioridazine

Haloperidol

Amitriptyline

Monoamine oxidase inhibitors

Pain killers

Opiates

Nonsteroidal antiinflammatory agents

Exogenous hormone administration

Vasopressin, desmopressin (dDAVP) or oxytocin

Miscellaneous

Interferon-alpha, interferon-gamma

Bromocriptine

Amiodarone

Ciprofloxacin

High-dose imatinib

“Ecstasy” (methylenedioxymethamphetamine)^[17-20]

SIADH: Syndrome of inappropriate secretion of anti diuretic hormone

Diagnose SIADH by comparing the urine and serum osmolalities. The normal response to hyponatremia would be to excrete free water in the urine; e.g., healthy patients would have a low serum osmolality and a low urine osmolality ($< 200 \text{ mOsm/L}$) because they are making dilute urine; this is what you see in psychogenic polydipsia. In SIADH, however, the urine is inappropriately concentrated ($> 250 \text{ mOsm/L}$) in the setting of a low serum osmolality. The patients are not excreting free water, so the serum osmolality is low, but the urine osmolality is high.

The *mechanism for ADH release* in moderate-to-severe hypothyroidism is decreased cardiac output, which stimulates the carotid baroreceptors. Rule out hypothyroidism and glucocorticoid deficiency in all patients with hyponatremia *before making a diagnosis of SIADH* because both causes can have low serum osmolalities and high urine osmolalities-more commonly seen in SIADH. Sometimes you cannot tell the difference using these tests, so look for the hormone deficiencies in everyone first, before diagnosing SIADH.

Schwartz diagnostic criteria for SIADH

Decreased measured serum osmolality (<275 mOsm/kg H_2O)

Clinical euvolemia

Urinary osmolality >100 mOsm/kg H_2O

Urinary $[Na^+] >40$ mmol/L with normal dietary sodium intake

Normal thyroid and adrenal function.

Normal renal functions

Exclude use of diuretic agents within the week prior to evaluation

No hypokalemia, no acid base disorders

Supporting diagnostic criteria for SIADH

Serum uric acid <4 mg/dL

Blood urea nitrogen <10 mg/dL

Fractional sodium excretion $>1\%$; fractional urea excretion $>55\%$

Failure to improve or worsening of hyponatremia after 0.9% saline infusion

Improvement of hyponatremia with fluid restriction

SIADH: Syndrome of inappropriate secretion of anti diuretic hormone

ملاحظات
في
المتابعة

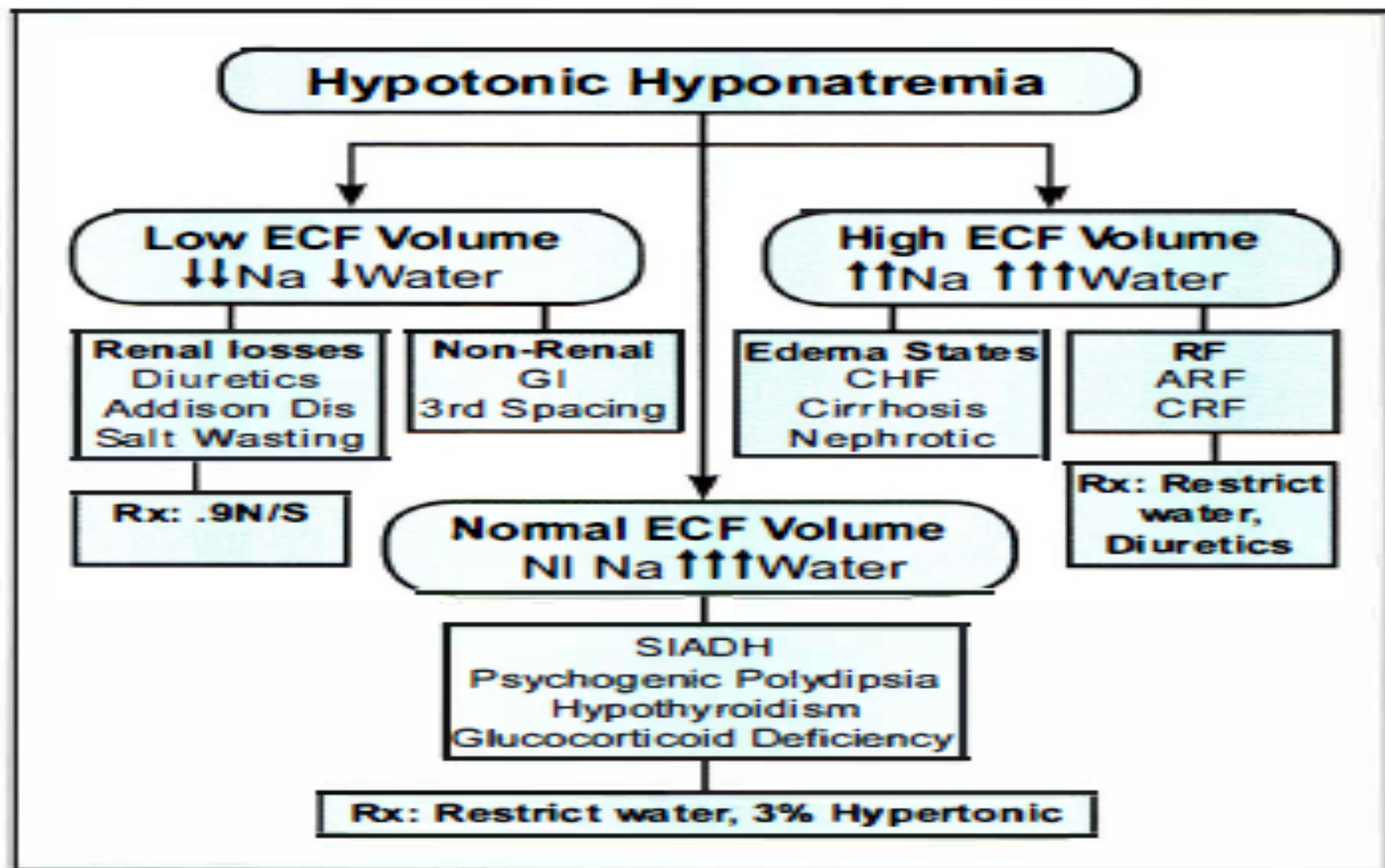


Figure 4-2: Causes of Hypotonic Hyponatremia

Thiazide Diuretics

Thiazides also can cause euvolemic low osmolality hyponatremia via several possible mechanisms, both ADH-related (by inducing mild volume depletion and directly stimulating ADH release) and non-ADH-related (by impairing urinary dilution in the early distal tubule). Elderly patients are highly susceptible to this effect of thiazides.

Treatment of Hyponatremia

Treat asymptomatic hyponatremia (no CNS changes) based on etiology:

- *Normal serum osmolality hyponatremia: This is artifact and does not require treatment.*
- *High osmolality hyponatremia: sometimes attributable to glucose or mannitol. Treating the underlying disease process (e.g., DKA) normalizes the sodium with time.*
- *Low osmolality and:*
 - o *Hypovolemic: normal saline to replenish deficit (watch for over-rapid correction!).*

o Hypervolemic: fluid restriction(- 800 cc/day)

+/- loop diuretics.

*o Euvolemic: SIADH is treated with fluid restriction (- 800 cc/day). Refractory cases can be treated with an ADH receptor antagonist, such as **conivaptan** or **tolvaptan**. Treat hypothyroidism or glucocorticoid deficiency with appropriate replacement.*

*Remember: **Isotonic saline worsens hyponatremia in patients with SIADH.***

If the symptoms of hyponatremia are severe (e.g., neurologic symptoms such as lethargy, confusion, coma, seizures) and the patient is not hypovolemic, treat with 3% saline. Correction of hyponatremia should never exceed 9 mEq/L over 24 hours due to the risk of osmotic demyelination syndrome (see next slide).

Standard therapy: Give enough 3% saline to increase the serum sodium by 6-8 mEq/L over 24 hours.

For severe symptoms (seizure, coma), a 100 mL bolus of 3% saline is recommended to quickly raise the serum sodium by 2-3 mEq/L. If symptoms persist, 2 more boluses can be given in 10-minute intervals.

For moderate symptoms (confusion, lethargy) and suspected SIADH, hypertonic saline can also be used. A reasonable initial rate is 0.5-1.0 mL/kg lean body weight/hour. The serum sodium should be checked frequently (every 2-4 hours) and the rate adjusted to achieve the target correction of 6-8 mEq/L over 24 hours. Watch carefully for the abrupt onset of a water diuresis, which can cause the serum sodium concentration to rise too fast, especially in patients with psychogenic polydipsia, hypovolemic hyponatremia, and hyponatremia due to thiazide diuretics.

Osmotic demyelination syndrome was previously referred to as central pontine myelinolysis because it is most prominent in the pons. If the sodium concentration is raised too rapidly, the cells can shrink (water rushes out of cells into the blood stream, where the osmolality has risen), potentially causing this demyelination syndrome. This rare effect is more likely to occur in the patient with chronic, severe hyponatremia ($\text{Na}^+ < 115 \text{ mEq/L}$ for > 2 days) whose sodium is corrected rapidly ($> 10 \text{ mEq/L}$ over 24 hours). Symptoms are delayed by about a week, compared to the rise in the sodium concentration, and are usually not reversible. Presentation includes speech and swallowing difficulties, weakness or paralysis, cognitive deficits, and coma. Seizures occasionally occur.

A related cause of severe and sometimes symptomatic hyponatremia is exercise-induced hyponatremia, reported in marathon and other endurance exercise participants and caused by both nonosmotic production of ADH and excessive intake of hypotonic fluids.

3% hypertonic saline should be promptly administered when diagnosed.

HYPERNATREMIA

Can You Drink Too Much Water?



Overview

Severe hypernatremia is fairly rare but always represents a water deficit. It does not occur unless the patient is unable to get to water (debilitated or H₂O unavailable) or the thirst mechanism is defective. Unlike hyponatremia, these patients are always hyperosmolar, so the 1st step is **determining volume status**. Low volume implies water and total body Na⁺ loss (water deficit exceeding Na⁺ deficit).

Treat severe hypovolemic hypernatremia with **normal saline first** to correct the volume deficit, and only then with hypotonic fluids to further replace the water deficit.

Remember: Even normal saline has a lower osmolality than serum in a patient with hypernatremia.

Cellular swelling can occur from too rapid correction of any severe hyperosmolar state, such as hypernatremia, nonketotic hyperglycemic coma, and severe uremia. (These are just the variables in the osmolality equation.) Cellular swelling can cause cerebral edema, seizures, and coma. So be careful with the fluid rate and measure serum sodium frequently

High-volume hyponatremia:

This is unusual and typically not serious. It most often occurs with mineralocorticoid excess, such as primary hyperaldosteronism. Usually, the only time a serious result occurs is after giving large amounts of sodium bicarbonate or hypertonic saline during advanced cardiac life support. Treat with loop diuretics and free water.

Normal-volume hypernatremia is most often seen in patients with diabetes insipidus (DI) and reduced access to water (and thus become hypernatremic) but have not yet developed frank volume depletion.

Typical DI patients with normal access to water have normal or borderline-high serum Na^+ levels because they are constantly drinking water (hyperosmolar, and therefore always thirsty). Their primary complaint is usually polyuria and polydipsia.

Think of central DI in the patient with high Na^+ and high urine volume who also has a history of recent neurosurgery, head trauma, or brain cancer/metastases. Otherwise, DI is typically nephrogenic DI (also called "ADH resistant").

Nephrogenic DI can be hereditary, with most cases presenting in childhood (mutations in the vasopressin 2 receptor or aquaporin 2 genes) or due to:

1. hypercalcemia (serum $\text{Ca}^{2+} > 11 \text{ mg/dL}$),
2. chronic hypokalemia (serum $\text{K} < 3 \text{ mEq/L}$),
3. intrinsic renal disease (especially Sjogren syndrome),
4. drugs (especially lithium).

Water Restriction Test ?

The water restriction test not only diagnoses DI but also differentiates between central and nephrogenic types.

In a healthy person, when plasma osmolality increases to 295, ADH level is high and urine is maximally concentrated (> 700 mOsm/L).

In central DI, even with water restriction, the ADH stays low and the urine dilute.

Treat mild cases of central DI with thiazides and salt restriction.

Chlorpropamide and carbamazepine can be used in cases of partial central DI, when desmopressin might be too potent or limited in supply. These drugs stimulate further ADH production if the patient has a partial defect.

Treat more resistant central DI with oral or intranasal desmopressin (synthetic vasopressin analog). Because the kidneys immediately respond to ADH, giving desmopressin results in a quick increase of the urine concentration and reduction in urine output. The intranasal preparation is the most potent. Be careful to titrate the dose properly and counsel the patient to drink only when thirsty, because volume overload and hyponatremia can easily occur (i.e., drug-induced SIADH).

*In nephrogenic DI, the ADH is appropriately high, but the urine is dilute: The collecting duct is resistant to the effect of ADH. Giving extra ADH (desmopressin) does not increase the concentration of the urine. **Treat nephrogenic DI with thiazide diuretics or amiloride.** NSAIDs are used to treat rare hereditary forms.*

Remember: SIADH (high ADH) usually presents as hyponatremia with normal volume. DI typically presents as polyuria/polydipsia, with or without hypernatremia, also with normal volume!.

Urine Osmolality

Urine osmolality can range from 50- 1,200 mOsm/L. To make sense of the osmolality, you must also know the urine output (L/d). Multiply the osmolality x output (1 kg = 1 L) to get total osmoles output per day. Normal is about 500. This is important in the case of a patient with high Na⁺ and high urine output. If the 24-hour solute output is > 900 mOsm, think of an osmotic cause of the hypernatremia (e.g., hyperglycemia); whereas in DI, the 24-hour osmoles are normal, so the urine is very dilute.

