Electrolyte Disturbances
Part 2: Sodium

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Objectives:

- Recognize the signs and symptoms of hypernatremia and hyponatremia
- Determine the etiology of serum sodium derangements and assess the risks of overly rapid correction
- Develop a pharmacotherapeutic plan for the management of serum sodium disturbances

Sodium

Sodium: Basics

- Sodium is the most abundant extracellular cation
- Normal serum sodium 135 – 145 mEq/L
  - Changes in sodium usually reflect changes in water balance
- Sodium function in the body:
  - Sodium is one of the major determinants of serum osmolality which determines the distribution of water (water flows to compartment with highest osmolarity until osmotic equilibrium)
  - Normal serum osmolality: 275 – 295 mOsm/kg
  - Serum osmolality calculation:

Calculated Serum Osmolality (mOsm/kg) =
2 x Na + Glucose/18 + BUN/2.8 + ethanol/4.6

HypERnatremia

Hypernatremia: Review

- Serum sodium > 145 mEq/L reflects a water deficit
- Signs and symptoms: lethargy, thirst, hyperreflexia, seizure, coma
  - Severity of symptoms correlates with the rate of development of hypernatremia (acute hypernatremia > 160 mEq/L associated with high mortality rate > 75%)

Classification of Hypernatremia	Etiology
Hypovolemic hypernatremia	Loss of hypotonic fluids (vomiting, diarrhea, NG suctioning, osmotic diuresis (hyperglycemia), burns, open wounds, sweat
Isovolemic hypernatremia	Diabetes insipidus (central DI, nephrogenic DI)
Hypervolemic hypernatremia	Hypertonic NaCl administration, sodium bicarbonate solutions, mineralocorticoid excess (hyperaldosteronism)

Kraft MD, et al. Treatment of electrolyte disorders in adult patients in the intensive care unit. Am J Health Syst Pharm. 2005 Aug 15;62(16):1663-82.

Hypernatremia Pathogenesis

- Intake of salt or water loss do not usually cause hypernatremia since the rise in serum osmolarity stimulates antidiuretic hormone (ADH) release and thirst → to prevent further water loss and promote water intake
- Common causes of hypernatremia:
  - Elderly patients with dementia or disability, or patients with developmental delays who cannot communicate thirst or who cannot seek water for themselves due to immobility or unavailability
  - Enteral tube feeding without adequate free water flushes
  - Unreplaced electrolyte-free water loss (skin loss (excess sweating), GI losses (vomiting and osmotic diarrhea), osmotic diuresis (hyperglycemia or mannitol)
  - Central or nephrogenic diabetes insipidus (decreased release of ADH or renal resistance to its effect) → excretion of dilute urine

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Diabetes Insipidus

- Central diabetes insipidus is the decreased release of antidiuretic hormone (ADH) causing polyuria due to failure to reabsorb free water which may lead to hypernatremia
- Symptoms: polyuria, polydipsia, nocturia
- Causes:
  - Most common: idiopathic
  - Familial and congenital hypopituitarism
  - Tumor, trauma, neurosurgery involving hypothalamus or pituitary
  - Hypoxic encephalopathy or severe brain ischemia
  - Brain death (organ donor patients)
- Treatment: Desmopressin (DDAVP)
  - CAUTION CONVERTING BETWEEN DOSAGE FORMS (PO/intranasal/IV/SC)
  - PO: initial = 0.05 – 0.2 mg PO qhs, titrated to usual maintenance dose of 0.1 – 0.8 mg/day in divided 2 – 3 divided doses
  - Intranasal (delivers 10 mcg/spray): usual maintenance dose 10 – 20 mcg once or twice daily
  - IV/SC: 0.25 – 1 mcg every 12 – 24 hours

Christ-Crain M, et al. Diagnosis and management of diabetes insipidus for the internist: an update. J Intern Med. 2021 Jul;290(1):73-87.

Hypernatremia: Treatment

1. Calculate total body water (TBW)
2. Calculate Water Deficit = TBW x [serum sodium/140) – 1]
3. Administer fluids to correct 50% of the calculated water deficit in the first 24 hours
4. Fluid of choice is intravenous dextrose 5% in water (NEVER order water IV)
5. Do not lower the serum sodium too rapidly

Calculating Free Water Deficit

- Calculate total body water (TBW):
  - TBW (men) = 0.6 L/kg x weight (kg)
  - TBW (women) = 0.5 L/kg x weight (kg)

- Calculate water deficit:
  - Water deficit (liters) =
    TBW x [serum sodium/140) – 1]

Example:
67 kg female
Total Body Water = 33.5 L

If serum sodium is 156 mmol/L
Water deficit = 33.5 L x
[(156/140) – 1] = 3.8 L

Kraft MD, et al. Treatment of electrolyte disorders in adult patients in the intensive care unit. Am J Health Syst Pharm. 2005 Aug 15;62(16):1663-82.

Example: Hyponatremia

- 87-year old female (67 kg) with advancing dementia and immobility found by neighbors in a chair and concern she had not been eating or drinking for several days. Serum sodium = 156 mEq/L
  - Calculate total body water = 0.5 L/kg x 67 kg = 33.5 L
  - Calculate water deficit = 33.5 L x [(156/140)] -1] = 3.83 L water deficit
  - Correct 50% of water deficit in first 24 hours = 1.91 L
- How quickly can the serum sodium be corrected from 156 mEq/L to normal (135 - 145 mEq/L)
- What fluid should be ordered?
- What rate?

Treatment: Safe Sodium Correction

- If hypernatremia developed rapidly (over hours) correction is usually well tolerated because compensation mechanisms of adaptation have not yet fully occurred in response to imbalance

  - **Acute hypernatremia**: correct Na^+ by 1 – 2 mEq/L/hr
  - **Chronic hypernatremia (> 48 hours duration) or unknown:** correct Na^+ more conservatively no faster than 0.5 mEq/L/hr to avoid risk of cerebral edema (maximum 8 – 10 meq/L reduction of Na^+ in 24 hours)

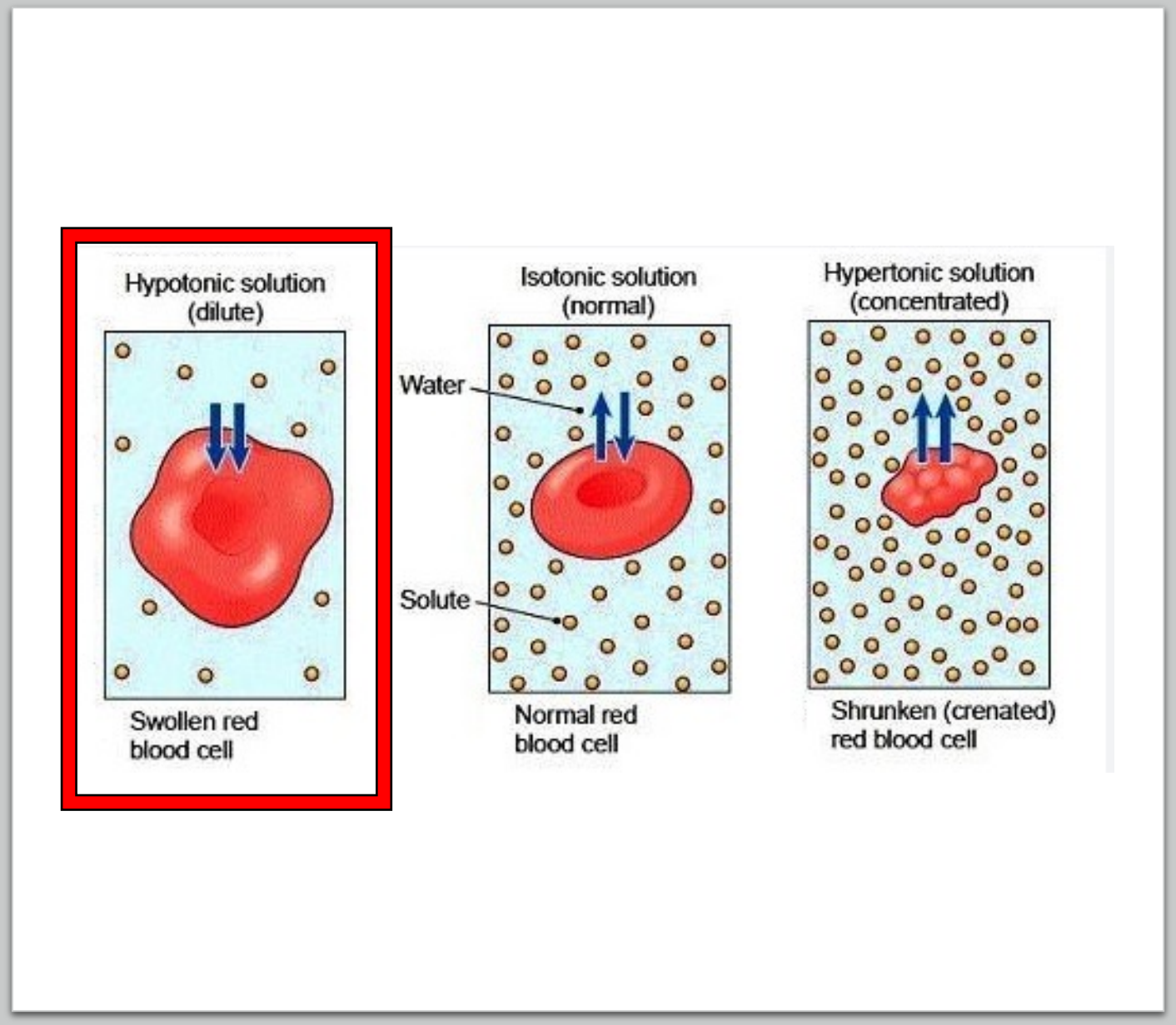
NEVER Order Water Intravenously

- A physician wanted to give “free water” to an elderly patient with severe hypernatremia and also hyperglycemia so he did not want to give additional sodium chloride or dextrose and instead ordered sterile water to be given intravenously at 100 mL/hr. The patient developed severe hemolytic anemia, acute renal failure, and died.

