Disorders of Plasma Sodium

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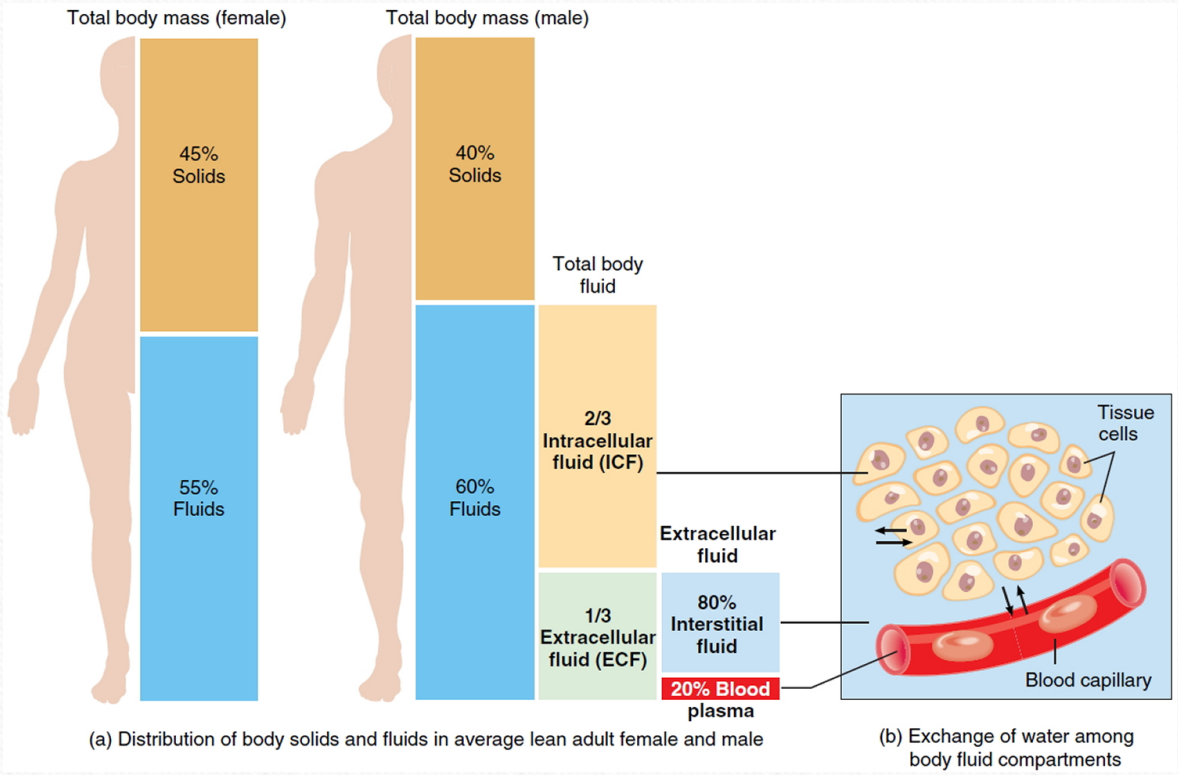
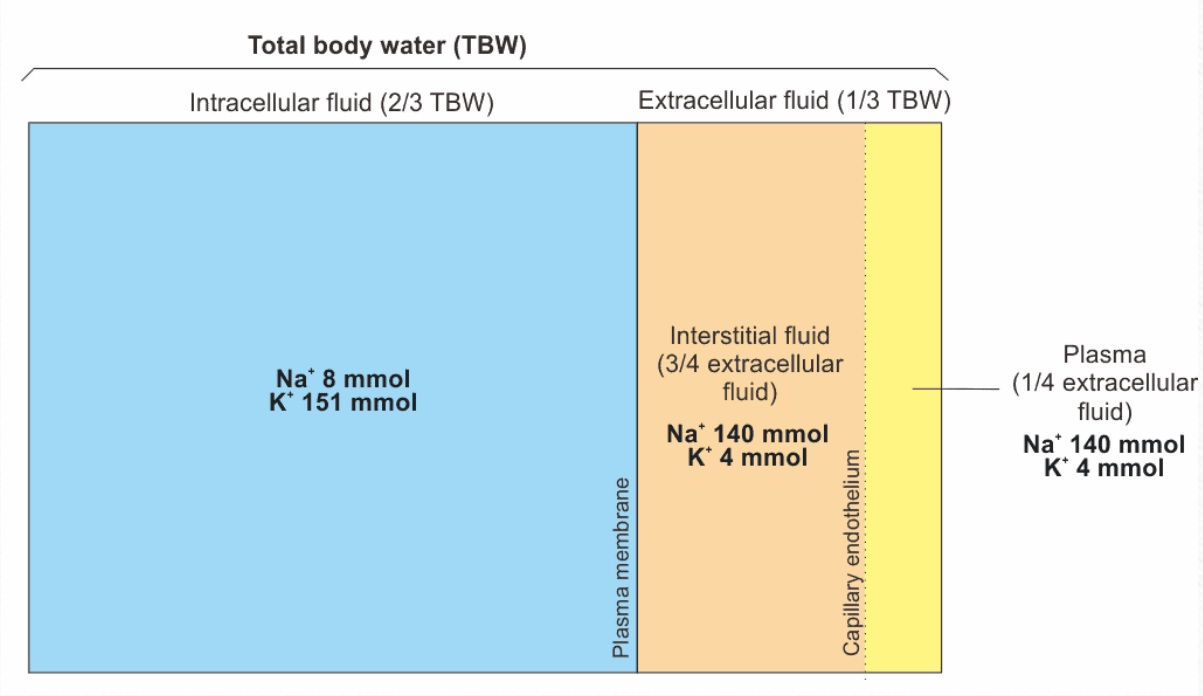
Objectives of the presentation