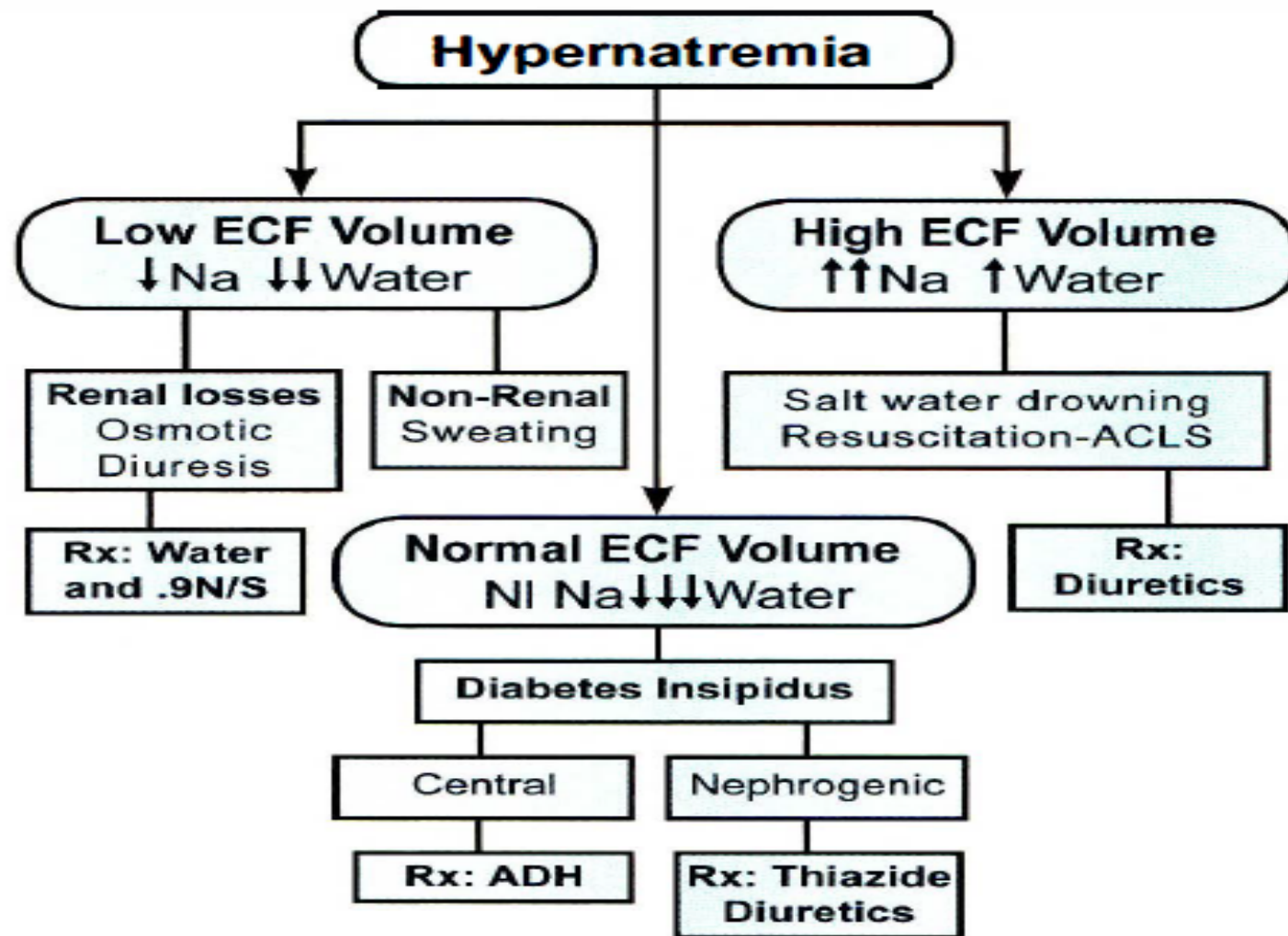


Figure 4-3: Causes of Hypertatremia



A Dreamy World

A man's dreams are an index to his greatness



POTASSIUM

TOP Potassium

Rich Foods



Yogurt



Apricot



Banana



Butter Milk



Beet Greens



Cantaloupe



Carrots



Peas



Plantains



Orange



Lentils



Peaches



Prunes



Milk



Pork



Rainbow



Spinach



Clams



Honeydew Melon



Soy Beans



Winter Squash



Tomatoes



Potatoes



Sweet Potatoes



Tuna

Aldosterone

Basically, aldosterone can be considered the hormone that regulates potassium level. K^+ secretion occurs in the late distal tubule and cortical collecting duct via aldo-regulated Na^+/K^+ active transport.

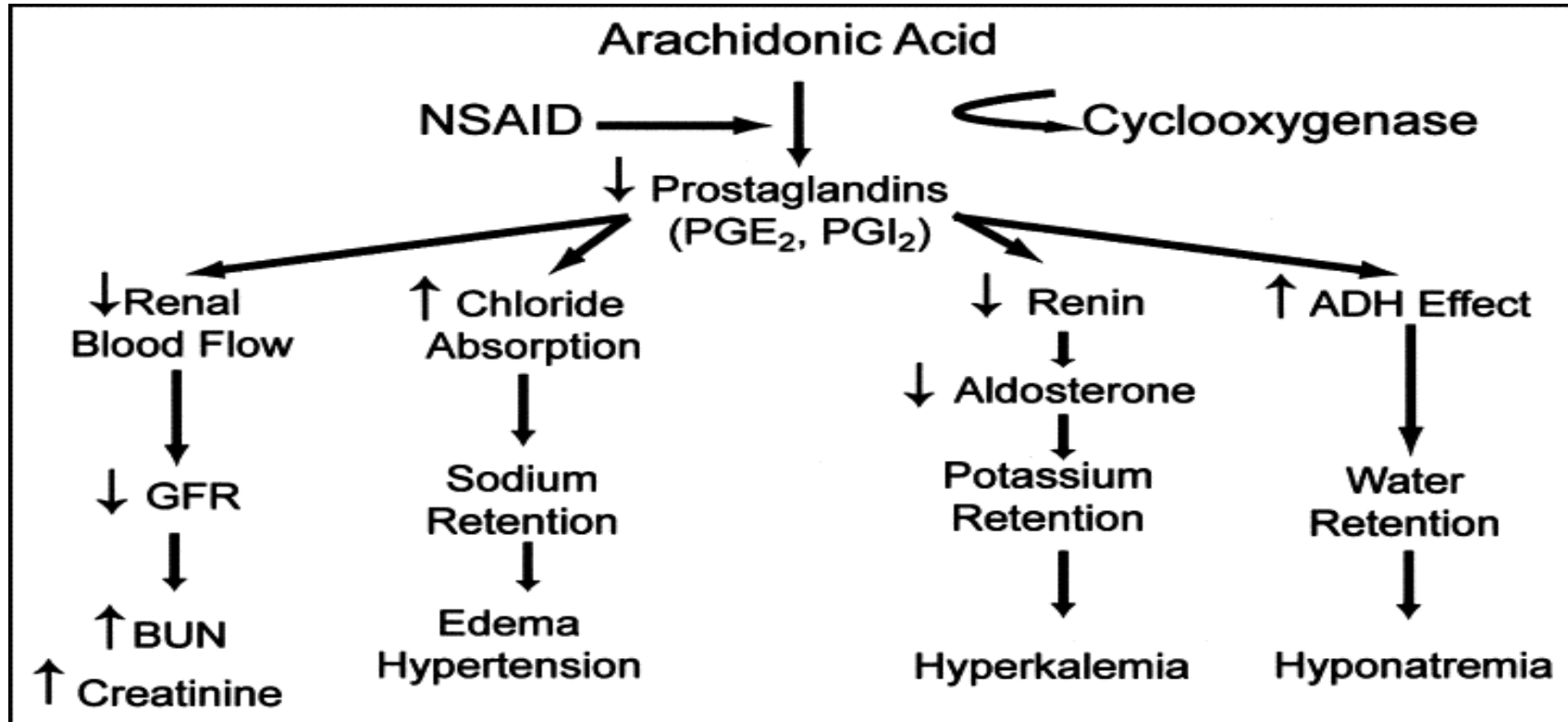
Any situation that causes aldo release (or mimics aldosterone) lowers the serum K^+ . These include:

- *Increased renin as a result of decreased effective arterial blood volume:*
 - o Volume depletion (GI losses, diuretic therapy)
 - o Decreased renal perfusion (HF, renovascular disease, NSAIDs)
- *Increased renin as a result of inappropriate release:*
 - o Renin-secreting renal tumors
- *Increased aldo as a result of inappropriate release:*
 - o Bilateral adrenal hyperplasia
 - o Aldo-secreting adrenal adenoma
- *Increased excretion of hormone with aldo-like effects:*
 - o Cushing syndrome

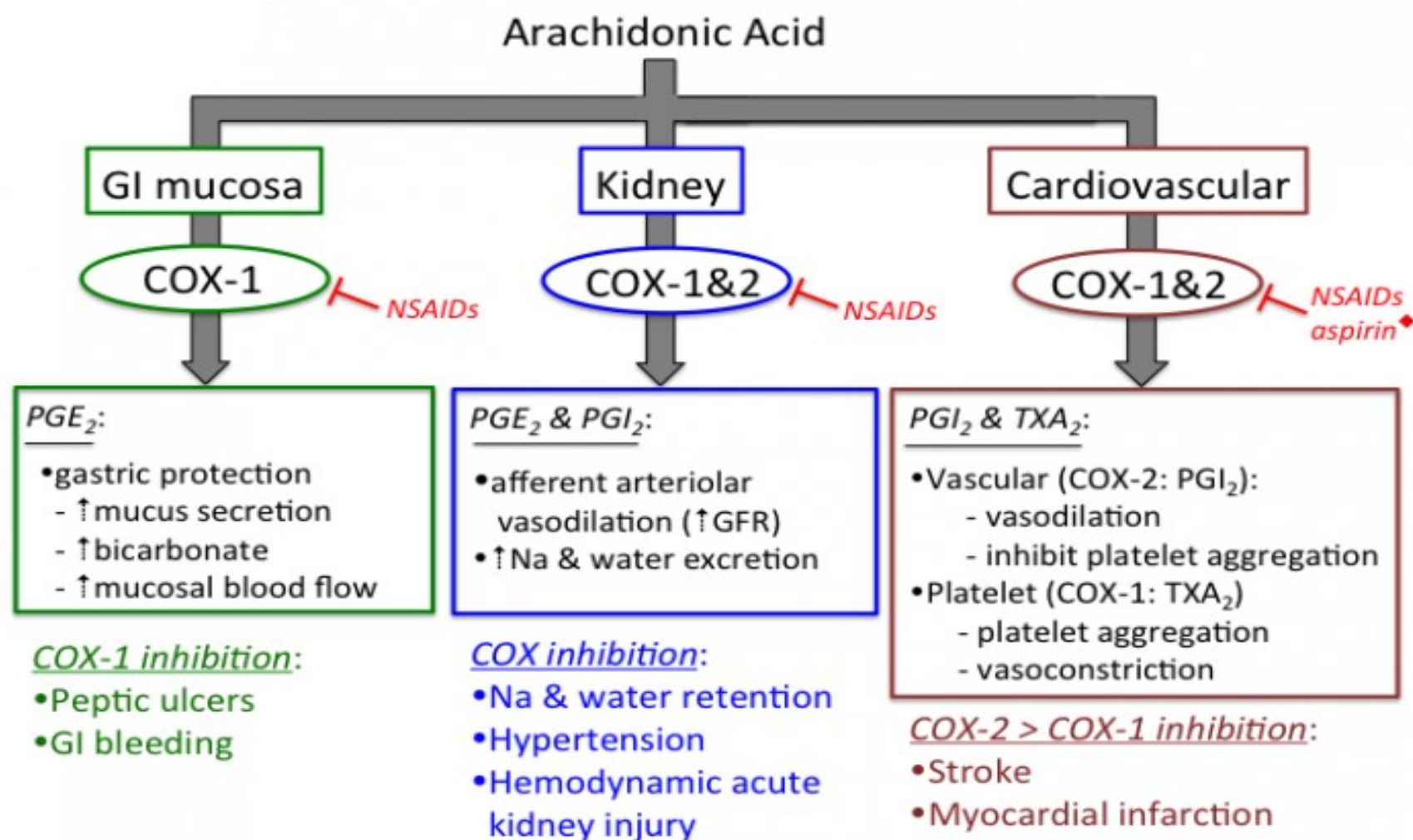
Conversely, *any situation that inhibits aldo release or aldo action increases the serum K⁺:*

- *Potassium-sparing diuretics* (Remember: Spironolactone blocks the aldosterone receptor; amiloride blocks the channel its action depends on.)
- *Dysfunctional kidneys that do not release renin* (termed "hyporeninemic hypoaldosteronism"); chronic interstitial nephritis; diabetes; exacerbated by NSAIDs
- *ACE inhibitors, angiotensin receptor antagonists, and renin inhibition*
- *Primary adrenal disease (Addison's)*, because it affects both the zona glomerulosa (site of aldo production) and fasciculata (site of cortisol production}-but not secondary adrenal insufficiency because lack of ACTH affects only the zona fasciculata
- *Heparins* (Both unfractionated and low molecular weight are directly toxic to the zona glomerulosa.)

Know: NSAIDs typically decrease renin, so they can make K⁺ go up-but generally only if the patient has an existing problem that affects the kidneys. Basically, NSAIDs make hyporeninemic states worse than they already are.



NSAID Side Effects:



♦ Low dose aspirin irreversibly inhibits platelet COX-1

Cellular Shifts

Cellular uptake also affects serum K⁺ level:

- *Alkalosis, beta-agonists, and insulin increase uptake*

So hypokalemia

- *Acidosis and alpha-agonists decrease uptake*

So hyperkalemia

So this works both ways.

Remember that

Hypokalemia can cause alkalosis, and hyperkalemia causes acidosis.

And the reverse is true: Alkalosis causes hypokalemia

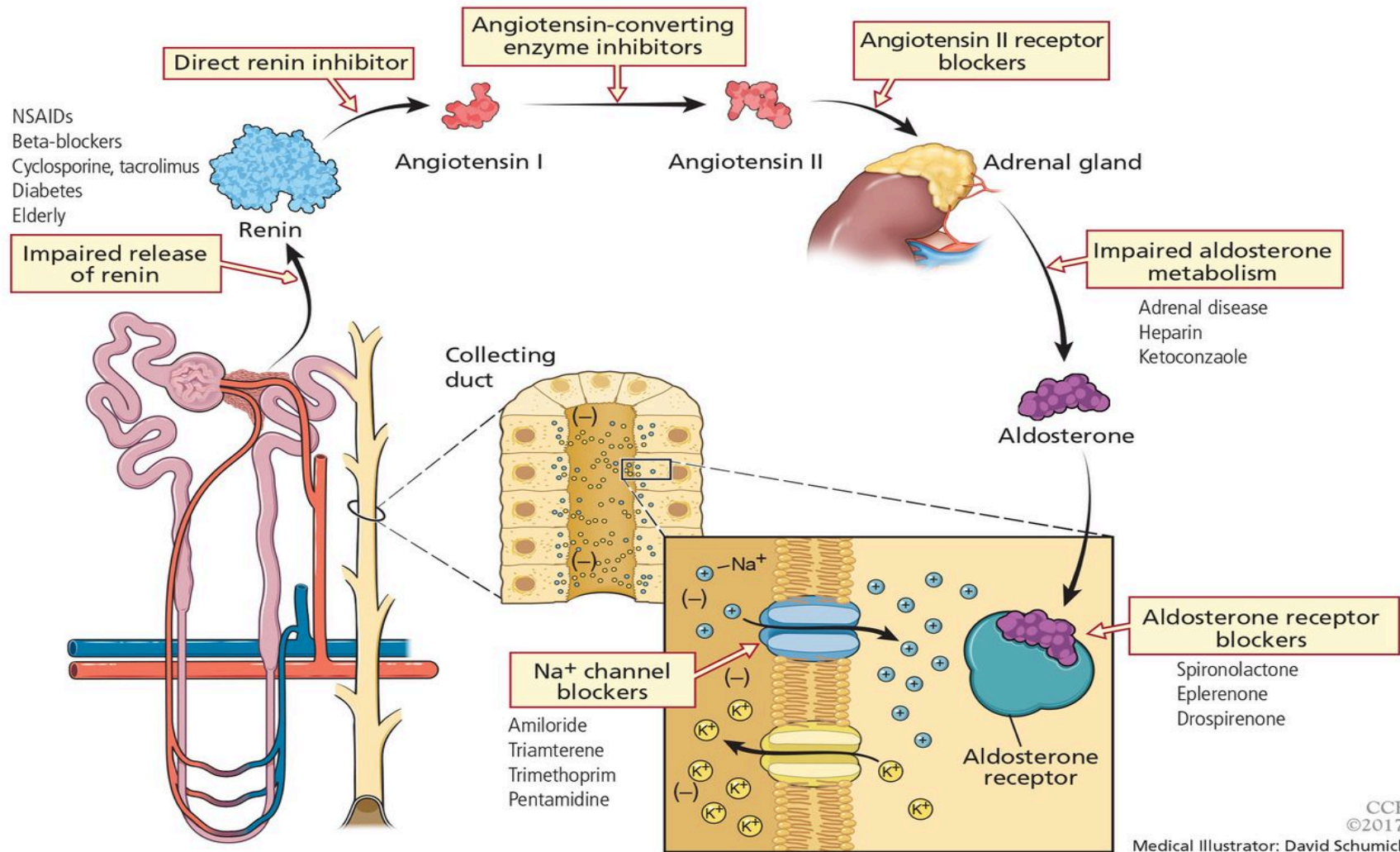
and acidosis causes hyperkalemia.