Water, Water, Everywhere, But Please Don't Give IV | Institute For Safe Medication Practices (ismp.org)

IV Administration of Hypotonic Fluids

- Intravenous fluids with an osmolarity that differs significantly from the normal range of serum osmolality (275 – 295 mOsm/kg) may cause harm when administered inappropriately
- When fluids are significantly hypotonic compared to cells, the water will shift to the higher tonicity inside the cell, causing swelling until the cell bursts (i.e. red blood cells hemolyze)
- Caution when ordering any IV fluid for continuous infusion that is < 154 mOsm/L (i.e. less than the osmolarity of 0.45% Sodium Chloride)



Treatment: Fluid Selection

Correct calculated water deficit over several days

- 50% of water deficit replaced in the first 24 hours with serial sodium monitoring every 2 – 4 hours

Choice of fluid to correct water deficit:

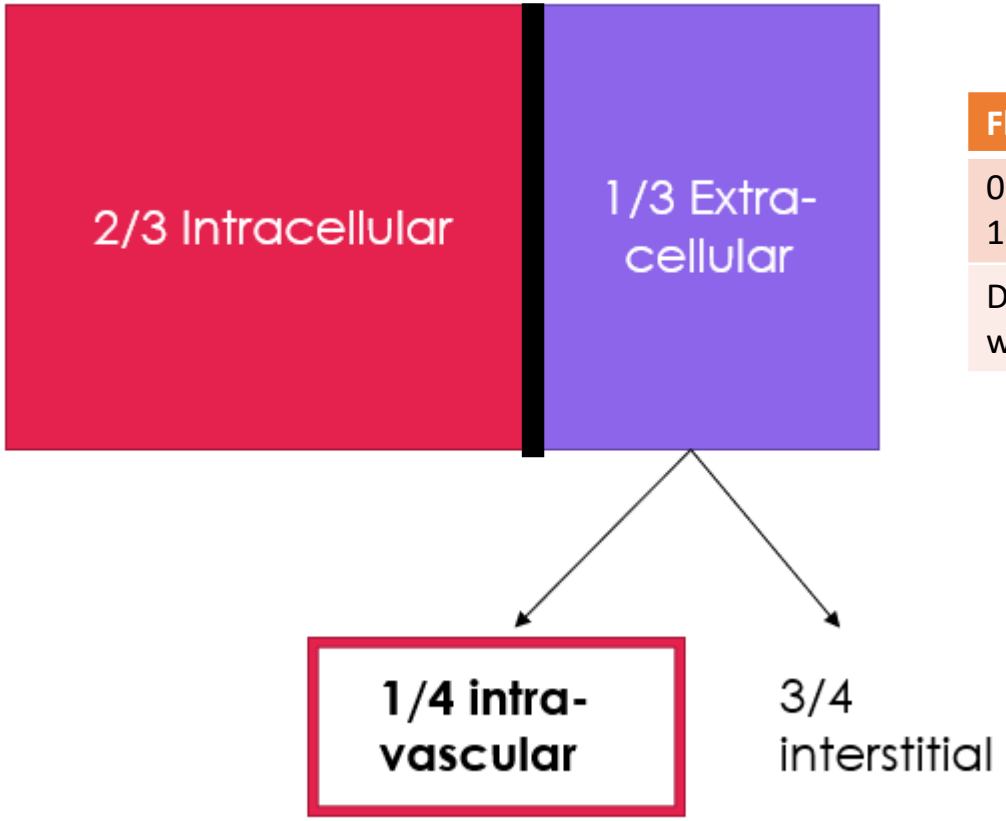
- Hypovolemic hypernatremia and *hypotensive:* initially use isotonic fluid until euvolemic and hemodynamically stable then change to D5W
  - Consider Lactated Ringers (osmolarity = 273 mOsm/L and contains 130 mEq Na/L)
- Euvolemic or hypervolemic:
  - IV: Dextrose 5% in water preferred, alternatives include D5/0.225% NaCL, or 0.45% NaCl
  - If non-severe asymptomatic hypernatremia and patient can swallow → may consider enteral water
  - Calculate expected change in sodium and monitor closely

Change in serum sodium per liter of IV infusion depends on the sodium content of the fluids infused:

Dextrose 5% in water (D5W)	• Change in serum sodium per L infused = (0 mEq Na/L – serum sodium)/(TBW + 1)
0.225% NaCl (with or without dextrose 5%)	• Change in serum sodium per L infused = (38.5 mEq Na/L – serum sodium)/(TBW + 1)
0.45% NaCl	• Change in serum sodium per L infused = (77 mEq Na/L – serum sodium)/(TBW + 1)

Body Fluid Compartments

Total Body Water = 0.5 L/kg (female), 0.6 L/kg (male)



Comparison of Distribution of IV Fluids:

Fluid	Intracellular	Extracellular	Intravascular	Interstitial
0.9% NaCl 1000 mL	0 mL	1000 mL	250 mL	750 mL
Dextrose 5% in water 1000 mL	667 mL	333 mL	83 mL	250 mL

Composition of Common IV Fluids

Fluid	Osmolarity (mOsm/L)	Na (mEq/L)	Cl (mEq/L)	K	Lactate (converts to HCO_3) (mEq/L)	Ca	Dextrose (g/L)
0.9% Sodium Chloride	308	154	154	0	0	0	0
0.45% Sodium Chloride	154	77	77	0	0	0	0
0.225% Sodium Chloride	77	38	38	0	0	0	0
Dextrose 5%	252	0	0	0	0	0	50
D5/0.9	560	154	154	0	0	0	50
D5/0.45	406	77	77	0	0	0	50
D5/0.225	321	38	38	0	0	0	50
D5/LR	525	130	109	4	28	3	50
Lactated Ringers	273	130	109	4	28	3 ppl	0
D2.5/0.45	204	77	77	0	0	0	25
D10	504	0	0	0	0	0	100
Sodium Chloride 3%	1025	513	513	0	0	0	0
Albumin 5%	310	145	0	< 1	0	0	0
Albumin 25%	312	145	0	< 1	0	0	0

Back to the Example:

- 87 year old female (67 kg) with advancing dementia and immobility found by neighbors in a chair and concern she had not been eating or drinking for several days. Serum sodium = 156 mEq/L
  - Calculate total body water = 0.5 L/kg x 67 kg = 33.5 L
  - Calculate water deficit = 33.5 L x [(156/140)] -1] = 3.83 L water deficit
  - Correct 50% of water deficit in first 24 hours = 1.91 L
- What fluid should be ordered? What rate?

- Until patient passes swallow evaluation, given age and likely confusion, best to correct the water deficit with dextrose 5% in water
- 50% of the calculated water deficit = 1.91 L (1910 mL) → divide by 24 hours = Dextrose 5% in water IV continuously at a rate of 80 mL/hr for first 24 hours with frequent re-assessment of serum sodium
- Remember the rule for correction →
  - Chronic hypernatremia (duration > 48 hours): correct conservatively no faster than 0.5 mEq/L/hr to avoid risk of cerebral edema (maximum 8 – 10 meq/L reduction of Na in 24 hours)

Example Continued…

- How rapidly will sodium level correct/lower when this patient is given Dextrose 5% in water infusion at 80 mL/hr (67 kg female, sodium 156 mEq/L?