- Short review on the body regulation of the plasma sodium.
- Discuss various etiologies of sodium disorders.
- Understand the diagnostic approach to hyponatremia and hypernatremia.
- Learn the basic management of sodium disorder.

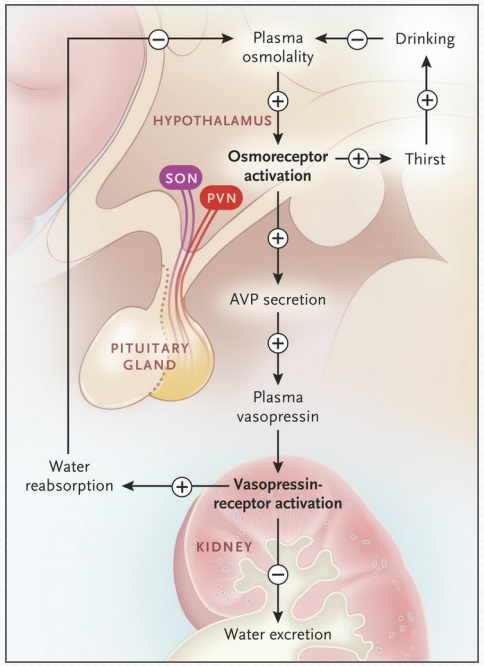
Plasma Sodium Concentration and the Electrolyte and Water Content of the Body