Other Factors Affecting K⁺ Level

Potassium excretion by the kidney is stimulated by increased urine flow, increased distal Na⁺ delivery, aldosterone, the presence of non-resorptive anions in the tubules, and metabolic alkalosis. The following factors also affect serum K and are important to know:

- Increased cell turnover is associated with hyperkalemia (tumor lysis syndrome, rhabdomyolysis, acute leukemia).*
- Trimethoprim in TMP/SMX interferes with K⁺ secretion in the principal cells of the late distal tubule and cortical collecting duct, especially in patients with preexisting renal disease, causing hyperkalemia.*
- Type 1 distal RTA is associated with hypokalemia for unclear reasons.*
- Type 2 proximal RTA can be associated with hypokalemia because of cotransport problems.*

- *Loop and thiazide diuretics block reabsorption of solutes and water. Thiazides increase distal delivery of solutes and up-regulates the Na^+/K^+ ATPase in the early distal tubule causing hypokalemia.*
- *Cisplatin and penicillins are associated with renal K^+ wasting, causing hypokalemia.*
- *3 genetic syndromes are associated with hypokalemia: Liddle's, Bartter's, and Gitelman's.*



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Medical Illustrator: David Schumick

Based on information in Palmer BF. A physiologic-based approach to the evaluation of a patient with hyperkalemia. Am J Kidney Dis 2010; 56:387-393.

Causes of Hypokalemia

Hypokalemia with metabolic alkalosis:

- Reduction in effective arterial blood volume
 - Volume contraction: vomiting, NG suction, bleeding, or diuretics (thiazides and loops)
 - Renovascular disease: renal artery stenosis or fibromuscular dysplasia
 - Secondary hyperaldosteronism: severe HF, cirrhosis, nephrotic syndrome
- Primary hyperaldosteronism
- Aldo-secreting tumor ("Conn syndrome")
- Renin-secreting tumor
- Cushing syndrome
- Liddle's, Bartter's, and Gitelman's (see next page)

Hypokalemia with metabolic acidosis:

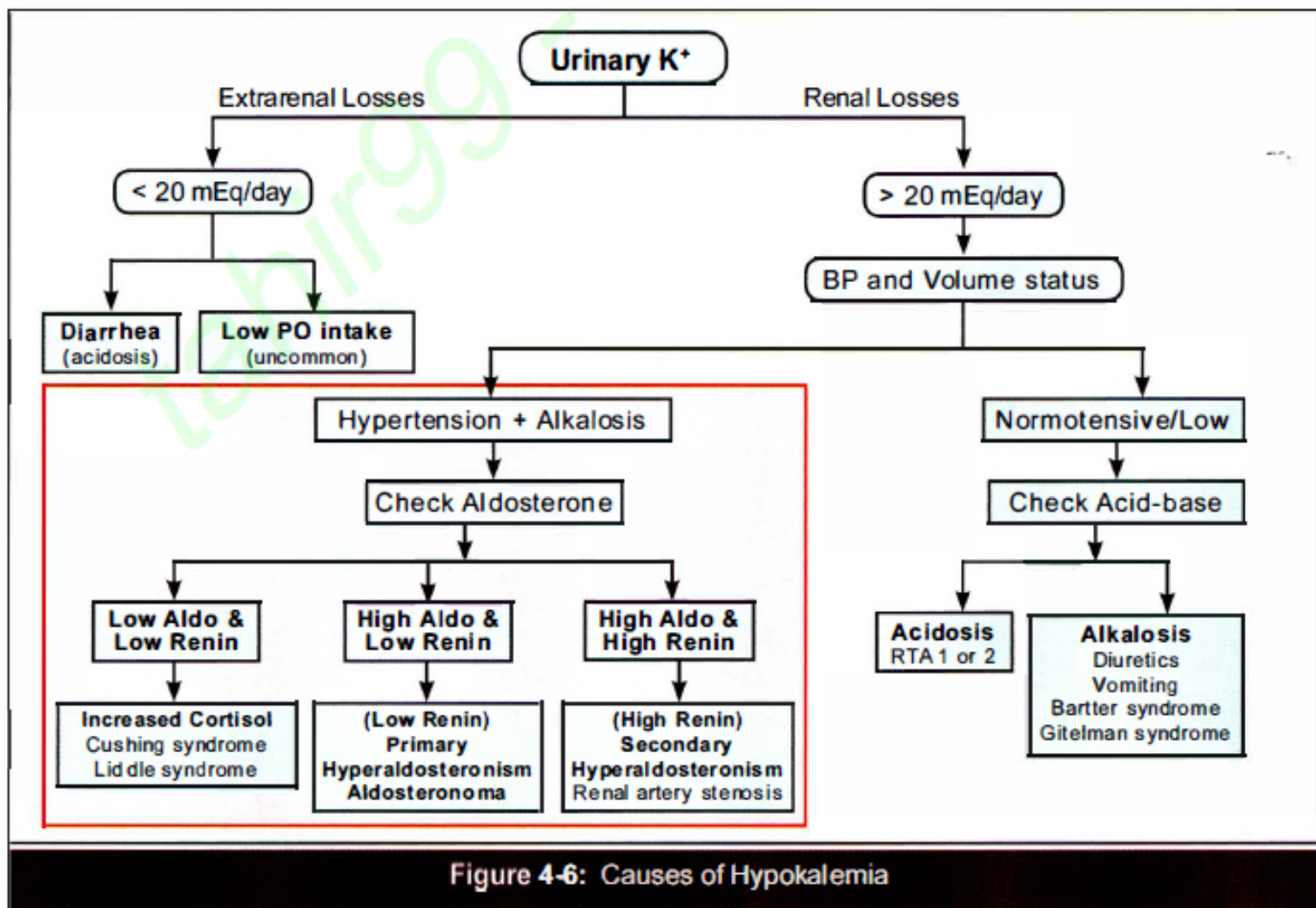
- Types 1 and 2 RTA
- Diarrhea

Hypokalemia associated with shifts into cells:

- Beta-agonists
- Insulin

Other causes of hypokalemia:

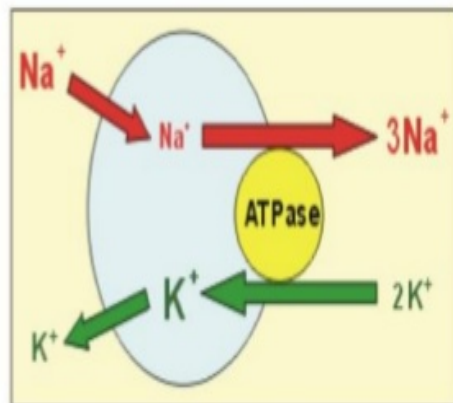
- Penicillins
- Cisplatin



Causes of Hyperkalemia

- Chronic interstitial nephritis
- Type 4 RTA (hyporeninemic hypoaldosteronism)
- Primary adrenal insufficiency (Addison disease)
- Acidosis
- Drugs
 - Potassium-sparing diuretics
 - NSAIDs
 - ACEIs/ARBs and renin inhibitors
 - Heparins
 - TMP/SMX
 - Cyclosporine, tacrolimus
 - Alpha-agonists

Distribution of potassium between the cells and the extracellular fluid



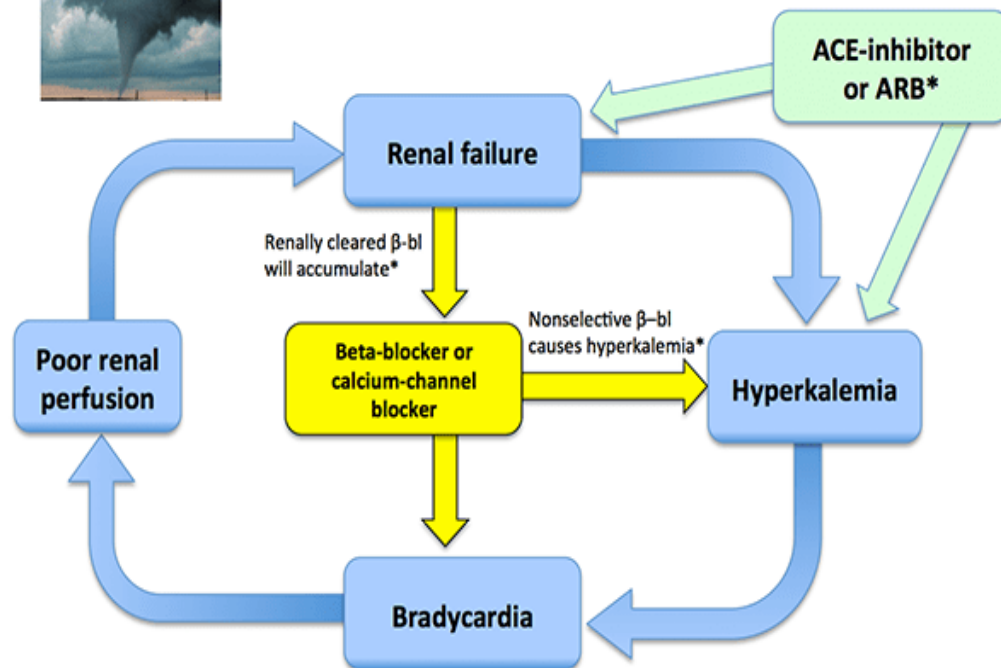
98 % K intracellular
Maintained by this pump

Pump block
eg digitalis toxicity
Beta blockers

Pump stimulation
Insulin, beta2 stimulation



Vicious cycle involved in BRASH syndrome



* Indicates components which are not required, but may contribute in some cases

HOW TO REMEMBER DRUGS CAUSING HYPERKALEMIA (INCREASED BLOOD POTASSIUM)

IN 6 MINS

K⁺-SPARING DIURETICS

SPIRONOLACTONE

AMILORIDE

TRIAMTERENE

Mechanism

- Block Na⁺ channels in collecting ducts
- Inhibit Na⁺ absorption & K⁺ excretion

BETA BLOCKERS (NONSELECTIVE)

Beta₂ agonists ↓↓ K⁺ levels
by moving K⁺ into cells

ACE INHIBITORS

CAPTOPRIL

ENALAPRIL

LISINOPRIL

Mechanism

- Blocks conversion of Ang I to Ang II
- Decreases production of Aldosterone

DIGOXIN OVERDOSE

Acute digoxin toxicity leads to ↑↑ K⁺ levels

Pneumonic – K⁺ ABCD PENS HIT

ANGIOTENSIN RECEPTOR BLOCKERS

LOSARTAN

VALSARTAN

IRBESARTAN

Mechanism

- Blocks Ang II (AT₁) receptors in adr. cortex
- Decreases production of Aldosterone

CALCINEURIN INHIBITORS

CYCLOSPORINE

TACROLIMUS

Mechanism

- Decrease Renin release from the kidneys
- Decreases production of Aldosterone

PENTAMIDINE

Block Na⁺ channels in CD

NSAIDs

↓↓ renal PG synthesis

SUCCINYLCHOLINE

↑↑ nicotinic ACh receptors in damaged skeletal muscles

HEPARIN

↓↓ aldosterone production

TRIMETHOPRIM

Block Na⁺ channels in CD

Calcineurin inhibitor-induced hyperkalemia and salt-sensitive hypertension in Early Post-Kidney Transplant Period

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Background

Calcineurin inhibitor (CNI) is the cornerstone of maintenance immunosuppression in kidney transplantation. However, it could lead to several fluid and electrolyte disturbances including salt-sensitive hypertension and hyperkalemia. Hyperkalemia could be treated with aldosterone agonist; however, this treatment is limited by salt and water retention and uncontrolled hypertension (HTN). We report a case of kidney transplant recipient with persistent posttransplant hyperkalemia, which was resolved with aldosterone agonist.

Case description

A 65-year-old Caucasian man with a past medical history significant for end-stage renal disease secondary to type 2 diabetes mellitus (T2DM) underwent an uneventful deceased donor renal transplantation with basiliximab induction. Maintenance immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone. Prophylaxis trimethoprim/sulfamethoxazole (TMP/SMZ) was initiated. Tacrolimus was started on postoperative day 1 and was titrated to maintain the 12-hour tacrolimus trough level of 8 ng/mL. Postoperative course was complicated by persistent hyperkalemia with serum potassium of 5.1 – 5.7 mmol/L and non-anion gap metabolic acidosis with serum bicarbonate down to 18 mmol/L. He also developed uncontrolled hypertension with average systolic and diastolic blood pressure (BP) of 180 and 60 mmHg, respectively ([Figure 1](#)). On the posttransplant day 11, serum potassium increased up to 6.4 mmol/L even though his urine output ranged from 1.6 to 2.2 L/day and serum creatinine had trended down to 2.34 mg/dL from the pretransplant serum creatinine of 10.31 mg/dL. In addition to low potassium diet, he was treated with sodium polystyrene sulfonate with several bowel movements; however, serum potassium still elevated. Therefore, fludrocortisone was started and serum potassium was normalized. BP remained high and dosing of antihypertensive medication were adjusted.

Discussion

Tacrolimus leads to hyperkalemia from inhibiting basolateral Na-K ATPase at the collecting duct causing impaired transepithelial potassium secretion from decreased sodium uptake. Our patient had new-onset hyperkalemic non-anion gap metabolic acidosis since early post-kidney transplant period even with improving renal allograft function and good urine output. Tacrolimus causing distal tubular defect mimicking type 4 renal tubular acidosis (T4RTA) that was corrected by aldosterone agonist. Even though diabetes is one of the most common causes of T4RTA, the new renal allograft should not be affected by the underlying T2DM in such a short posttransplant period. TMP/SMX could contribute to hyperkalemia. Tacrolimus also causes hypertension from renal afferent arteriolar vasoconstriction and activation of Na-Cl cotransporter (NCC) in the distal collecting tubule (DCT) and subsequently salt-sensitive hypertension.