Dextrose 5% in water (D5W)	• Change in serum sodium per L infused = (0 mEq/L – serum sodium)/(TBW + 1)

- 67 kg female → Total body water 0.5 L/kg = 33.5 L
- Change in serum sodium per L of D5W infused = (0 – 156 mEq/L)/(34.5 L) = 4.52 mEq per L of D5W
- 80 mL/hr x 24 hr = 1.9 L → if 1 L lowers sodium by 4.52 L, then 1.9 L expected to lower serum sodium by 8.6 mEq in 24 hr (within the safe limit of 8 – 10 mEq/24 hr)

EQUATIONS:

Total Body Water (TBW):
TBW (men) = 0.6 L/kg x weight (kg)
TBW (women) = 0.5 L/kg x weight (kg)

Water deficit:
Water deficit (liters) =
TBW x [serum sodium/140) – 1]

Change in serum sodium per LITER of D5W =
(0 mEq Na/L – serum sodium)/(TBW + 1)

Bottom Line: Treating Hypernatremia

Hypernatremia represents a free water deficit → Calculate it and correct 50% of the free water deficit in first 24 hours

Use Dextrose 5% in water as preferred "free water" replacement

Do not lower sodium faster than 0.5 - 1 mEq/L/hr (maximum 8 – 10 mEq/L per 24 hours) to prevent cerebral edema

HypOnatremia

Hyponatremia

- Serum sodium is determined by the content of sodium and the total body water
- Hyponatremia = serum sodium < 135 mEq/L
- Hyponatremia is complicated because it may reflect increased, decreased, or normal total body sodium concentration and develop in the presence of hypovolemia, hypervolemia, or normal plasma volume

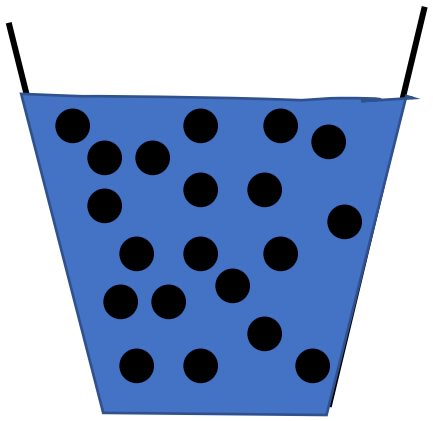
$$\text{Serum } [Na^+] = \frac{Na^+}{\text{Total Body Water}}$$

Hyponatremia

$$\text{Serum } [Na^+] = \frac{Na^+}{\text{Total Body Water}}$$

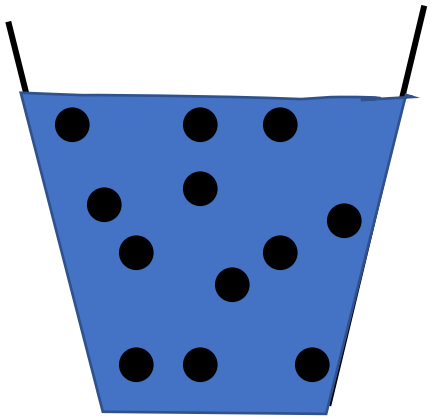
NORMAL

Normal serum sodium
Normal Sodium body content
Normal total body water



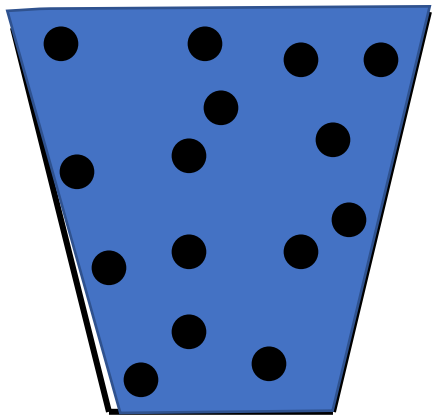
Euvolemic Hyponatremia

LOW serum sodium
LOW Sodium body content
Normal total body water



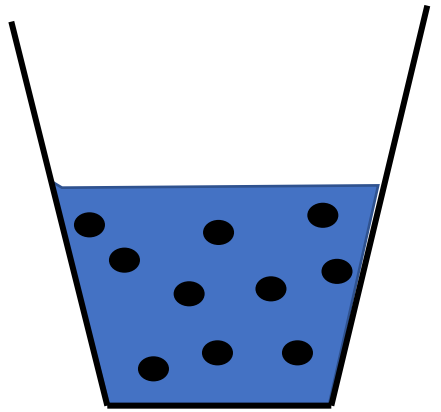
Hypervolemic Hyponatremia

LOW serum sodium
Normal Sodium body content
HIGH total body water



Hypovolemic Hyponatremia

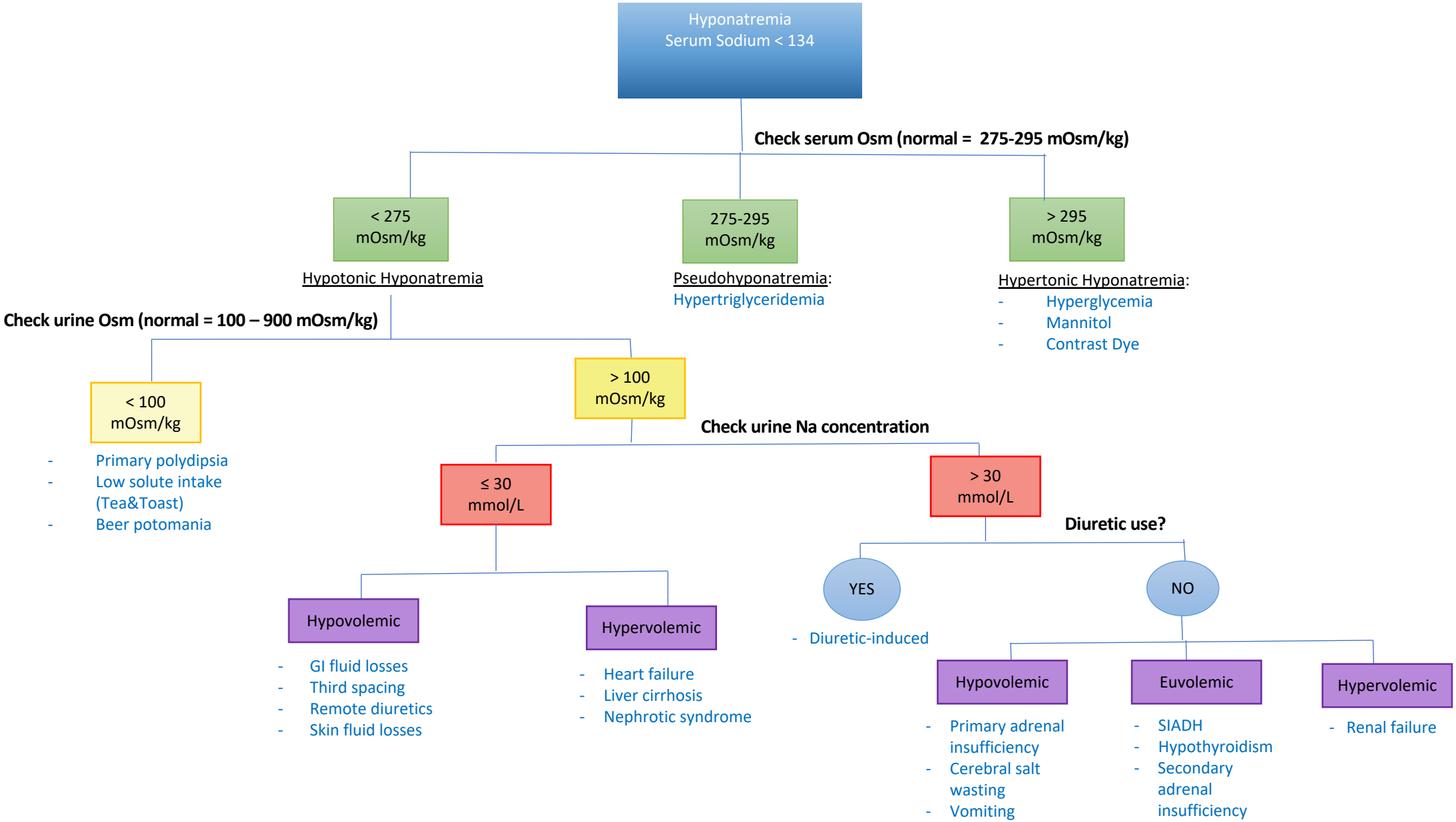
LOW serum sodium
LOW Sodium body content
LOW total body water



Hyponatremia: Diagnosis

- Headache, lethargy, disorientation, restlessness, nausea, vomiting, depressed reflexes, seizure, coma, death
- Work-up includes:
  - Immediately identify if severe symptoms that would warrant more rapid initial correction
  - Check serum osmolality
  - Rule out pseudohyponatremia (hyperglycemia, hypertriglyceridemia)
  - Obtain TSH and cortisol to rule out hypothyroid or adrenal insufficiency
  - Determine the chronicity (acute vs chronic (developed over > 48 hours))
  - Assess patient volume status
  - Check urine osmolality and electrolytes including urine sodium level

Kraft MD, et al. Treatment of electrolyte disorders in adult patients in the intensive care unit. Am J Health Syst Pharm. 2005 Aug 15;62(16):1663-82.


Hyponatremia
Serum Sodium < 134
Check serum Osm (normal = 275-295 mOsm/kg)
< 275 mOsm/kg
275-295 mOsm/kg
> 295 mOsm/kg
Hypotonic Hyponatremia
Pseudohyponatremia:
Hypertriglyceridemia
Hypertonic Hyponatremia:
- Hyperglycemia
- Mannitol
- Contrast Dye
Check urine Osm (normal = 100 – 900 mOsm/kg)
< 100 mOsm/kg
- Primary polydipsia
- Low solute intake (Tea&Toast)
- Beer potomania
> 100 mOsm/kg
Check urine Na concentration
≤ 30 mmol/L
> 30 mmol/L
Hypovolemic
- GI fluid losses
- Third spacing
- Remote diuretics
- Skin fluid losses
Hypervolemic
- Heart failure
- Liver cirrhosis
- Nephrotic syndrome
Diuretic use?
YES
- Diuretic-induced
NO
Hypovolemic
- Primary adrenal insufficiency
- Cerebral salt wasting
- Vomiting
Euvolemic
- SIADH
- Hypothyroidism
- Secondary adrenal insufficiency
Hypervolemic
- Renal failure

Pseudohyponatremia (secondary to hyperglycemia or hypertriglyceridemia)

- Always remember to correct serum sodium for hyperglycemia and hypertriglyceridemia
- Example: patients presenting with diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic syndrome (HHS) will often present with low sodium on basic metabolic panel
  - Hyperglycemia translocates water from cells into extracellular fluid transiently → calculate corrected sodium because it does not represent a clinically significant hyponatremia
- Equation (corrected sodium for hyperglycemia):

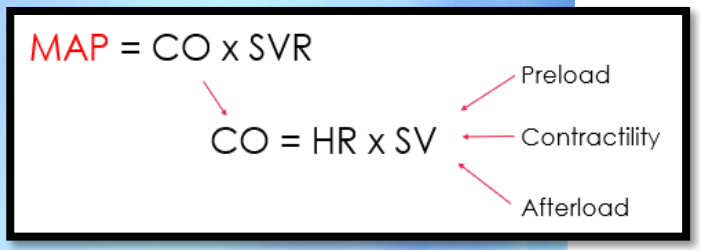
Corrected Sodium :

$$\text{Corrected Sodium [mEq/L]} = \text{Measured Sodium [mEq/L]} + 0.024 * (\text{Glucose [mg/dL]} - 100)$$

CHEM PROFILE	
Sodium	126
Potassium	5.1
Chloride	90
CO2	19
Anion Gap	17
Glucose	696
BUN	27
Creatinine	1.08
Calculated GFR	94

Example: corrected sodium = 126 + 0.024 x (696 mg/dL) – 100) = 140 mEq/L

Hypervolemic Hyponatremia: Heart Failure



Hyponatremia that is due to water retention diluting urine and serum osmolality

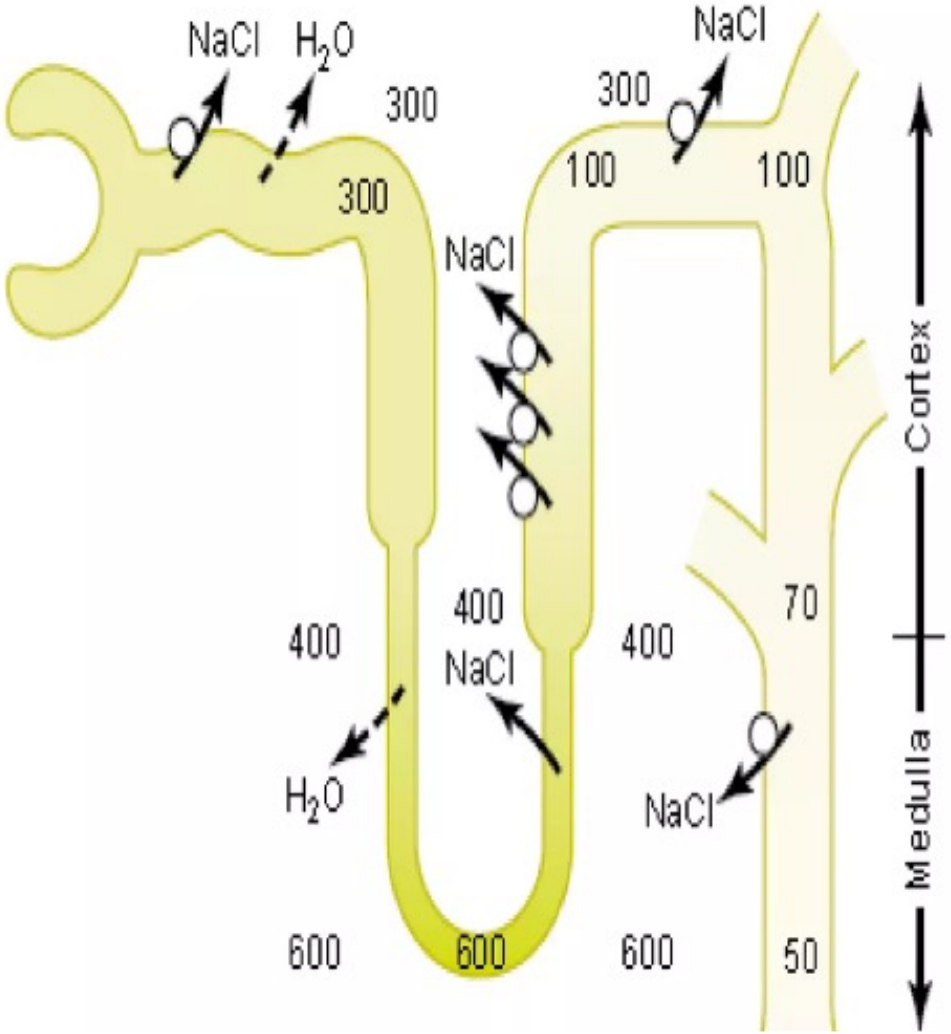
At an early stage of congestive heart failure decreased cardiac output and systemic blood pressure lead to increasing renin, angiotensin II, and ADH to cause vasoconstriction as well as water retention → leads to expansion of extracellular fluid volume and subsequent peripheral edema which may eventually suppress ADH and prevent clinically significant hyponatremia

At later stage of heart failure, even lower cardiac output further increases angiotensin II which limits water delivery to kidneys → further increases in ADH cause more water reabsorption → and in combination with use of diuretics and dietary sodium restriction patients may develop chronic hyponatremia

Leier CV, et al. Am Heart J. 1994;128(3):564.

Hypotonic Hyponatremia

- Major compensation of the body to prevent hyponatremia is the ability to excrete large volumes of dilute urine with low concentration of sodium
- Drinking water (hypotonic fluid) will suppress ADH → which removes water channels in the collecting duct thus water is not reabsorbed, rather it is excreted as dilute urine
- General US diet = 900 mOsm solute/day (urea from protein, sodium, potassium) and usual fluid intake is 2 – 2.5 L/day
- Maximum attainable urine volume in normal patients is 10 L/day and normal diluting mechanisms can make urine osmolality as low as 60 - 100 mOsm/kg
- However, when water intake exceeds water excretion hyponatremia will occur by a dilutional effect



Other Causes of Hypotonic Hyponatremia

- Beer potomania → malnourished alcoholic drinking large quantities of beer which contains mostly water and almost no sodium
  - Carbohydrates and alcohol energy suppresses protein breakdown so almost no solutes in urine to allow for normal concentrating mechanisms
  - Even with maximum urine dilution and volume, hyponatremia will result if > 4 L/day of water is ingested in a patient with poor solute intake (~ 12 cans of beer 12 oz each)

- Primary polydipsia due to psychosis → disorder causing increased thirst and excessive water intake
- Water intoxication can also occur without psychiatric condition

- 28-year old, mother of 3, died from water intoxication after participating in a radio contest "Hold Your Wee for a Wii" where participants were competing to drink the most water without using the restroom to win a video game console
- She drank two gallons of water (7.47 L) and vomited and had to quit. She developed a headache on her way home and was found dead
- Autopsy revealed she died of water intoxication

Water Intoxication

Other Causes of Hypotonic Hyponatremia:

Hypothyroid:

- Hypothyroidism-induced reduction in cardiac output stimulates carotid baroreceptors to release ADH (causing water reabsorption)

Adrenal insufficiency:

- Hyponatremia and hyperkalemia can be seen in primary adrenal insufficiency
- Cortisol deficiency may cause hypersecretion of ADH
- Aldosterone deficiency may cause renal sodium wasting (and also hyperkalemia since aldosterone normally promotes urinary excretion of dietary potassium)

Liamis G, et al. Management of endocrine disease: hypothyroidism-associated hyponatremia: mechanisms, implications, and treatment. Eur J Endocrinol. 2017 Jan;176-(1):R15-R20.
Mount D, et al. Hyponatremia and hyperkalemia in adrenal insufficiency. UpToDate. Updated January 2023.

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

- Normally water homeostasis is dependent upon tonicity →
  - ADH is secreted by the pituitary gland normally in response to *hypertonicity* and decreased effective arterial blood volume to promote water retention (activates vasopressin receptors in the nephron collecting duct to insert water channels (aquaporin 2) to increase water reabsorption ("antidiuresis")
- If ADH is released in the setting of *hypotonicity* (low serum sodium serum osmolality) this indicates there is a non-osmotic stimulus for ADH release → the reason it is deemed "inappropriate" to reabsorb more water and waste sodium in the presence of an already low serum sodium level
- To diagnose SIADH →
  - Serum osmolality and serum sodium are low
  - Rule out adrenal, thyroid, renal, hepatic, and cardiac causes of hyponatremia
  - Euvolemic
  - Urine sodium is > 30 mmol/L

Peri A, et al. SIADH: differential diagnosis and clinical management. Endocrine. 2017 Jan;55 (1):311-319.