Conclusions

Aldosterone agonist could treat tacrolimus-induced hyperkalemia from distal tubular injury; however, hypertension from salt and fluid retention limits this therapy. Since tacrolimus stimulates NCC, thiazide diuretics could potentially be used for BP control once renal allograft function is stable. Both low dietary potassium and sodium intakes should be part of therapeutic strategies to control serum potassium and HTN.

EFFECT OF TACROLIMUS ON RENAL K^+ EXCRETION

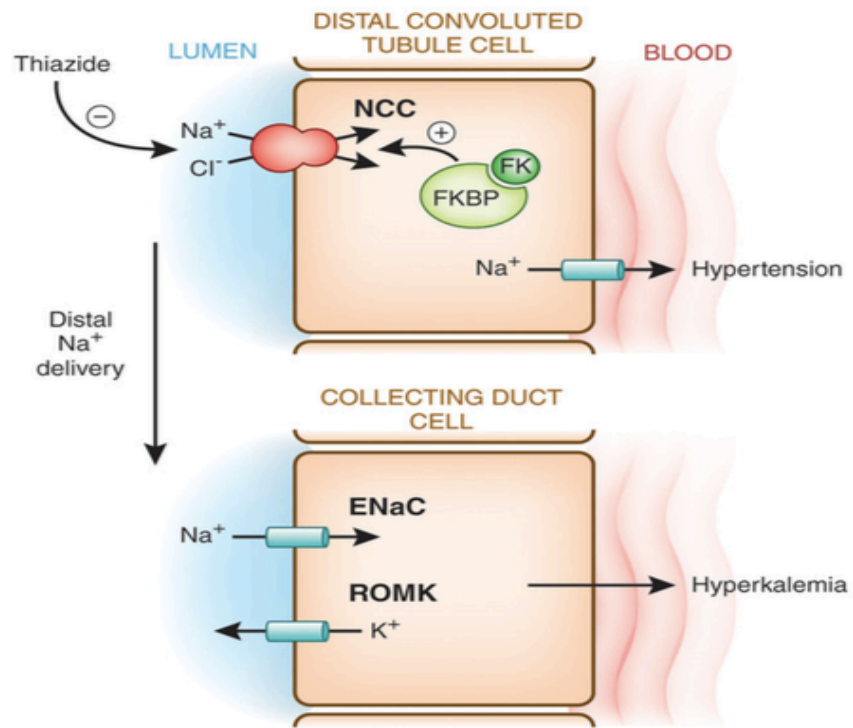
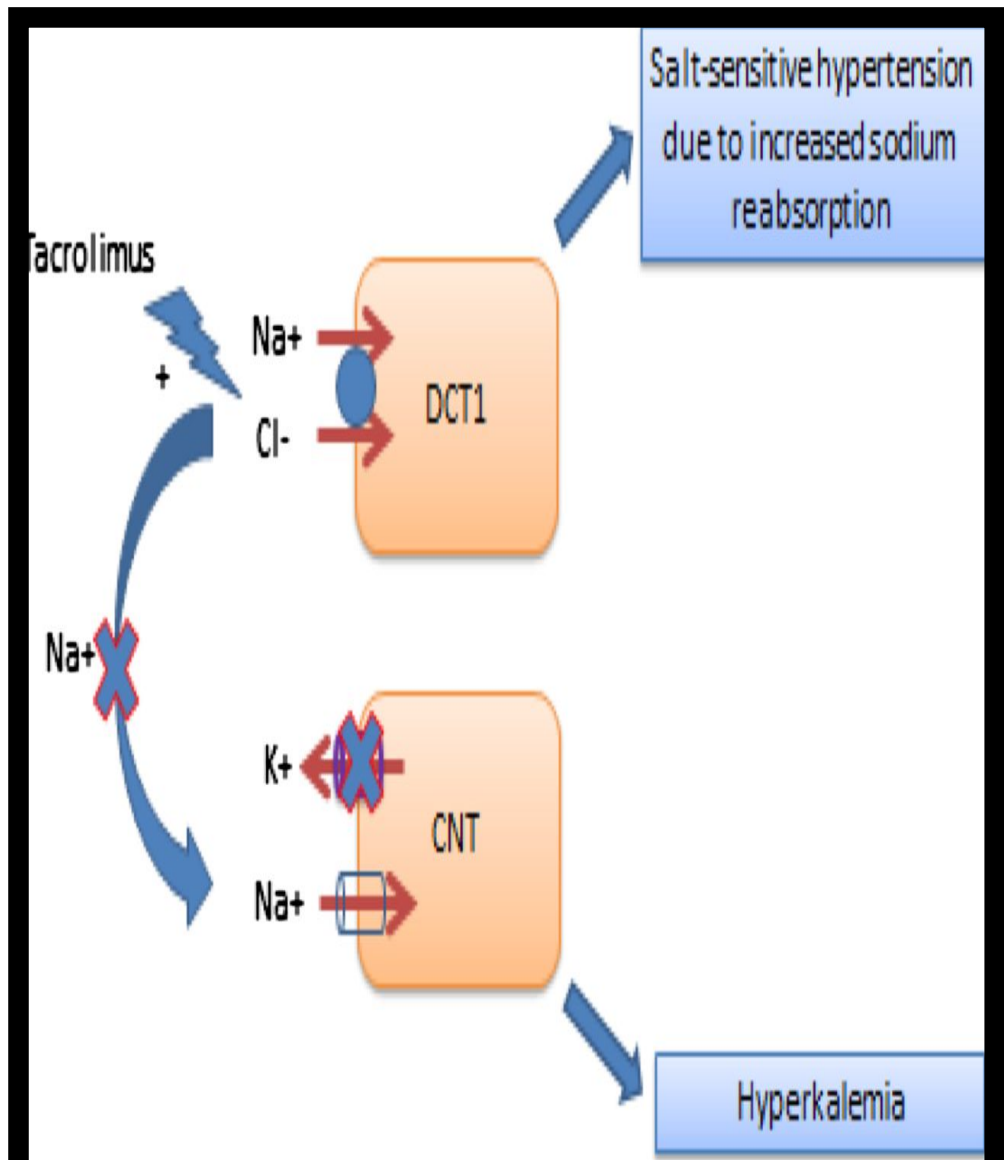
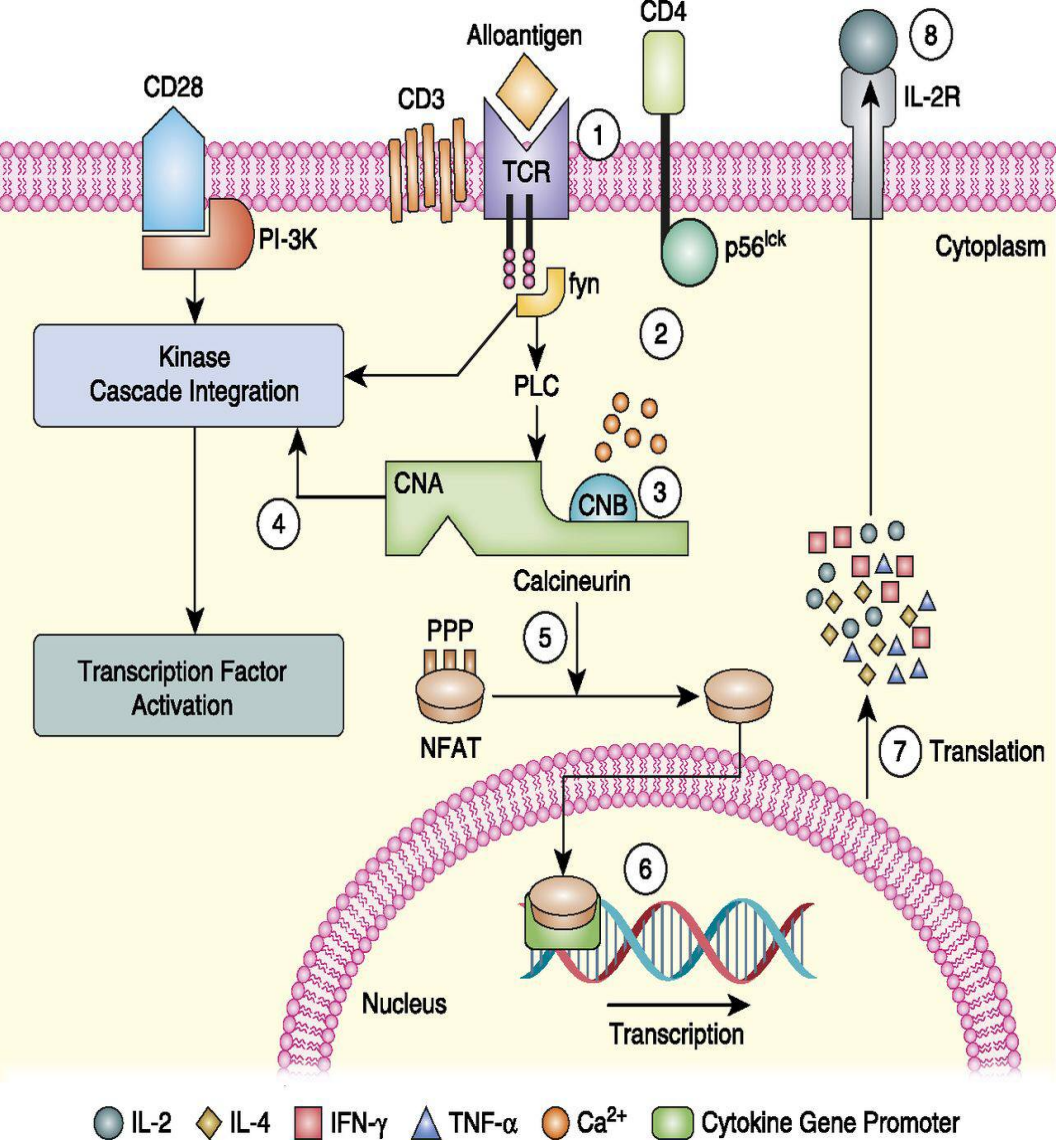


Figure 16. Effect of tacrolimus on renal K^+ excretion. FK (tacrolimus) binding to FKBP in the distal convoluted tubule increases NCC stimulation and salt absorption, causing salt-sensitive hypertension. Increased sodium absorption by NCC decreases distal sodium delivery and makes less Na available for epithelial sodium channel (ENaC)-dependent K^+ excretion *via* renal outer medullary potassium (ROMK). This leads to hyperkalemia. Thiazide blocks NCC and reverses the process.





Calcineurin Inhibitor Toxicities

Cyclosporine

Tacrolimus

Nephrotoxicity

Hypertension

NODAT

Dyslipidemias

Hyperuricemia

Hypomagnesemia
Metabolic acidosis
Hypercalciuria

Hyperkalemia

Hypertrichosis

Alopecia

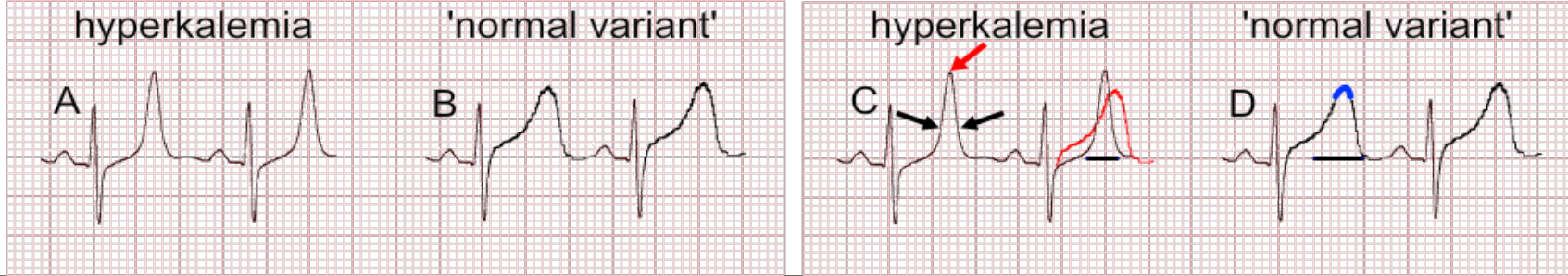
Gingival hyperplasia

Hyperkalemia Manifestations

Most patients have no symptoms if the increase in the potassium has been chronic, even with a level near 7 mEq/L. Symptoms can manifest at lower serum levels when the increase is acute. Presentation can include significant weakness or paralysis, conduction abnormalities or arrhythmias. Typically, if a patient is experiencing weakness, they also have ECG changes, although the opposite is not necessarily true.

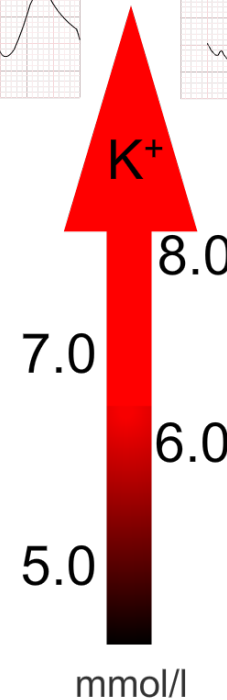
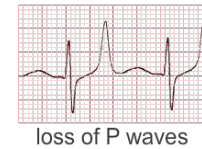
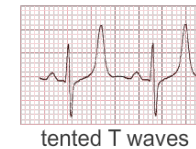
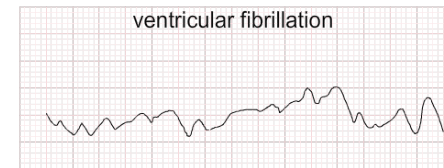
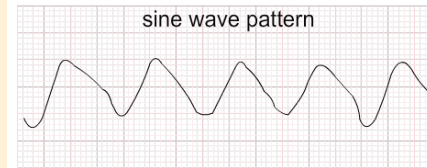
Know the sequence of ECG changes that occur with progressive hyperkalemia:

- peaked T wave and short QT interval, then
- progressive lengthening of PR and QRS intervals, then
- loss of P wave+ QRS widening into sine wave, then
- ventricular fibrillation or cardiac standstill.



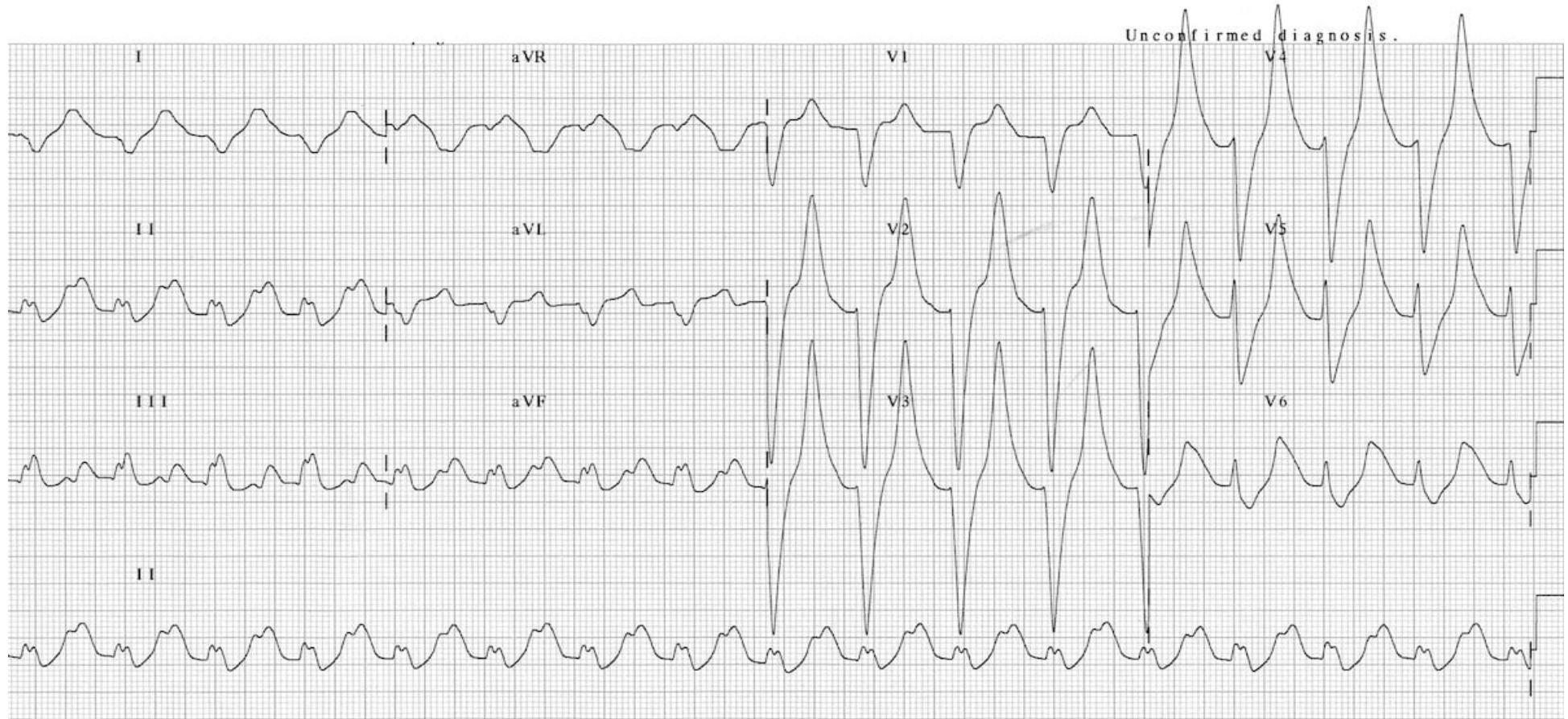
Serum potassium	Typical ECG appearance	Possible ECG abnormalities
Mild (5.5–6.5 mEq/L)		Peaked T waves Prolonged PR segment
Moderate (6.5–8.0 mEq/L)		Loss of P wave Prolonged QRS complex ST-segment elevation Ectopic beats and escape rhythms
Severe (>8.0 mEq/L)		Progressive widening of QRS complex Sine wave Ventricular fibrillation Asystole Axis deviations Bundle branch blocks Fascicular blocks

ECG/EKG changes in hyperkalemia



Normal T-wave Physiology

Normal T waves are upright in leads I, II, and V3-V6, inverted in AVR. Less than five mm in limb leads, less than ten mm in precordial leads, and variable presentations in III, AVL, AVF, and V1-V2



Hyperkalemia Treatment

Treatment is aimed at decreasing the serum concentration and stabilizing cardiac membranes. Problems usually occur when $K^+ = > 7 \text{ mEq/L}$, but there is no absolute number that requires treatment. IV calcium is always given to patients with ECG changes.

Treatment of acute hyperkalemia with ECG changes:

- *IV calcium gluconate (OK for peripheral injection) or IV calcium chloride (requires central access); use only if there is a wide QRS or absence of P waves. IV calcium can enhance the effect of digoxin; therefore do give to patients on this therapy.*
- *Insulin with glucose infusion (15 minutes for effect).*
- *Sodium bicarbonate injection or infusion, if acidosis is present (30 minutes for effect; minimal response in patients without acidosis).*
- *Albuterol nebulization (90 minutes for effect) or injection (30 minutes for effect), but be careful in patients with heart disease.*
- *Loop diuretics (in patients who make urine).*
- *Dialysis.*

Sodium polystyrene sulfonate ([SPS]; Kayexalate[®], Kionex[®], Marlexate[™]) is a cation-exchange resin given orally or as an enema that exchanges Na⁺ for K⁺ across the gut wall and also induces an osmotic diarrhea full of potassium. SPS can be used to treat hyperkalemia, but it should not be used for treatment of severe hyperkalemia because it may take hours to work. Know that SPS insorbitol (most common preparation) has been associated with colon necrosis, especially within a week after surgery and especially in patients with ileus.

*Patients with severe chronic kidney disease or on dialysis should be treated as above, but they may also need immediate dialysis. SPS without sorbitol can be given if there is a delay in dialysis. **Treat K+ more than 6.5 without symptoms or ECG changes** with insulin + glucose, beta-agonists, sodium bicarbonate (if acidosis), and SPS enema. K+ less than 6.5 can be treated with loop diuretics and dietary restriction.*

Know that sodium bicarbonate infusions can cause edema and may precipitate cardiac decompensation.

Make sure you check the patient's medication list and discontinue all of the drugs that cause hyperkalemia (ACE/ ARBs, K-sparing diuretics, beta-blockers, heparin, NSAIDs, trimethoprim-sulfamethoxazole).

Table 1. Summary of Approved Therapy Options for Hyperkalemia

Medication	Recommended Doses for Hyperkalemia	Route of Administration	Onset of Action
Calcium	10 mL calcium chloride or calcium gluconate (10%)	IV	Immediate 1-3 min
Insulin (short-acting)	10 units	IV	20 min
Albuterol	10-20 mg	Inhalation	30 min
Furosemide	40-80 mg	IV	15 min
Sodium polystyrene sulfonate (available sorbitol-free)	15-60 g 30-50 g	Oral Rectal	>2 h
Patiromer ^a	8.4-25.2 g daily	Oral	7 h

^a Should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. Source: References 11-14, 16, 19.

Hypokalemia Manifestations and Treatment

Overview

Severe hypokalemia may cause U waves, decreased deep tendon reflexes, and rhabdomyolysis. Serum K⁺ does not decrease to below normal until there is a net loss of 200-300 mEq. The consequence of this is that large amounts of KCl are usually required for replacement.

Treat contributing factors such as volume depletion and/or metabolic alkalosis; also, do whatever tests are necessary to diagnose the cause (e.g., measure urine free cortisol to diagnose Cushing's; consider hyperaldosteronism).

Replace potassium orally when possible.

Poor response generally means the deficit is large, and the patient merely requires more potassium. Comorbid magnesium deficiency causes renal potassium wasting, so always check and replenish mg stores.

Hyperaldosteronism

Primary hyperaldosteronism is caused by disease in the adrenal gland.

Hyporeninemia, hypertension, and hypokalemia occur-as in other states of mineralocorticoid excess, such as Cushing syndrome. The adrenal disease is either bilateral adrenal hyperplasia or an aldo-secreting tumor in the zona glomerulosa ("Conn syndrome").

Secondary hyperaldosteronism is caused by disease in the kidneys or a restricted blood flow in the renal arteries.

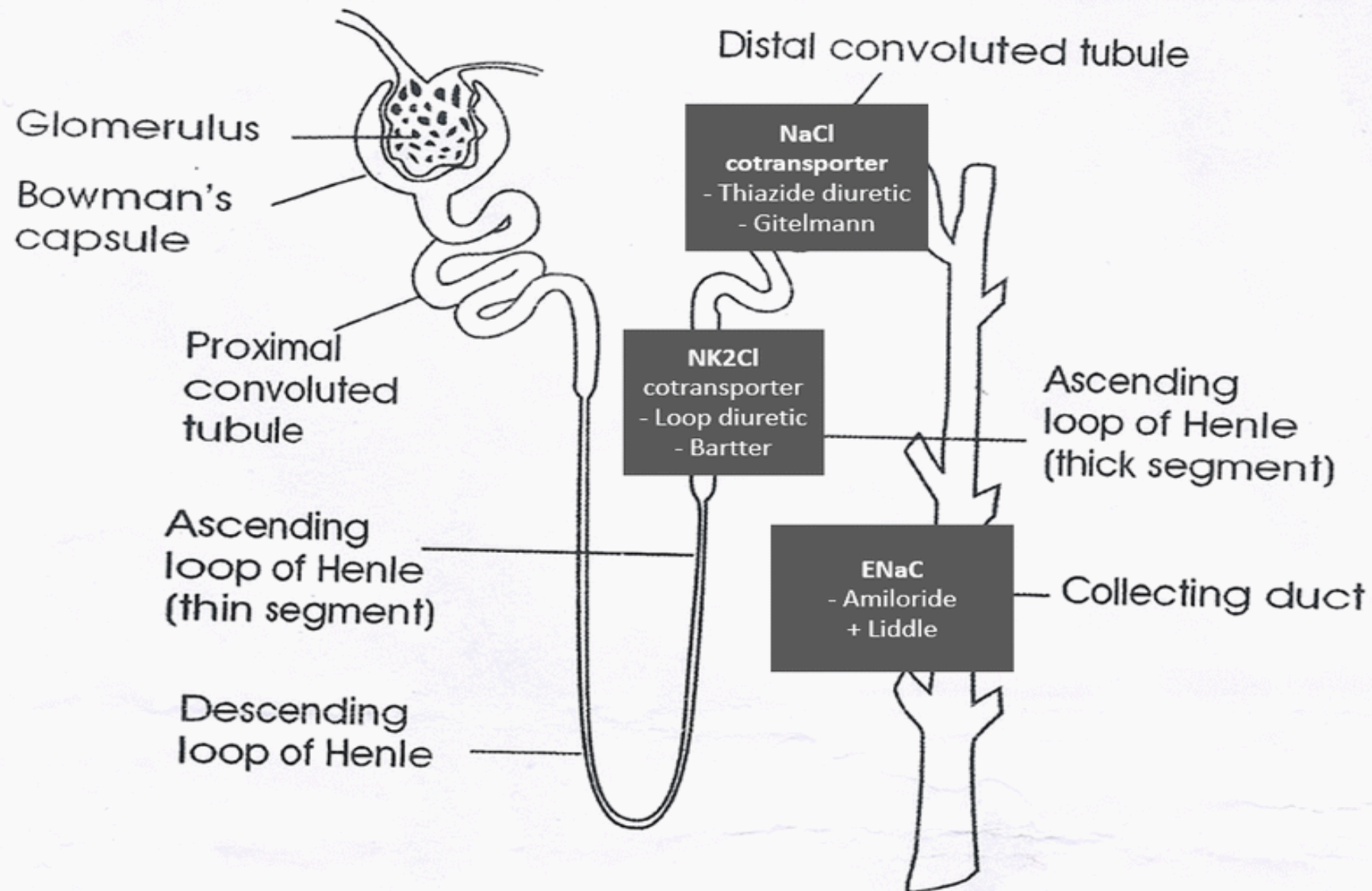
Hyperreninemia, hypertension, and, sometimes, hypokalemia occur. Decreased renal blood flow so increased renin so increased angiotensin II so increased aldosterone.

Renin-secreting tumors of the kidney are rare.

Renovascular disease can be due to either atherosclerotic renal artery stenosis or fibromuscular dysplasia.

In both primary and secondary disease, aldosterone is increased, so the Na^+/K^+ ATPase in the late distal tubule and cortical collecting duct is up-regulated, resulting in increased reabsorption of sodium and increased secretion of potassium and hydrogen ions.

Hypokalemia without an obvious cause, in a patient with hypertension and metabolic alkalosis, should always cause you to deliberately consider hyperaldosteronism.



Liddle Syndrome

Liddle syndrome is a rare genetic cause of hypertension and hypokalemic metabolic alkalosis in which there is primary Na^+ retention, mediated by an activating mutation of the epithelial Na^+ channel in principal cells of the late distal tubule and cortical collecting duct. Renin and aldosterone levels are decreased. Liddle's is treated with amiloride or triamterene.

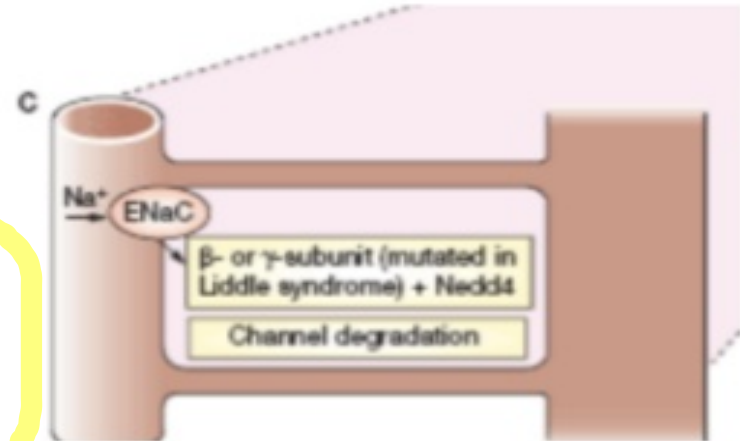
LIDDLE SYNDROME

Liddle syndrome is an autosomal dominant disorder caused by mutations in the β - or γ -subunit of the ENaC prevent binding to Nedd4 protein, which is involved in degradation of the channels.

The typical presentation of patients with Liddle syndrome includes early-onset severe hypertension, hypernatremia, hypokalemia, metabolic alkalosis in the setting of low plasma renin and aldosterone, low rates of urinary aldosterone excretion, and a family history of hypertension

The treatment is with a low sodium (low salt) diet and a potassium sparing diuretics (amiloride and triamterene) that directly blocks the sodium channel.

Spironolactone is not effective because it acts by regulating aldosterone and Liddle syndrome does not respond to this regulation.



Bartter and Gitelman Syndromes

Bartter's and Gitelman's usually are due to rare genetic or sporadic defects that cause abnormal solute transport in the thick ascending segment and the early distal tubule. Both are associated with severe sodium losses and eventual volume contraction with activation of the reninangiotensin-aldosterone system. Renin and aldo levels are increased. Release of aldosterone is the mechanism for development of hypokalemia and alkalosis.

Bartter syndrome (4 types) is typically an autosomal recessive disorder, in which there is abnormal solute transport in the thick ascending segment that results in loss of Na, Cl, Ca, and Mg in the urine. Clinically, patients look like they are taking a loop diuretic. Bartter's type 4 has associated deafness. This syndrome sometimes presents in the neonatal period or early childhood due to salt-wasting and significant hypercalciuria, with stones or nephrocalcinosis.