Drug-Induced Hyponatremia

Drug-Induced Hyponatremia	
Increase sodium excretion	
Disrupt sodium/water hemostasis	• Thiazide diuretics (hydrochlorothiazide, chlorothiazide) • Amiloride • Thiazide-related (chlorthalidone, metolazone, indapamide) • Loop diuretics (furosemide, bumetanide, torsemide, etc)
Decrease water excretion (induce SIADH*)	
Increase central secretion of ADH	• Antidepressants (tricyclic, SSRIs, MAOIs) • Citalopram, escitalopram, amitriptyline, paroxetine, mirtazapine, sertraline, doxepin, venlafaxine, duloxetine) • Antipsychotics (risperidone, thioridazine, haloperidol, chlorpromazine, fluphenazine) • Antiepileptics (carbamazepine, oxcarbazepine, valproic acid, phenytoin, lamotrigine) • Chemotherapy (vinka alkaloids (vincristine), alkylating agents, cyclophosphamide) • Methotrexate • Opiates • MDMA (ecstasy)
Increase effect of endogenous ADH in kidney	• Carbamazepine • Lamotrigine • Tolbutamide • Cyclophosphamide • NSAIDS
Lower threshold of ADH secretion	• Venlafaxine • Carbamazepine

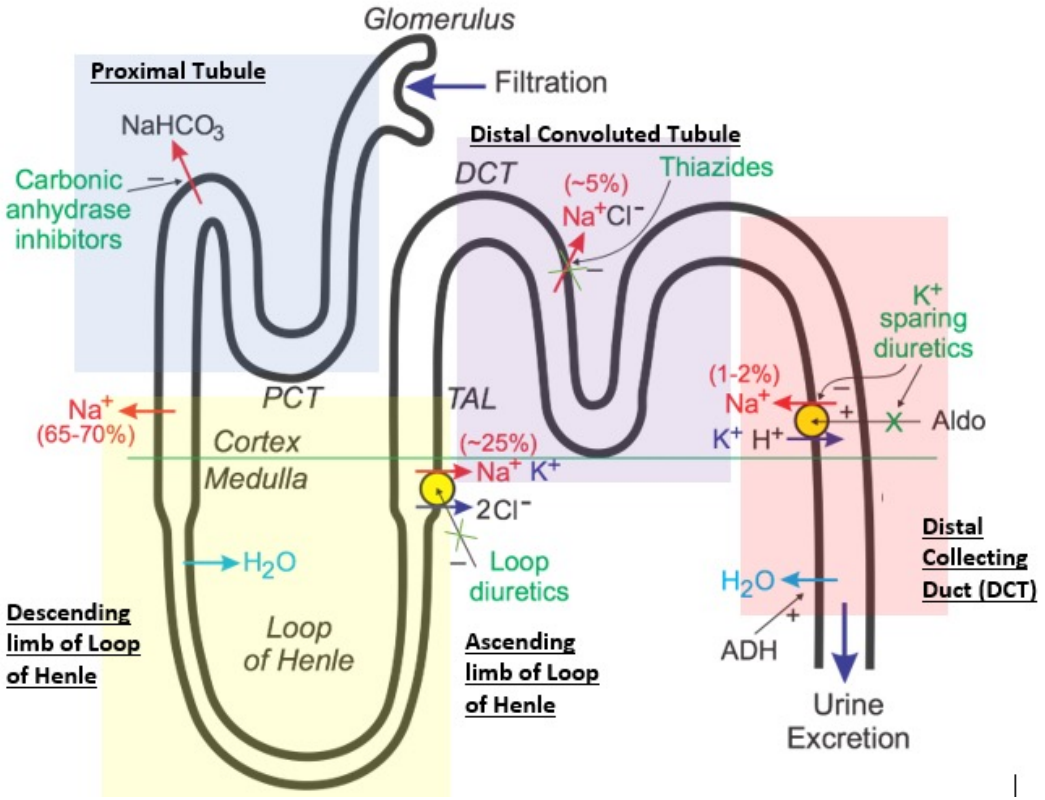
*SIADH = syndrome of inappropriate antidiuretic hormone

Liamis G, et al. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008 Jul;52(1):144-53.

MDMA/Ecstasy-Induced Hyponatremia

- Ecstasy (MDMA) is a synthetic drug used recreationally for mood-enhancing properties since it is an amphetamine derivative releasing neuroactive compounds such as serotonin, dopamine, and norepinephrine in the CNS
- Ecstasy is also known to increase levels of arginine vasopressin (aka antidiuretic hormone (ADH)) and to cause excessive thirst which leads to a perfect storm of SIADH and dilutional hyponatremia which can be severe
    - Severe cases of ecstasy-induced hyponatremia are more common in females aged 15 – 30 years

Campbell GA, et al. The agony of ecstasy: MDMA (3,4-methylenedioxymethamphetamine) and the kidney. Clin J Am Soc Nephrol. 2008 Nov;3(6):1852-60.

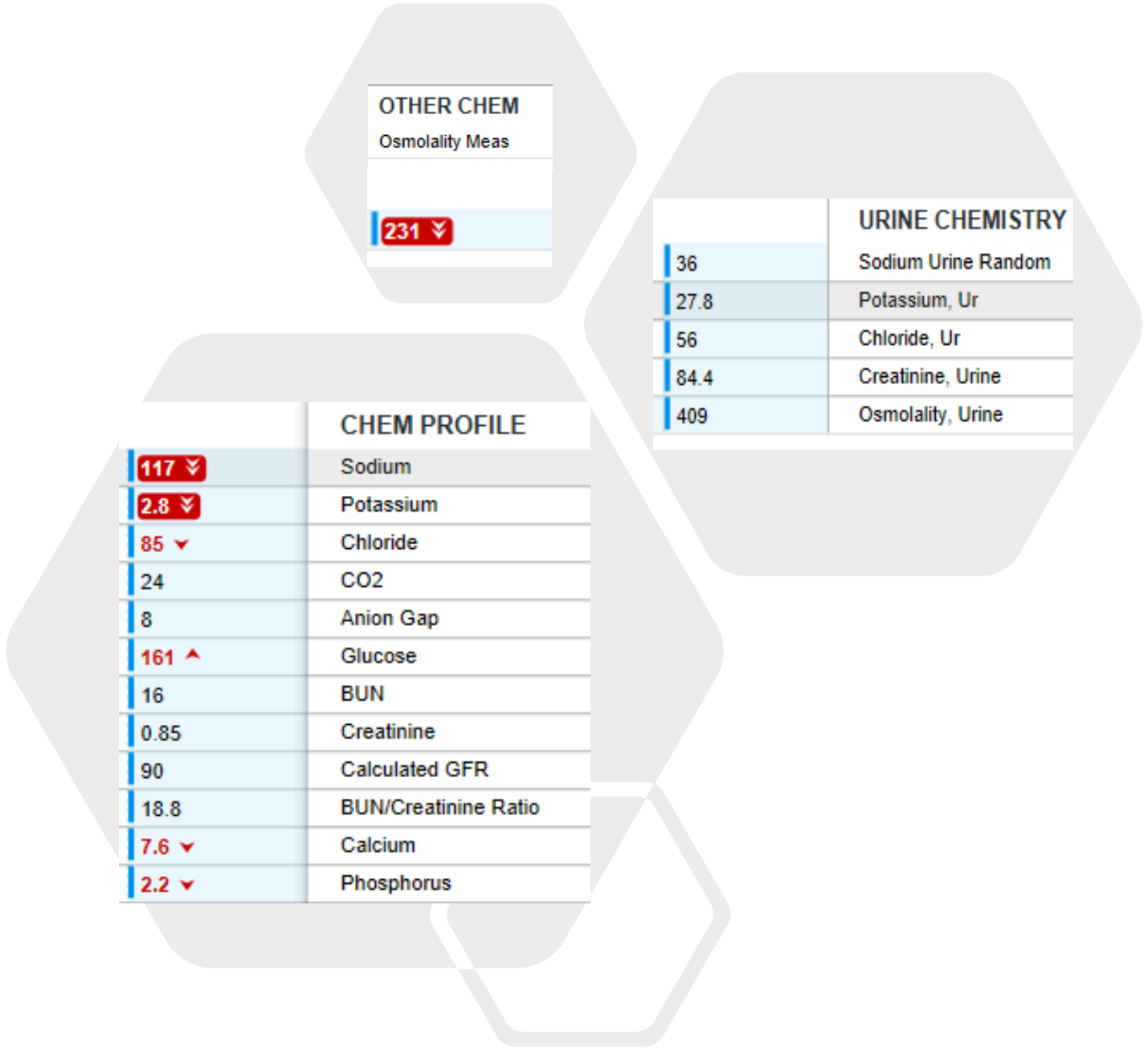


DIURETICS	MECHANISM OF ACTION
Thiazide diuretics: Hydrochlorothiazide, Chlorothiazide **Thiazide-related diuretics:** Chlorthalidone, metolazone, indapamide	Inhibits sodium reabsorption (by inhibiting the Na/Cl symporter) in the distal collecting tubule causing increased excretion of sodium and water as well as potassium and hydrogen ions
Loop diuretic: Furosemide, Bumetanide, Torsemide, ethacrynic acid	Primarily inhibits reabsorption of sodium and chloride (by inhibiting the Na/K/2Cl symporter) in the thick segment of the ascending loop of Henle and proximal and distal renal tubules, interfering with the chloride-binding cotransport system, thus causing its natriuretic effect
Potassium sparing diuretic and Aldosterone receptor antagonist: Spironolactone, eplerenone	Competes with aldosterone for receptor sites in the distal renal tubule, increasing sodium chloride and water excretion while conserving potassium and hydrogen ions; may block the effect of aldosterone on arteriolar smooth muscle.
Potassium sparing diuretic: Triamterene, amiloride	Block epithelial sodium channels in late distal convoluted tubule and collecting duct which inhibits sodium reabsorption from the lumen reducing intracellular sodium, decreasing the function of the Na/K/ATPase, leading to K retention and decreased Ca, Mg, H+ excretion. As sodium uptake capacity in the DCT is limited, the natriuretic and diuretic effect are weak.