Gitelman syndrome is caused by a defect in the Na^+/Cl^- -cotransporter in the early distal tubule. This transporter is normally inhibited by thiazide diuretics; hence, patients with Gitelman's appear clinically as if they are taking a thiazide diuretic, except the patients have severe magnesium-wasting that is incompletely understood. Gitelman's is milder than Bartter's and generally presents later with symptoms of muscle weakness, cramps, and spasms due to hypomagnesemia.

Summarizing these 2 syndromes:

- **Both** cause **hypokalemic metabolic alkalosis** and salt-wasting without HTN.
- Bartter's: defect = furosemide-sensitive transporter; less common, childhood, disease of thick ascending limb, sometimes deafness, significant hypercalciuria.
- Gitelman's: defect = thiazide-sensitive transporter; more common, later presentation, disease of early distal tubule, significant hypomagnesemia, and hypocalciuria.
- The easiest way to distinguish Bartter's from Gitelman's: Bartter's patients have **hypercalciuria**, Gitelman's patients have **hypocalciuria**. This is easy to remember because loop diuretics are sometimes used to treat hypercalcemia (increase urinary calcium excretion), and thiazide diuretics are sometimes used to treat calcium-containing kidney stones (decrease urinary calcium excretion).

Table 4-8: Comparison of Bartter and Gitelman Syndromes

	Bartter Syndrome	Gitelman Syndrome
Onset	Infants/Children	Early adults
Low K, metabolic alkalosis	+	+
Low Mg	+	+
Hypocalciuria	—	+
Chondrocalcinosis	—	+
Defect	Ascending loop	Distal convoluted tubule
Looks like patient is taking ...	A loop diuretic	A thiazide diuretic

Bartter's syndrome

Features	Bartter Syndrome (Mimics Loop Diuretics)	Gitelman's Syndrome (Mimics Thiazide Diuretics)
Inheritance	• Autosomal recessive disorder.	• Autosomal recessive disorder
Pathophysiology	• Genetic defect in the thick ascending limb of the Loop of Henle • Defects in Na-K-2Cl co-transporter, K or Cl channels result in lack of concentrating ability	• Genetic defect in the distal tubule • Defect in Na-Cl cotransporter in the distal tubule
Age of Presentation	• Early in life.	• Late childhood or early adulthood.
Clinical presentation:	• No Hypertension 🚫 • Polyuria and polydipsia common • Neuromuscular symptoms are uncommon or mild Often presents with sensorineural deafness, triangular facies with drooping mouth, large eyes and pinnae, and renal failure.	• No Hypertension (Can see lower than average blood pressure due to salt wasting). • Polyuria and nocturia in 50-80%. • Often present with neuromuscular symptoms such as muscle cramping and spasms, 🚫 significant fatigue.
Lab data:	• Chloride resistant metabolic alkalosis • Hypokalemia • Normal serum magnesium (may be low). • Increased Urinary Calcium Excretion (Hypercalciuric so at risk for kidney stones or nephrocalcinosis)	• Chloride-resistant metabolic alkalosis • Hypokalemia. • Hypomagnesemia • Decreased Urinary calcium excretion • Hypocalciuric so no increased risk of kidney stones or nephrocalcinosis)
Renal PGE2 production	• Increased 🚫	• Normal

✳ Note that serum calcium tends to be normal in patients with Gitelman's Syndrome due to **lower PTH levels, Increased plasma renin and aldosterone/ K⁺ ratio.** → (P)

Presentation	Diagnosis
Hypokalemic Metabolic alkalosis with Hypertension	Liddle's Syndrome
Hypokalemic Metabolic Alkalosis without Hypertension	Bartter Syndrome (Increased Urinary Ca Excretion) Gitelman's Syndrome (Decreased Urinary Ca Excretion)

Site	Reduced function (responsible proteins)	Increased function (responsible proteins)
Thick ascending limb	Bartter syndrome (NKCC2, ROMK, CLC-Ka and Kb, Barttin*, CaSR)	---
DCT	Gitelman syndrome (NCC, CLC-Kb)	Gordon syndrome (WNK1, WNK4, KLHL3, CUL3)
Collecting duct	Pseudohypoaldosteronism type 1 (ENaC, mineralocorticoid receptor)	Liddle syndrome (ENaC)

*β subunit of CLC-Ka and Kb

A Clinical Approach to Hypokalemia

It's hard to remember all of the conditions associated with low serum K⁺. The most helpful way to approach hypokalemia is to categorize patients according to whether or not they have a metabolic acid-base disorder, then whether or not they have hypertension.

Hypokalemia+ NAGMA without HTN:

- K⁺ loss is usually from diarrhea or Type 1 or 2 RTA.
- Clinical history and the UAG help differentiate. UAG is neGUTive in diarrhea, UAG is positive in RTA.

Hypokalemia+ metabolic alkalosis+ HTN:

- Diuretics (most common) causing contraction alkalosis. The urine sodium is increased in spite of the volume contraction.
- Hyperaldosteronism (primary or secondary).
- Cushing syndrome.
- Liddle syndrome .
- Adrenal hydroxylase deficiencies.

Hypokalemia+ metabolic alkalosis without HTN:

- Bartter syndrome
- Gitelman syndrome

CALCIUM

Overview

Calcium is regulated by PTH and vitamin D metabolites, which affect rates of absorption in the kidneys and gut and rates of resorption of bone.

The measured plasma calcium concentration is a total of free/ionized calcium (45%), calcium bound to albumin (40%), and calcium bound to other substances (15%). Ionized calcium is the state available for immediate use by the body and correlates with consequences of hyper- or hypocalcemia. Measure ionized calcium directly to get the most reliable assessment of a patient's calcium status

Routinely, however, we measure the total plasma calcium.

If albumin decreases, the measured plasma calcium decreases, and you need to make a mathematical correction to estimate true calcium concentration (or measure an ionized calcium level to be precise). For each 1 g/dL decrease in albumin, increase the measured plasma calcium by 0.8 mg/dL. In pregnancy, calcium absorption and excretion is increased because the active form of vitamin D, 1,25-(OH)₂-D, is > 2x normal.

Hypercalcaemia: causes

Thiazides cause hypercalcaemia

The most common causes of hypercalcaemia are primary hyper-parathyroidism and malignancy (90 %).

In the presence of hypercalcaemia and hypophosphataemia, is highly suggestive of hyperparathyroidism.

The most common causes of hypercalcaemia are:

1. primary hyperparathyroidism (**Thyrotoxicosis**) due to increased bone turnover.
 - The most useful investigation is → Sesta MIBI scan of the neck
2. malignancy (bone metastases, myeloma, PTHrP from squamous cell lung cancer)
 - In malignancy, roughly 80% of cases are due to parathyroid-hormone-related peptide release. The vast majority of remaining cases are due to osteolysis, and some due to calcitriol-mediated hypercalcaemia and ectopic PTH secretion.
 - Raised alkaline phosphatase associated with hypercalcaemia is more likely to be due to bony metastases;
 - Normal alkaline phosphatase raises the possibility of underlying myeloma.
 - The LFTs show increased globulin fraction (TP-ALB) indicating the possibility of myeloma.
 - In myeloma, hypercalcaemia is primarily due to increased osteolysis and high-dose steroids - e.g. prednisolone 40 mg od can rapidly reduce the calcium level.
 - malignancy should be considered in hypercalcaemia without hypophosphataemia.
 - the best initial investigation to contribute to the underlying diagnosis → Skeletal survey

- **Tertiary hyperparathyroidism**

- in a patient with chronic renal failure with prolonged hypocalcaemia the parathyroids become autonomous, even if renal function is improved with transplantation. This can **lead to hypercalcaemia**.
- Tertiary hyperparathyroidism occurs when PTH production becomes autonomous and levels do not fall once serum calcium is corrected with supplementation of calcium and vitamin D.
 - Note that secondary hyperparathyroidism is a response to hypocalcaemia, not a cause of hypercalcaemia.

- **Sarcoidosis** (Granulomatous disease - sarcoidosis, leprosy, TB and histoplasmosis)

- Increased intestinal absorption is the main cause for raised calcium levels in sarcoidosis due to increased production of 1,25-OH vitamin D from activated pulmonary macrophages
 - Sarcoidosis → activated pulmonary macrophages → ↑vitamin D → ↑intestinal absorption of Ca → ↑Ca

- **vitamin D intoxication**

- **Increased sun exposure** results in increased vitamin D production.
- Patients often drink more cola drinks whilst on holiday, leading to increased phosphate intake.
- The combination of increased vitamin D and phosphate availability in the presence of sarcoidosis is thought to lead to hypercalcaemia.

- **acromegaly**

- **Milk-alkali syndrome**

- **Milk-alkali syndrome** - the triad of hypercalcaemia, metabolic alkalosis and renal impairment secondary to the ingestion of large amounts of calcium and absorbable alkali (such as sodium bicarbonate for the treatment of peptic ulcer disease).
- **The age of the patient, the dyspeptic symptoms and the raised bicarbonate level suggest the most likely diagnosis is the milk-alkali syndrome, caused by the ingestion of antacids.**
- The condition can lead to mild renal impairment, but this may well return to normal once calcium intake is reduced.

- **drugs:**

- thiazides, → reduce excretion → hypercalcaemia.
(Furosemide → hypocalcaemia but thiazides → hypercalcaemia).
- calcium containing antacids
- **lithium,**
- vitamin D overdose,
- vitamin A toxicity (including analogs used to treat acne)

- **dehydration**

- **Addison's disease**

- **Paget's disease of the bone****

- ****usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation**

- **Infections: HIV, histoplasmosis**

Differentiate between hypercalcaemia in primary hyperparathyroidism and malignancy:

- in primary hyperparathyroidism
 - ⇒ Parathyroid hormone is elevated or normal
 - ⇒ calcium level is often $< 3 \text{ mmol/l}$
 - ⇒ Hypercalcaemia is often asymptomatic and might have been present for months or years.
- in malignancy
 - ⇒ patients are usually acutely ill
 - ⇒ often with neurological symptoms
 - ⇒ calcium level is usually $> 3 \text{ mmol/l}$
 - ⇒ Parathyroid hormone is suppressed
 - ⇒ Cancer (eg lung, breast or myeloma) is often clinically apparent.

Features

Features include the classic mnemonic, "**bones, stones, groans, and moans**":

- **Bones** - bone pain, especially if the PTH is elevated
- **Stones** - renal calculi
- **Groans** - constipation and likely subsequent abdominal pain
- **Psychic moans** - depression and confusion

- **Musculoskeletal manifestations (Bones)**

- Bone pain
- Malaise, fatigue, muscle weakness
- **Osteoporosis** of cortical bone, such as the wrist, is mainly associated with primary hyperparathyroidism.
- Excess PTH also can result in **subperiosteal resorption**, leading to **osteitis fibrosa cystica** with bone cysts and **brown tumors** of the long bones.

- **Renal manifestations (Stones)**

- **polydipsia and polyuria**
 - due to a type of nephrogenic diabetes insipidus - modification of the renal response to antidiuretic hormone causing dehydration.
- **Dehydration** → thirst
- **nephrolithiasis** resulting from hypercalciuria.
- **nephrocalcinosis**.

- **Gastrointestinal manifestations (Groans)**

- **abdominal pain**,
- Nausea, anorexia, dyspepsia,
- constipation
- **peptic ulcer disease**
 - Calcium stimulates gastrin release and promotes increased secretion of gastric acid.
- **pancreatitis**

- **Neurological manifestations (Psychic moans)**

- **impaired concentration**, confusion,
- **Hyporeflexia**
- **corneal calcification**,
- **depression**

- Cardiovascular manifestations
 - hypertension,
 - vascular calcification
 - Cardiac arrhythmias are rare.
 - ECG changes include:
 - **Short QT interval** → significantly increases the risk of cardiac arrhythmias.
 - PR prolongation (but is much less common than QT shortening).
 - Bradycardia
 - Ventricular fibrillation has been reported in extreme cases.
 - widened T waves
 - In severe hypercalcaemia J (osborn) waves can be seen.
- Others
 - Itching
 - Keratitis, conjunctivitis
 - Hypokalaemia
 - hypercalcaemia → ↓ reabsorption of potassium, promoting its loss in the urine.

MECHANISM OF VOLUME DEPLETION IN HYPERCALCEMIA

- High calcium levels inhibit the effect of ADH on the collecting duct, inducing nephrogenic diabetes insipidus.
- High calcium filtration also promotes osmotic diuresis.

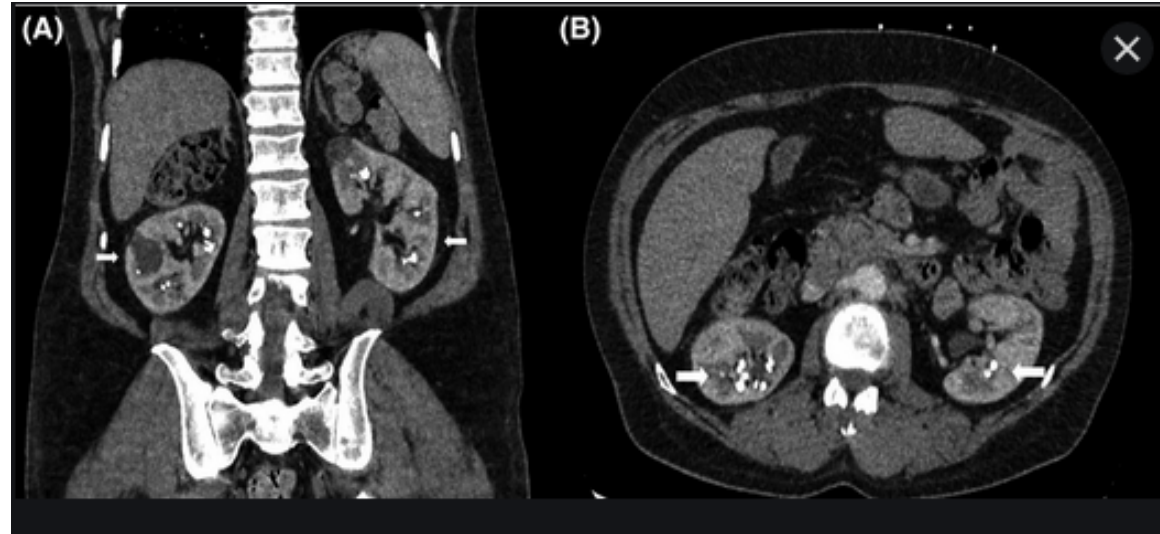
Osteitis fibrosa cystica



Image from Wikipedia.org, licensed under available at wikipedia.org/wiki/File:Osteitis_fibrosa_cystica_tibiae_X-ray.jpg



Nephrocalcinosis, once known as Albright's calcinosis after Fuller Albright, is a term originally used to describe deposition of calcium salts in the renal parenchyma due to hyperparathyroidism. The term **nephrocalcinosis** is used to describe the deposition of both calcium oxalate and calcium phosphate



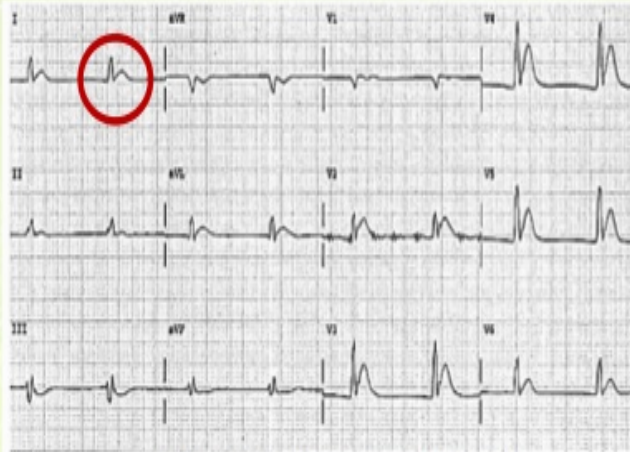
QT interval

1. A prolonged QT:

(Hypokalaemia, Hypomagnesaemia, Hypocalcaemia, Hypothermia, Myocardial ischemia, Post-cardiac arrest, Raised intracranial pressure, Congenital long QT syndrome, DRUGS)

2. A short QT:

1. familial/genetic:
(short Q-T syndrome)
1. Digoxin toxicity
2. Hypercalcemia
3. Hyperthermia



Marked shortening of the QTc (260ms) due to hypercalcaemia

Table 3. Systemic Etiologies for Pruritus

Autoimmune

Dermatitis herpetiformis
Dermatomyositis
Linear immunoglobulin A disease
Sjögren syndrome

Hematologic

Hemochromatosis
Iron deficiency anemia
Mastocytosis
Plasma cell dyscrasias
Polycythemia vera

Hepatobiliary

Biliary cirrhosis
Chronic pancreatitis with obstruction of biliary tracts
Drug-induced cholestasis
Hepatitis, particularly hepatitis C
Sclerosing cholangitis

Infectious disease

AIDS
Infectious hepatitis
Parasitic disease (giardiasis, onchocerciasis, schistosomiasis, ascariasis)
Prion disease

Malignancy

Leukemia
Lymphoma
Multiple myeloma
Solid tumors with paraneoplastic syndrome

Metabolic and endocrine

Carcinoid syndrome
Chronic renal disease
Diabetes mellitus
Hyper/hypothyroidism
Hyperparathyroidism

Neurologic

Cerebral abscess
Cerebral tumor
Multiple sclerosis
Stroke

Other

Drug ingestion
Eating disorders with rapid weight loss
Neuropsychiatric disorders
Pregnancy

Information from references 2, 3, 5, 7, 9, and 10.

Systemic diseases	Examples of diagnoses
Endocrine and metabolic diseases	Chronic renal failure, liver diseases with or without cholestasis, hyperthyroidism, malabsorption, perimenopausal pruritus
Infectious diseases	HIV-infection, helminthosis, parasitosis
Hematological and lymphoproliferative diseases	Iron deficiency, polycythemia vera, Hodgkin's disease, non-Hodgkin's lymphoma, plasmacytoma
Visceral neoplasms	Solid tumors of the cervix, prostate, colon, carcinoid syndrome
Pregnancy	Pruritus gravidarum with and without cholestasis
Drug-induced pruritus (selection)	Opioids, ACE-inhibitors, amiodarone, hydrochlorothiazide, estrogens, simvastatin, hydroxyethyl starch, allopurinol

ACE: Angiotensin-converting enzyme

Table 1. Historical Findings That Suggest Etiologies for Pruritus

<i>Historical finding</i>	<i>Possible etiologies</i>
New cosmetics or creams	Allergic contact dermatitis, urticaria, photodermatitis
New medications, supplements, or illicit drugs	Urticaria, fixed drug eruptions
Recent travel	Pediculosis, scabies infestation, photodermatitis, urticaria
Hobby or occupational exposure to solvents, adhesives, cleaners	Irritant contact dermatitis, xerosis, atopic dermatitis, eczema
New animal exposures	Flea infestation, allergic contact dermatitis, urticaria
Sick contacts, especially those with febrile diseases and rashes	Rubeola, mumps, varicella, scarlet fever, cellulitis, fifth disease, folliculitis
Unexplained weight changes, menstrual irregularity, heat/cold intolerance	Thyroid disease with secondary urticaria or xerosis
Unexplained weight loss, night sweats, unexplained fevers, fatigue	Lymphoma with secondary generalized pruritus
Malaise, nausea, decreased urine output	Renal failure with generalized pruritus

Interpreting Laboratory Values in **Hypercalcaemia**

Condition	Serum Phosphate	Serum Alkaline Phosphatase	Urine Calcium	Urine Phosphate	PTH
Hyperparathyroidism	Low	Normal-high	High (in 67% of patients)	High	High
Vitamin D excess	Normal-high	Low	High	High	Low
Malignancy	Often low	High (except in haematological malignancy, when normal)	Variable	High	Variable
Granulomatous disease	Normal-high	Normal-high	High	Normal	Low
Calcium alkali syndrome	Normal-high	Normal	Normal	Normal	Low
Familial hypocalciuric hypercalcaemia	Normal or low	Normal	Low (<200 mg/day)	Normal	High

Hypercalcaemia: management

- The initial management of hypercalcaemia is rehydration with normal saline, typically 3-4 litres/day.
 - The most appropriate management is with 0.9% sodium chloride.
 - If the sodium level were 150 or above an initial treatment would be with 0.45% sodium chloride reverting to 0.9% sodium chloride when the sodium concentration fell below 150.
 - gentle hydration with intravenous saline may be enough but if congestive heart failure ensues or if more rapid lowering of serum calcium is desired, a loop diuretic will enhance calcium excretion
 - ECF volume depletion must be avoided because this will worsen hypercalcaemia
 - in a setting of renal insufficiency, higher doses of loop diuretics are needed
 - intravenous saline plus a loop diuretic should decrease the serum calcium rapidly, usually by 0.25-0.75 mmol/L in 1 or 2 days. if this reduction is insufficient bisphosphonate may be required.
- Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days
 - If calcium is still elevated despite adequate hydration with saline. The most appropriate next step is to give pamidronate, a bisphosphonate, to inhibit bone resorption and formation, thus reducing bone turnover.

In the context of hypercalcaemia secondary to malignancy the below advice is suggested by NICE:

- Advice about maintaining good hydration (drinking 3 - 4 L of fluid per day), provided there are no contraindications (such as severe renal impairment or heart failure).
- Reassure that a low calcium diet is not necessary, as intestinal absorption of calcium is usually reduced.
- Advise the person to avoid any drugs or vitamin supplements that could exacerbate the hypercalcaemia.
- Encourage mobilization where possible to avoid exacerbating the hypercalcaemia.

Other options include:

- **calcitonin - quicker effect than bisphosphonates**
 - If hydration and furosemide do not control the calcium and you need something faster than a bisphosphonate, then calcitonin is the answer.
 - Calcitonin use is limited by its association with anaphylaxis.
- Non-steroidal anti-inflammatory drugs (NSAIDs) **should not be prescribed** in patients with hypercalcaemia as they reduce renal blood flow thus inhibiting urinary calcium excretion.
- **steroids in sarcoidosis**
- There is a limited role for the use of furosemide in hypercalcaemia. It may be useful in patients who cannot tolerate aggressive fluid rehydration
- loop diuretics such as furosemide increase urine calcium excretion but may also induce ECF volume depletion, increasing renal calcium resorption and worsening the hypercalcaemia

Parathyroidectomy:

NICE guidelines clearly stipulate the circumstances under which parathyroidectomy should be considered in primary hyperparathyroidism. These are listed below:

- **Age under 50 years.**
- Adjusted serum calcium concentration that is 0.25 mmol/L or more above the upper end of the reference range.
- Estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m² although this threshold depends on other factors, such as age.
- creatinine clearance reduced by 30% or more
- Renal stones or presence of nephrocalcinosis on ultrasound or CT.
- 24 hour total urinary calcium excretion greater than 10 mmol
- Presence of osteoporosis or osteoporotic fracture.
 - bone mineral density T-score less than -2.5 at any site
- Symptomatic disease
- unwillingness of patient to follow advice of medical surveillance.

Pseudohypercalcaemia

- **heat cramps**
 - (painful muscular cramping during or after exertion in hot environments).
 - The patient developed haemoconcentration and elevated protein (and albumin), leading to a phenomenon of pseudohypercalcaemia.
 - In this condition, the total serum calcium is high but the ionised calcium should be normal.
 - As a rule of thumb, the first step in the diagnostic evaluation of hypercalcaemia (and more often hypocalcaemia) should be to make sure that the "abnormality" in the total serum calcium levels is not due to abnormal albumin concentrations. In cases of
 - Only ionised (or free) calcium is physiologically active and should be checked if in doubt, such as in patients with very abnormal albumin level. Extensive investigation, such as protein electrophoresis, should be omitted if pseudohypercalcaemia is confirmed.
 - Pseudohypercalcaemia is asymptomatic and should not affect the ECG.
 - **the most appropriate immediate management → Intravenous saline infusion and check ionised calcium.**

Familial benign hypocalciuric hypercalcaemia (FHH)

- FHH is a rare, benign, **autosomal dominant** disorder
- due to a defect in the **calcium sensing receptor**
- pattern of inheritance with complete penetrance.
- The mutation causes a reduced ability of the calcium sensor to detect hypercalcaemia, so the body tolerates levels of serum calcium that would usually be said to be outside the normal range.
- It leads to **reduced calcium excretion** and **consequent mild to moderate hypercalcaemia**.

Feature

- asymptomatic hypercalcaemia (often diagnosed incidentally)
- Affected heterozygous patients typically present in childhood with the incidental discovery of:
 - **mild hypercalcemia**
 - **hypocalciuria**
 - **a normal PTH level**, and
 - **high-normal to frankly elevated serum magnesium levels**. can present with **renal stones**.
- Rarely, can be associated with episodes of acute pancreatitis.
 - **Management**
 - Mild → **adequate hydration to reduce the risk of stone formation**.
 - **Total parathyroidectomy effective for recurrent severe pancreatitis**.

Diagnosis

- We recommend a two-step diagnostic procedure (The diagnostic sensitivity of this setup is 98%)
 - First, the **calcium/creatinine clearance ratio is measured from a 24-h urine**.
 - Second, all patients with calcium/creatinine clearance ratio of 0.020 or less are tested for mutations in the **CASR gene**.

Treatment

- In general, FHH does not require treatment.
- individuals with FHH are typically advised to avoid parathyroidectomy

Hypocalcaemia

Parathyroid hormone is the single most useful test in determining the cause of hypocalcaemia

Causes

- $\downarrow\downarrow$ calcium and phosphate + $\uparrow\uparrow$ alkaline phosphatase $\rightarrow$ Osteomalacia
- normal calcium and phosphate + $\uparrow\uparrow$ alkaline phosphatase $\rightarrow$ Paget's disease
- Serum biochemistry is normal in osteoporosis, although alkaline phosphatase can be elevated following a fracture.
- vitamin D deficiency (osteomalacia) (Osteomalacia causes hypocalcaemia associated with a low serum phosphate, rather than a raised phosphate level)
- chronic renal failure
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH) (short fourth finger, round face, and mental retardation)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
 - Magnesium is needed to release PTH from the gland.
 - Patients with ileostomies can lose large amounts of magnesium through their stomas; hypomagnesaemia $\rightarrow$ $\downarrow\downarrow$ PTH $\rightarrow$ hypocalcaemia that is resistant to an increased provision of calcium
- Acute hyperphosphatemia: Phosphate binds with the calcium and lowers it.
- Fat malabsorption: This binds calcium in the gut.
- massive blood transfusion
 - anticoagulant citrate in the bags $\rightarrow$ citrate accumulation in blood $\rightarrow$ chelates (binds to) circulating ionized calcium (iCa) $\rightarrow$ $\downarrow$ plasma iCa.
- Acute pancreatitis may also cause hypocalcaemia.
- Contamination of blood samples with EDTA may also give falsely low calcium levels

Features

Hypocalcaemia: Trousseau's sign is more sensitive and specific than Chvostek's sign

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen a result of neuromuscular excitability

Features

- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- Carpopedal spasm (wrist flexion and fingers drawn together)
- Muscle cramps.
- Hyperreflexia
- Bronchospasm
- Laryngospasm
- Seizures
- if chronic: depression, cataracts

- **Trousseau's sign**
 - carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
 - wrist flexion and fingers drawn together
 - seen in around 95% of patients with hypocalcaemia and around 1% of normo-calcaemic people
- **Chvostek's sign**
 - tapping over parotid causes facial muscles to twitch
 - seen in around 70% of patients with hypocalcaemia and around 10% of normo-calcaemic people
- ECG changes are associated with hypocalcaemia:
 - Common: Corrected QT interval prolongation
 - Rare: Atrial fibrillation or torsade de pointes

Management

- acute management of severe hypocalcaemia is with intravenous replacement. The preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
- intravenous calcium chloride is more likely to cause local irritation
- ECG monitoring is recommended
- further management depends on the underlying cause

Primary hyperparathyroidism

MECHANISM OF PARATHYROID HORMONE (PTH) EFFECT

- Reabsorbs calcium at distal tubule
- **Excretes phosphate at proximal tubule**
 - A mnemonic to remember this is **PTH** = "**Phosphate Trashing Hormone.**"
- Activates vitamin D from 25 to the 1,25 dihydroxy form
 - increased activity of renal **1- α -hydroxylase** (which converts inactive 25-hydroxycholecalciferol into active 1, 25-dihydroxycholecalciferol),
- Reabsorbs both calcium and phosphate from bone

In exams primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level.