Diuretic-Induced Hyponatremia

Example Case:

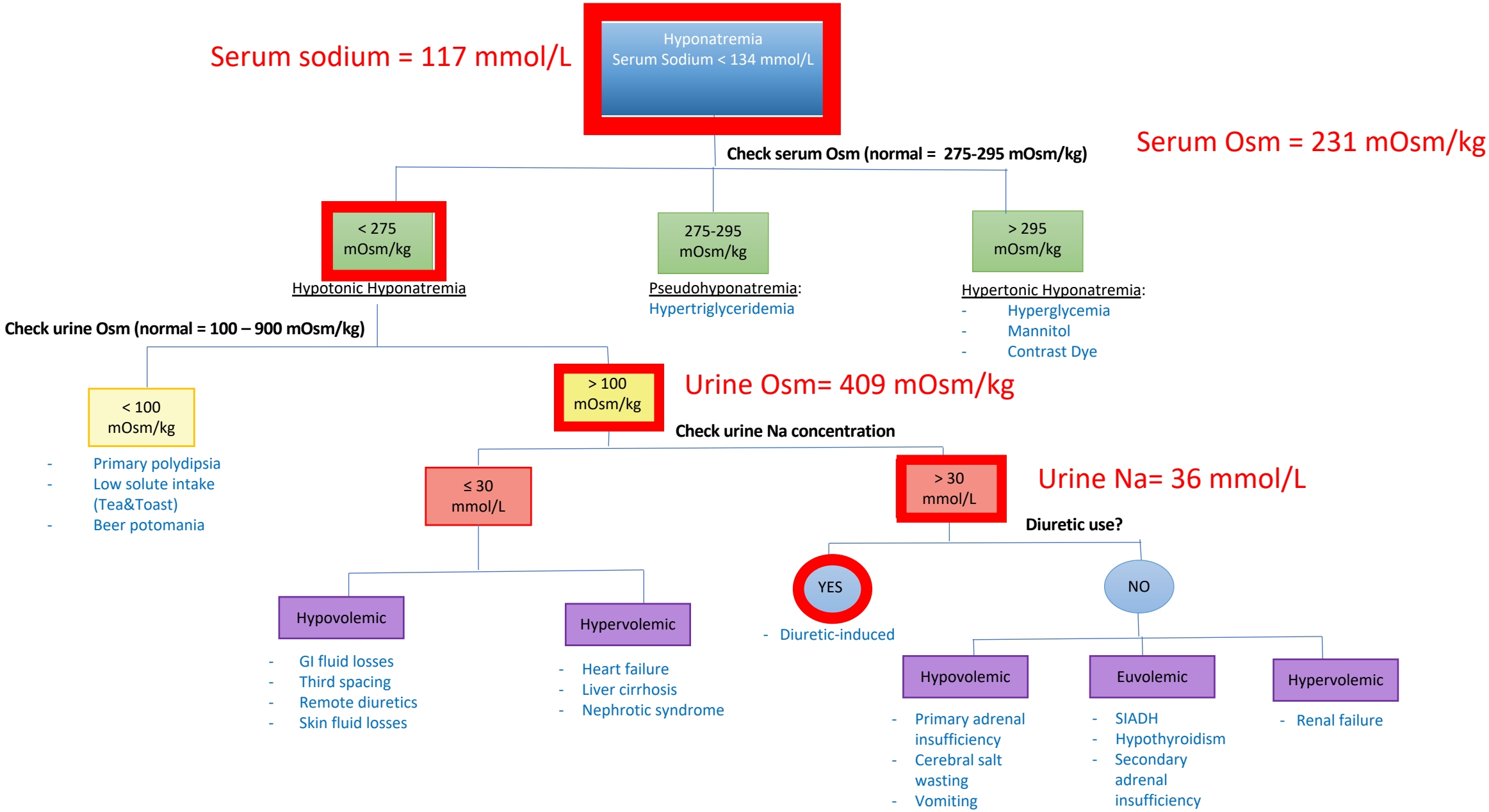
- 67/M presented to ER with weakness and confusion and found to have a serum sodium level of 117 mEq/L
- PMH: recent COVID-19, current smoker 1 ppd, HTN, gout, former alcohol abuse
- Home meds:
  - Amlodipine 10 mg daily
  - Lisinopril 40 mg daily
  - Maxzide 37.5/25 mg daily



OTHER CHEM	
Osmolality Meas	
231 ⌄⌄	

	URINE CHEMISTRY
36	Sodium Urine Random
27.8	Potassium, Ur
56	Chloride, Ur
84.4	Creatinine, Urine
409	Osmolality, Urine

	CHEM PROFILE
117 ⌄⌄	Sodium
2.8 ⌄⌄	Potassium
85 ⌄	Chloride
24	CO2
8	Anion Gap
161 ⌃	Glucose
16	BUN
0.85	Creatinine
90	Calculated GFR
18.8	BUN/Creatinine Ratio
7.6 ⌄	Calcium
2.2 ⌄	Phosphorus


Serum sodium = 117 mmol/L
Hyponatremia
Serum Sodium < 134 mmol/L
Serum Osm = 231 mOsm/kg
Check serum Osm (normal = 275-295 mOsm/kg)
< 275 mOsm/kg
275-295 mOsm/kg
> 295 mOsm/kg
Hypotonic Hyponatremia
Pseudohyponatremia:
Hypertriglyceridemia
Hypertonic Hyponatremia:
- Hyperglycemia
- Mannitol
- Contrast Dye
Check urine Osm (normal = 100 – 900 mOsm/kg)
< 100 mOsm/kg
- Primary polydipsia
- Low solute intake (Tea&Toast)
- Beer potomania
> 100 mOsm/kg
Urine Osm= 409 mOsm/kg
Check urine Na concentration
≤ 30 mmol/L
> 30 mmol/L
Urine Na= 36 mmol/L
Diuretic use?
YES
- Diuretic-induced
NO
Hypovolemic
- GI fluid losses
- Third spacing
- Remote diuretics
- Skin fluid losses
Hypervolemic
- Heart failure
- Liver cirrhosis
- Nephrotic syndrome
Hypovolemic
- Primary adrenal insufficiency
- Cerebral salt wasting
- Vomiting
Euvolemic
- SIADH
- Hypothyroidism
- Secondary adrenal insufficiency
Hypervolemic
- Renal failure

Patient Case: Diagnose Etiology

DIURETICS	MECHANISM OF ACTION
Thiazide diuretics: Hydrochlorothiazide, Chlorothiazide **Thiazide-related diuretics:** Chlorthalidone, metolazone, indapamide	Inhibits sodium reabsorption (by inhibiting the Na/Cl symporter) in the distal collecting tubule causing increased excretion of sodium and water as well as potassium and hydrogen ions

117 ⌄⌄	Sodium
2.8 ⌄⌄	Potassium
85 ⌄	Chloride
24	CO2
8	Anion Gap
161 ⌃	Glucose
16	BUN
0.85	Creatinine
90	Calculated GFR
18.8	BUN/Creatinine Ratio
7.6 ⌄	Calcium

- Maxzide = hydrochlorothiazide and triamterene
- Thiazide-diuretic induced hyponatremia
- Severe hyponatremia due to increased sodium excretion AND note concomitant hypokalemia

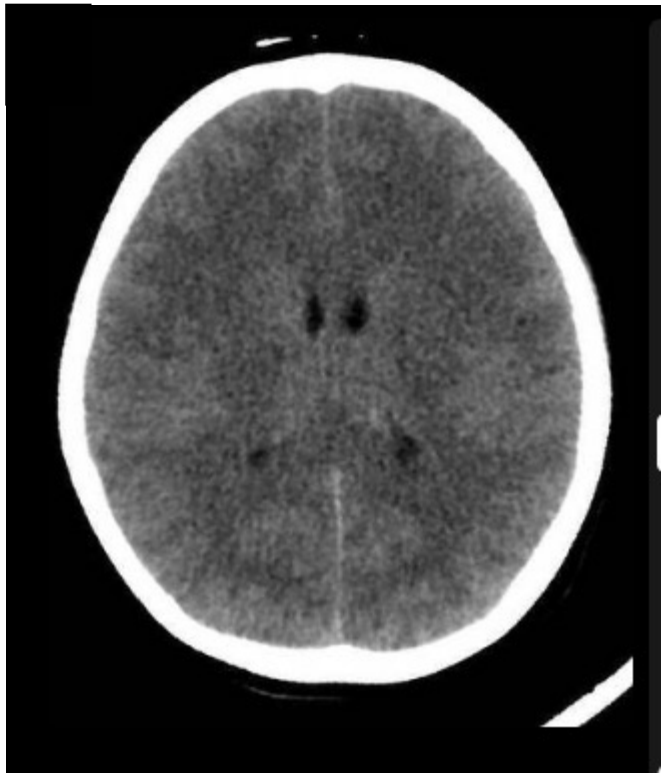
Pretreatment Evaluation

- Determine degree of hyponatremia
  - Severe hyponatremia: serum sodium < 120 mmol/L → much higher risk of complications from overly rapid correction of sodium
  - Moderate hyponatremia: serum sodium: 120 – 129 mmol/L
  - Mild hyponatremia: serum sodium 130 – 134 mmol/L
- Determine chronicity → to determine rate of safe correction of sodium
  - Acute: developed over a period of < 48 hours
  - Chronic: developed over a period of ≥ 48 hours or unknown
- Assess severity of symptoms
  - Severe symptomatic: seizures, obtunded, coma, → more common in acute hyponatremia without time for brain to adapt in order to minimize edema → severe symptoms may be evidence of cerebral edema and risk of impending brain herniation
  - Mild-moderate symptoms: headache, fatigue, lethargy, nausea, vomiting, dizziness, gait disturbance, confusion, muscle cramps → more common with chronic hyponatremia with serum sodium < 120 mmol/L
  - Asymptomatic

Androgue HJ, et al. Diagnosis and Management of Hyponatremia: A Review. JAMA 2022 Jul 19;32(3):280-291.