- the most common cause of hypercalcemia
- most commonly found in women between 50 and 60 years of age
- Two to three times more common in women than men.
- **most commonly due to a solitary adenoma**
- **Parathyroid carcinoma is more likely when PTH is grossly elevated**

Causes of primary hyperparathyroidism

- | | |
|-------------------------|------------------------|
| • 80%: solitary adenoma | • 4%: multiple adenoma |
| • 15%: hyperplasia | • 1%: carcinoma |

Parathyroid hormone has a number of direct effects:

- it enhances the release of calcium from bones by binding to osteoblasts which stimulates the formation of osteoclasts, and
- **it enhances reabsorption of calcium in the distal tubules.**

Features - 'bones, stones, abdominal groans and psychic moans'

The PTH level in primary hyperparathyroidism may be normal

- polydipsia, polyuria (Chronic hypercalcaemia can compromise the renal concentrating ability leading to polydipsia and polyuria from nephrogenic diabetes insipidus).
- peptic ulceration/constipation/pancreatitis
- bone pain/fracture (kyphosis due to osteoporosis)
- renal stones → calculi-induced hydronephrosis → Renal impairment
- depression , Confusion
- hypertension, Short QT syndrome on the ECG

Associations

- hypertension
- multiple endocrine neoplasia: MEN I and II
 - **The association of primary hyperparathyroidism and a gastrinoma would suggest a diagnosis of multiple endocrine neoplasia type 1.**

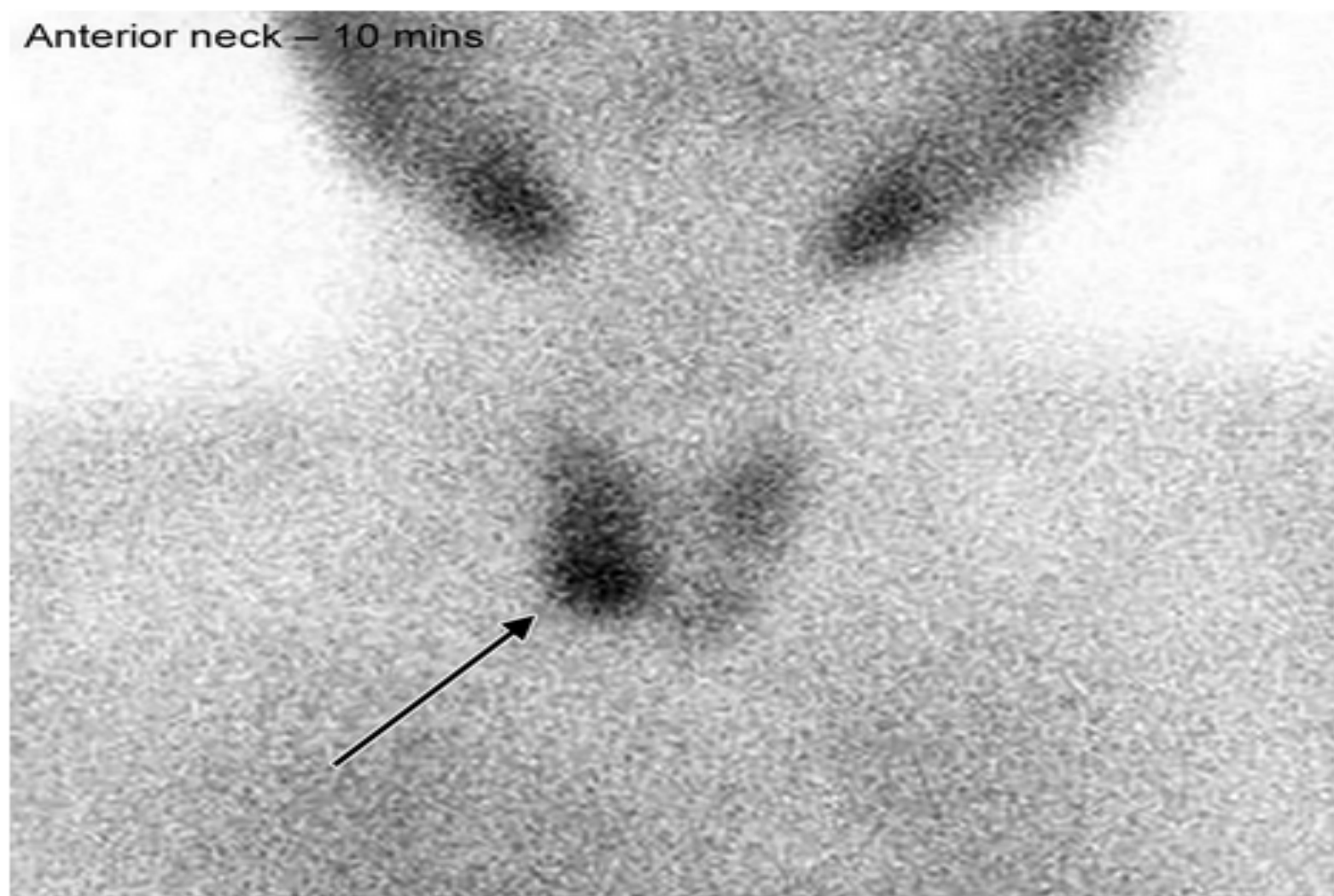
MECHANISM OF NEURAL INHIBITION IN HYPERCALCEMIA

- $\uparrow$ calcium levels $\rightarrow$ $\downarrow$ depolarization of excitable tissue such as nerves.
- $\uparrow$ calcium moves the threshold for depolarization away from the resting membrane potential.
- Bowels are a long muscular tube.
- $\uparrow$ calcium $\rightarrow$ $\downarrow$ smooth muscle contraction $\rightarrow$ constipation
- Low calcium = Hyperexcitable

Investigations

- raised calcium, low phosphate
 - **Hypophosphataemia is due to $\rightarrow$ reduced renal reabsorption of phosphate.**
 - **PO_4^{3-} is usually elevated or normal in Bone metastases (this clue could differentiate primary hyperparathyroidism from cancer metastases)**
- PTH may be raised or normal (**A high or even normal PTH concentration in the presence of hypercalcaemia would support the diagnosis of hyperparathyroidism**)
- technetium-MIBI subtraction scan
 - Technetium ($^{99\text{mTc}}$) sestamibi scanning has a high specificity and sensitivity for parathyroid adenoma.
 - **Sestamibi (Technetium-99m sestamibi) scanning** is most likely to inform on location of any adenoma prior to a surgical approach.
 - ❖ **The most sensitive and specific technique for tumor localization**
 - ❖ has a sensitivity of 90.7% and specificity of 98.8%.
 - ❖ Sestamibi is a derivative of technetium that avidly incorporates into mitochondria.
 - ❖ The large amounts of mitochondria in hyperactive parathyroid glands allow for more intense labeling of parathyroid tumors relative to the surrounding tissue.

Anterior neck – 10 mins



3A and B: Technetium Sestamibi scan (parathyroid scintigraphy) showing persistent tracer uptake at 90 min (shown in arrow) of the right inferior parathyroid adenoma. A B

Secondary hyperparathyroidism

- Raised PTH, low calcium, **high phosphate**, high alkaline phosphatase
- Due to chronic renal failure.

Feature

- Raised parathyroid hormone (PTH) (low calcium increases PTH release from the parathyroid glands)
- Low serum calcium (kidneys are involved in the activation of vitamin D)
- Raised serum phosphate (kidneys normally excrete phosphate so levels of the latter increase in renal failure)
- High alkaline phosphatase (renal osteodystrophy).

Mechanism

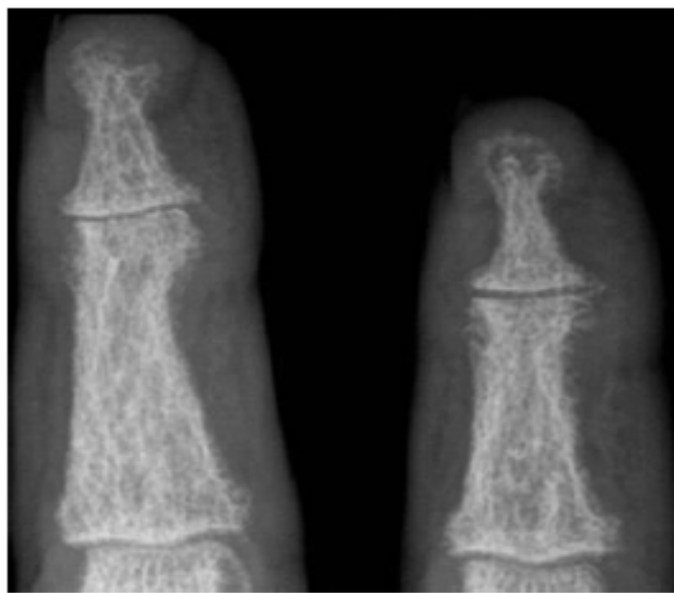
- occurs because of loss of tubules and decreased calcium absorption. Calcium wasting causes a reactive elevation in parathyroid hormone.
- kidneys are involved in the activation of vitamin D

Management

- **vitamin D replacement** (Alphacalcidol) normally given dose twice per week.
- Surgery may be considered if parathyroidism does not respond to medical management.
- NICE guidelines suggest only using cinacalcet in patients with end stage renal failure on renal replacement or in those who are unable to undergo surgery.

Hungry bone syndrome

- Hungry bone syndrome is an uncommon entity but can occur after parathyroidectomy if the hyperparathyroidism has been long standing.
- The mechanism is thought to be thus: high pre-operative levels of parathyroid hormone provide a constant stimulus for osteoclast activity creating the hypercalcaemic state by de-mineralizing the bones.
- This process can result in x-ray changes very similar to metastatic lytic lesions if left untreated. Upon removal of the parathyroid adenoma the hormone levels fall rapidly (they have a very short half life) and the osteoclast activity is subsequently diminished and the bones rapidly begin re-mineralisation - 'hungry bone syndrome'.
- This process can be uncomfortable and also result in systemic hypocalcaemia.



Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and sub-periosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

Hypoparathyroidism

Primary hypoparathyroidism

- decrease PTH secretion
 - e.g. secondary to thyroid surgery
 - **Frequency increased in alcoholics, particularly in association with hypomagnesaemia.**
 - Alcohol → Hypercalciuria & hypermagnesuria → hypocalcemia and hypomagnesemia → hypoparathyroidism (↓PTH & ↓Ca)
- low calcium, high phosphate
- treated with alfacalcidol

The main symptoms of hypoparathyroidism are secondary to hypocalcaemia:

- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- Trousseau's sign: carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- Chvostek's sign: tapping over parotid causes facial muscles to twitch
- if chronic: depression, cataracts
- ECG: prolonged QT interval

Pseudohypoparathyroidism

Pathophysiology

- Pseudohypoparathyroidism is caused by target cell insensitivity to parathyroid hormone (PTH) due to a mutation in **alpha subunit of** the G-protein.
- It is an autosomal dominant condition and is due to defects in the gene (GNAS1) encoding the alpha subunit of the stimulatory G protein (Gsa)
- **The G-protein-coupled receptor for parathyroid hormone (PTH) becomes unresponsive to the hormone, hence patients become hypocalcaemic in the face of normal or elevated PTH levels.**

Epidemiology

- occurs twice as frequently in females as in males.

Types

- type I: there is a complete receptor defect
- type II : the cell receptor is intact.

Bloods

- **PTH: high**
- **calcium: low**
- **phosphate: high**
- alkaline phosphatase: high

Features

- **short fourth and fifth metacarpals**
- **short stature**
- **obesity**
- **round face**
- **subcutaneous calcification**
- **cognitive impairment, low IQ**
- **dental hypoplasia**
- **Slipped femoral epiphysis**

Pseudopseudohypoparathyroidism

- similar phenotype to pseudohypoparathyroidism but normal biochemistry

Pseudohypoparathyroidism is when the defect is inherited from the **mother** while pseudopseudohypoparathyroidism is inherited from the **father**.

MAGNESIUM

Hypomagnesemia

Hypomagnesemia is **very common**. Causes are:

- **GI disease**, especially **small bowel-associated malabsorption**, **chronic diarrhea**, **acute pancreatitis**, and **small bowel bypass procedures**
- **Kidney losses**, especially **tubular disease** (**acute tubular necrosis**, **Bartter's**, **Gitelman's**) and **drugs** that affect the tubules (**loop** and **thiazide diuretics**, **amino-glycosides**, **amphotericin B**, **cisplatin**, **pentamidine**, **cyclosporine**, **tacrolimus**)
- **Miscellaneous causes**, e.g., **proton pump inhibitors** ([PPI]; unknown mechanism, but patients can be so severely depleted that levels rise only after the PPI is discontinued), **hungry bone syndrome** (after **parathyroidectomy**), **alcohol abuse**, **post-surgical state**, and **foscarnet use** (due to chelation)
- **Hypercalcemia**

The relationship between **calcium** and **magnesium** is difficult to remember. Here's the quick synopsis:

- **Both increased and decreased magnesium** can cause **hypocalcemia**.
- **Increased calcium** can cause **hypomagnesemia**.

The relationship between calcium and magnesium is difficult to remember. Here's the quick synopsis:

- Both increased and decreased magnesium can cause hypocalcemia.
- Increased calcium can cause hypomagnesemia.

Low magnesium also causes hypokalemia, so always check for low magnesium in patients presenting with hypocalcemia and/or hypokalemia because these

deficiencies are not correctable until magnesium stores (not just the serum level) are replenished!

Clinical manifestations of hypomagnesemia most often occur with other electrolyte and/or mineral derangements such as hypokalemia or hypocalcemia. Muscle weakness, spasms, and tetany are the more common neuromuscular manifestations. ECG abnormalities precede cardiac manifestations (wide QRS and peaked T waves). Refractory cardiac arrhythmias are associated with depleted magnesium stores (even with a normal serum level). Treatment can be oral in patients without symptoms, using a sustained release preparation—appreciating that the deficit is usually huge if the serum Mg level is low. Symptomatic patients should receive 50 mEq parenterally over 8–24 hours.

Hypermagnesemia

Hypermagnesemia, on the other hand, is rare and occurs from the use of:

- Mg-containing laxatives, antacids, or enemas in patients with renal failure (all are contraindicated in this group of patients)
- MgSO_4 over-infusion during eclampsia treatment
- Less common, but noteworthy, causes: tumor lysis syndrome, milk-alkali syndrome, lithium overdose, Epsom salts ingestion (even as a gargle)

Symptoms begin when magnesium level is $> 4-6 \text{ mEq/L}$. There is initial nausea, followed by sedation, muscle weakness, and a loss of deep tendon reflexes, progressing to paralysis (including heart and respiratory muscles).

Treatment: Treat acute symptoms with volume and calcium as an antagonist. Hemodialysis is necessary in renal failure. Do not forget about hypocalcemia, which can develop as a result of increased magnesium concentrations.

PHOSPHATE

Hyperphosphatemia

Hyperphosphatemia—acute increase can be from:

- ATN (especially if due to rhabdo)
- IV solutions
- Rapid cell turnover (tumor lysis or acute leukemia)

Chronic increase of phosphate is seen in:

- Chronic kidney disease
- Hypoparathyroidism

Hypophosphatemia

Hypophosphatemia—think **alcoholism** and **alcoholic ketoacidosis**. If severe ($\text{PO}_4 < 1 \text{ mg/dL}$), it may cause

rhabdomyolysis (as can low K^+), **cardiomyopathy**, **respiratory insufficiency with failure of diaphragm function**, and **nervous system problems**, initially consisting of irritability and hyperventilation, then profound muscle weakness, then seizures, coma, and death. **Refeeding** of malnourished patients, (think ICU patients) can cause severe hypophosphatemia by redistribution of phosphorus into cells.

Chronic malnutrition (as in alcoholics) results in **increased catabolic release of phosphate**, which then gets excreted by the kidneys, depleting total body stores. Even though an alcoholic may have a normal phosphate level on admission, he or she may become symptomatic with extreme muscle weakness a few days after a normal diet is established. This is because, as the glycogen level is returned to normal, the muscle cells become anabolic and take up phosphate, thereby reducing serum levels. This form of “refeeding hypophosphatemia” is a common clinical scenario.

Additionally, alcoholic patients with hepatic encephalopathy often have a respiratory alkalosis and may receive glucose solutions, both of which cause phosphate to enter cells, in turn causing severe hypophosphatemia, which may precipitate acute rhabdomyolysis.

Treatment of hypophosphatemia: Give supplemental phosphate to patients with DKA or those having alcohol withdrawal; it should be included in hyperalimentation fluid.

Patients with reduced renal function require less supplemental phosphate; phosphate supplementation may actually cause severe hyperphosphatemia.