Hyponatremia Induced Cerebral Edema

- Hyponatremia results in decrease in plasma osmolality compared to brain cell osmolality causing water movement into the brain in response to the osmotic gradient → causing cerebral edema
- Astrocytes (component of the blood brain barrier) and glial cells are commonly involved due to presence of water channels
- Cerebral edema can progress to herniation and death if it happens acutely without time for adaptation to compensate

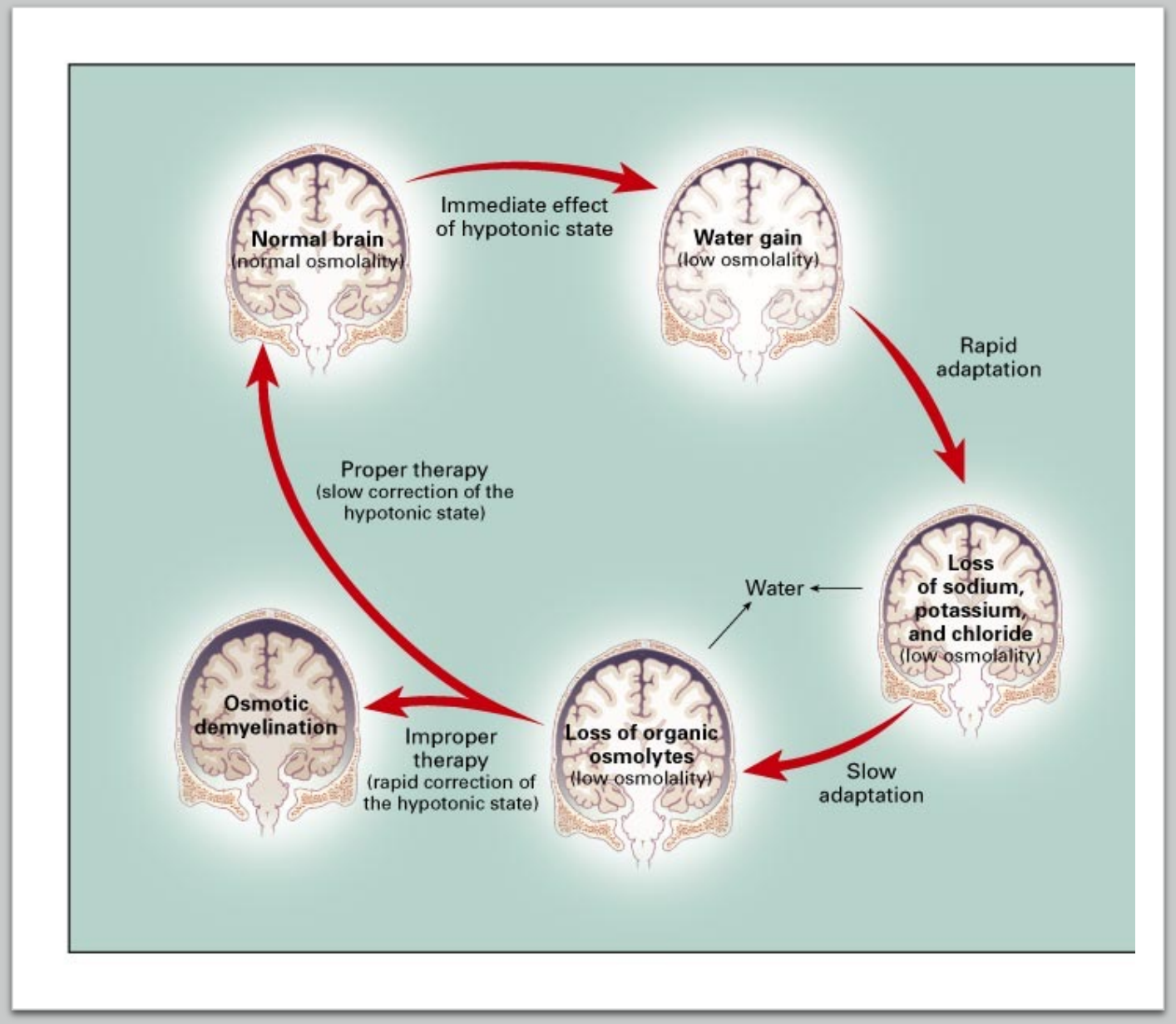


Giuliani C, et al. Effects of hyponatremia on the brain. J Clin Med. 2014 Dec; 3(4):1163-1177.

Hyponatremia | Radiology Reference Article | Radiopaedia.org

Brain Adaptation to Chronic Hyponatremia

- Initially hyponatremia causes water shifting into the brain causing cerebral edema
- Initial adaptation is for brain to force out electrolytes (Na, K, Cl) (through energy dependent activation of Na-K ATPase pump and the K-Cl co-transporter and volume sensitive Cl channel) → into the cerebrospinal fluid
- Chronic adaptation is slow efflux of organic osmolytes (amino acids, myoinositol, glutamate) and the new/adapted state will persist as long as the hyponatremia is present



NEJM 2000 May 25;342(21):1581-9

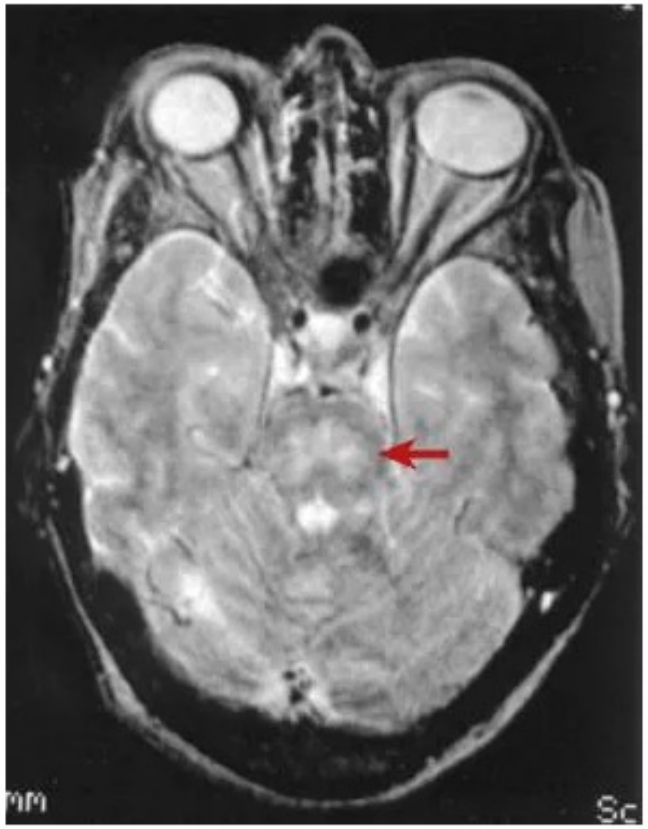
Osmotic Demyelination Syndrome

- Once the brain has adapted to chronic hyponatremia through the loss of organic solutes, brain cells become sensitive to rapid shifts in fluid since the adapted cells cannot immediately replace the lost organic solutes (amino acids, myoinositol, glutamate)
- If the serum sodium is overly rapidly corrected, the adapted brain cells will shrink in response to the increased tonicity as the sodium normalizes in the serum before the osmolarity in the cell can come into equilibrium
- The result can be demyelination in the areas of the brain that are the slowest at re-accumulating osmolytes
- Osmotic demyelination syndrome occurs over 2 – 6 days after overly rapid elevation in sodium after chronic hyponatremia
- Symptoms include dysarthria, dysphagia, paraparesis or quadriparesis, behavior changes, movement disorders, seizures, lethargy, confusion, coma → these symptoms are frequently irreversible with severe cases causing “locked in” syndrome

Aegisdottir H,, et al. Incidence of osmotic demyelination syndrome in Sweden: A nationwide study. Acta Neurol Scand 2019; 140:342.

Osmotic Demyelination Syndrome (Central Pontine Myelinolysis)

- Mechanism is proposed to be that fluctuating osmotic forces result in compression of fiber tracts which induces demyelination → occurs when prolonged hyponatremia is followed by rapid sodium correction resulting in edema
- Demyelination occurs in the central pontine region but may also occur in extrapontine regions (mid brain, thalamus, cerebellum)



T2-weighted MRI scan of the brain demonstrating patchy areas of signal change within the pons that are consistent with demyelination or central pontine myelinolysis. Courtesy of Dr Andrew Waclawik, Department of Neurology, University of Wisconsin, Madison.

Luzzio C, et al. Central Pontine Myelinolysis. Medscape. Updated October 28, 2022.

Risk Factors For Osmotic Demyelination Syndrome

- Serum sodium < 120 mmol/L (and especially < 105 mmol/)
- Duration of hyponatremia ≥ 48 hours
- Overly rapid correction of serum sodium > 15 mEq Na^+ correction per day, but cases with correction of chronic hyponatremia by > 8 mEq Na^+ per day

Verbalis JG, et al. Kidney Int. 1991 Jun;39(6):1274-82.

Goals of Therapy

1

Prevent further decline in serum sodium

- To prevent seizures, further increases in cerebral edema, intracranial hypertension, and brain herniation

2

Relieve symptoms of hyponatremia

3

Avoid overcorrection of sodium especially in patients at high risk for osmotic demyelination syndrome

Rate of Serum Sodium Correction

Asymptomatic or acute hyponatremia	Increase serum sodium *no faster than* 0.5 – 1 mEq/L/hr (MAXIMUM: 8 mEq/L in any 24 hour period)
Chronic hyponatremia (≥ 48 hours duration)	Increase serum sodium *no faster than* 0.5 – 1 mEq/L/hr (more conservative MAXIMUM: 4 – 6 mEq/L in any 24 hour period)
Severely symptomatic hyponatremia (seizures, coma, etc)	May be necessary to increase serum sodium by 4 – 6 mEq/L *within first 6 hours* with frequent re-assessment of serum sodium and efforts to prevent further correction of sodium over the next 24 hours

Treatment with 3% Sodium Chloride

Clinical Scenario	3% Sodium Chloride Treatment Strategy	Monitoring
Acute hyponatremia with serum sodium < 130 mEq/L and mild-moderate symptoms	3% sodium chloride 100 mL over 10 minutes, repeat if symptoms do not improve	Monitor serum sodium every 1 -2 hours
Chronic hyponatremia: Asymptomatic	3% sodium chloride generally not recommended	n/a
Chronic hyponatremia: mild-moderate symptoms	3% sodium chloride 15 – 30 mL/hr	Monitor serum sodium every 2 hours
Severe symptoms	3% sodium chloride 100 mL over 10 minutes, repeat if symptoms do not improve	Monitor serum sodium every 1 -2 hours

Calculating the Change in Serum Sodium when Administering 3% Hypertonic Saline

- Calculate total body water → **Men:** 0.6 L/kg x patient weight (kg)
  Women: 0.5 L/kg x patient weight (kg)

- Calculate the change in serum sodium concentration after infusion of 3% sodium chloride

$$\frac{(513 \text{ mEq per L} - \text{patient's serum sodium } \_\_\_\_\_ \text{ mEq/L})}{(\text{patient's total body water } \_\_\_\_\_ \text{ L} + 1)} = \_\_\_\_\_ \text{ mEq (per L 3\% NaCl infused)}$$

Example Case:

75 kg female with serum sodium 120 mEq/L believed to have developed chronically with mild-moderate symptoms → Total body water = 0.5 L/kg x 75 kg = 37.5 L

Rate of sodium change per L of 3% sodium chloride =

(513 mEq Na/L – 120 mEq Na/L)/(37.5 L + 1) = 393/38.1 = **10.31 meq/L Na change per each 1 L of 3% NaCl infused**

For *chronic* hyponatremia, serum sodium should not correct faster than 0.5 mEq/L/hr, but no more than **6 mEq in 24 hours**

- In this example one liter of 3% sodium chloride corrects serum sodium by 10.31 meq/L → set up a proportion to see how much 3% NaCl increases serum sodium by 6 mEq/L

$$\frac{10.31 \text{ mEq Na/L}}{1000 \text{ mL 3\% NaCl}} = \frac{6 \text{ mEq Na/L}}{x \text{ mL 3\% NaCL}} \qquad x = 581.99 \text{ mL}$$

Chronic hyponatremia with mild-moderate symptoms → may consider 3% NaCl infusion

What infusion rate should be selected for this patient? Take the total volume calculated and divide by 24 hours

581.99 mL 3% NacL / 24 hours = 24.25 mL/hr

This is a safe infusion rate but is not guaranteed to correct as the calculation predicts because other variables such as urine output, etiology of hyponatremia, other fluids and electrolytes administered, etc.

Prevention of Overcorrection with Desmopressin (DDAVP)

Reactive Administration of desmopressin:

- If patient serum sodium begins correcting faster than desired administer desmopressin (along with dextrose 5% infusion if needed) to prevent further increase in sodium and/or to bring sodium back down to acceptable level

- Consider proactive desmopressin:
  - High risk for rapid serum sodium increase in patients who autocorrect
    - Hypovolemia corrected suppressing ADH causing water diuresis
    - Water intoxication from psychosis (primary polydipsia)
    - High risk of ODS (see previous slide, i.e. very low sodium and longer duration)
- Desmopressin (DDAVP) 1 – 2 mcg IV or SC every 6 – 8 hours for 24 – 48 hours or until serum sodium is corrected to safe level
  - ADJUNCTIVE in the management of hyponatremia: given along with 3% sodium chloride to make the rate of correction of sodium more predictable because it prevents unexpected water diuresis
  - Mechanism: synthetic analogue of ADH, increases water permeability resulting in decreased urine volume (water reabsorption)

Sood L, et al. Hypertonic saline and desmopressin: a simple strategy for safe correction of severe hyponatremia. Am J Kidney Dis. 2013 Apr;61(4):571-8.

Example Case Continued:

- 75 kg female with serum sodium 120 mEq/L believed to have developed chronically with mild-moderate symptoms
- 3% sodium chloride was initiated at 25 mL/hr and serial sodium levels were obtained

08:00	10:00	12:00	14:00
Na = 120 mEq/L	Na = 122 mEq/L	Na = 126 mEq/L	130 mEq/L

- What would you do if you were the provider caring for this patient?
  - Chronic hyponatremia should be corrected no faster than 0.5 – 1 mEq/L/hr (maximum 4 – 6 mEq/24 hours)
  - Should have stopped the 3% sodium chloride when sodium increase demonstrated trend of rise > 0.5 – 1 mEq/L/hr
  - Sodium is correcting too fast → has already increased by 10 mEq/L in 6 hours → this patient is at risk to develop osmotic demyelination syndrome
  - Need to stop 3% NaCl infusion administer DDAVP 1 mcg IV and start D5W infusion to push sodium back down and continue serial monitoring of sodium until lowered to ~ 124 – 126 mEq/L and maintain this sodium level for the remainder of the 24 period since presentation

Treatment Hypernatremia: Other Considerations

- Identify reversible causes and treat:
  - Hypovolemic hyponatremia (less common) → fluid replacement will suppress ADH → leading to water diuresis (likely without the need for hypertonic saline)
  - Hyponatremia due to adrenal insufficiency → give steroids with mineralocorticoid potency
  - Hyponatremia due to primary polydipsia → fluid restriction
  - Treatment of SIADH → may be caused by malignancy or medications → remove offending agents
    - Fluid restriction < 1 L/day
    - Urea (in patients who do not respond to fluid restriction): 15 – 30 grams daily, titrate in increments of 15 grams at weekly intervals to maximum 60 grams/day
      - Normalizes serum sodium levels by inducing osmotic excretion of free water, and increasing medullary urea blocks natriuresis associated with SIADH
    - Oral Sodium Chloride (available as 1g tabs):
      - Sodium chloride 1 gram tablet PO TID initially
      - 9 g oral NaCl tablets = 1 liter of 0.9% sodium chloride (154 mEq)
    - Tolvaptan (Samsca) $$ if failed first-line therapies: 15 grams once daily, titrate after initial 24 hours to 30 mg daily
      - Arginine vasopressin receptor (AVP) antagonist to block ADH to promote excretion of free water without loss of sodium

EQUATIONS:

Total Body Water (TBW):
TBW (men) = 0.6 L/kg x weight (kg)
TBW (women) = 0.5 L/kg x weight (kg)

Change in serum sodium per LITER of 3% sodium chloride =
(513 mEq Na/L – serum sodium)/(TBW + 1)

Bottom Line: Treating Hyponatremia

Order BMP, serum osmolality, and urine electrolytes (sodium) to aid in determination of etiology of hyponatremia

If concern for SIADH, hold medications that may be the culprit, especially thiazide diuretics and SSRIs

Calculate the rate of correction of sodium when using 3% sodium chloride and reassess serum sodium frequently (every 2 – 4 hours)

Do not lower sodium faster than 0.5 - 1 mEq/L/hr (maximum 6 - 8 mEq/L per 24 hours) to prevent overcorrection and reduce risk of osmotic demyelination syndrome

Questions