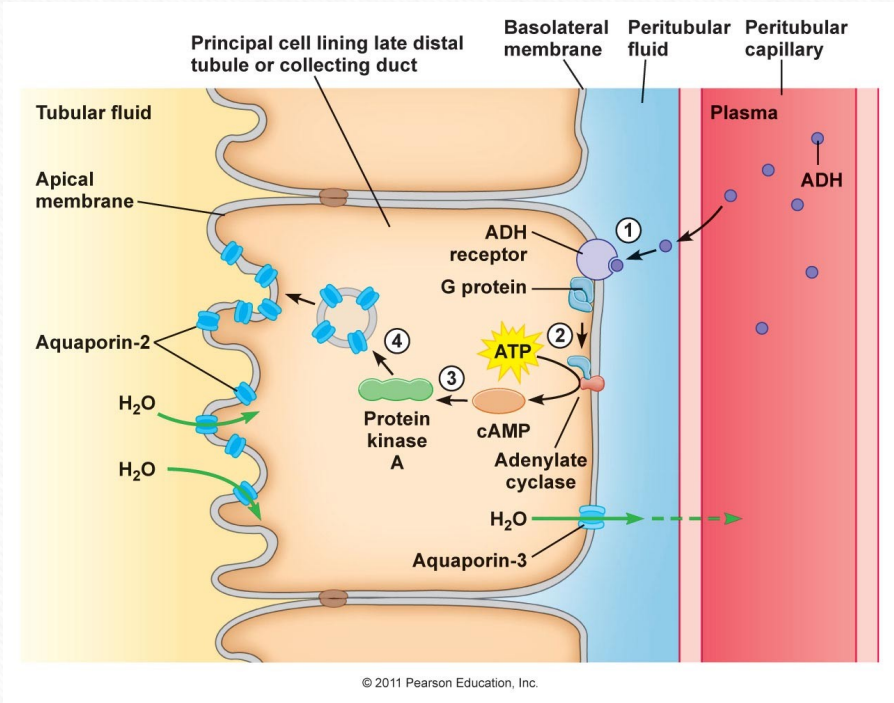
Plasma Sodium Concentration and the Electrolyte and Water Content of the Body



Hypothalamic-pituitary axis to influence water intake through thirst and water excretion via the effect of vasopressin, or antidiuretic hormone, on renal collecting duct water permeability



Paraventricular nucleus (PVN), Supraoptic nucleus (SON)



Hypo/Hypernatremia- how does it happen?

Normal sodium concentration = $\frac{Na}{H_20}$

Hyponatremia = $\frac{Na}{H_2O}$ Or $\frac{Na}{H_2O}$

Hyponatremia

- Hyponatremia is common findings in the elderly.
  - Inpatient (15-20%)
  - Outpatient (7-11%) settings.

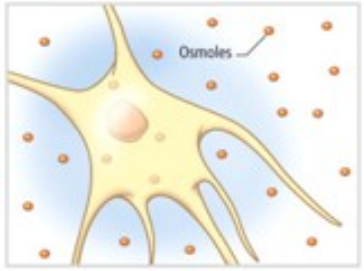
Calculated Plasma osmolality (mosm/kg) = 2 serum Sodium + Serum Urea (mmol/l) + plasma glucose (mmol/l)

Adverse Outcomes Associated With Chronic Mild to Moderate Hyponatremia

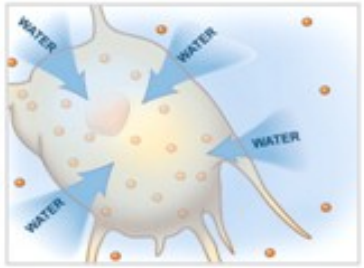
- Cognitive impairment
- Falls
- Fractures and osteoporosis
- Gait instability
- Mortality
- Calcium-forming kidney stones

Hyponatremia Importance

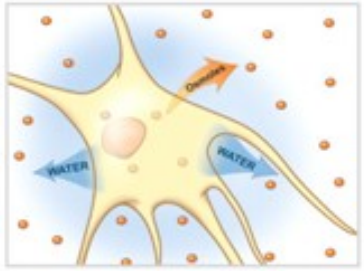
- The most common electrolyte disorder encountered in clinical practice



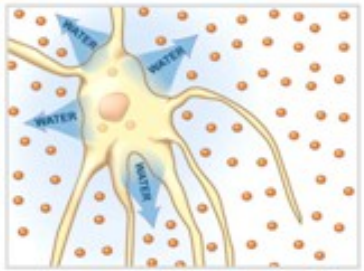
Normal State



Acute Hyponatremia

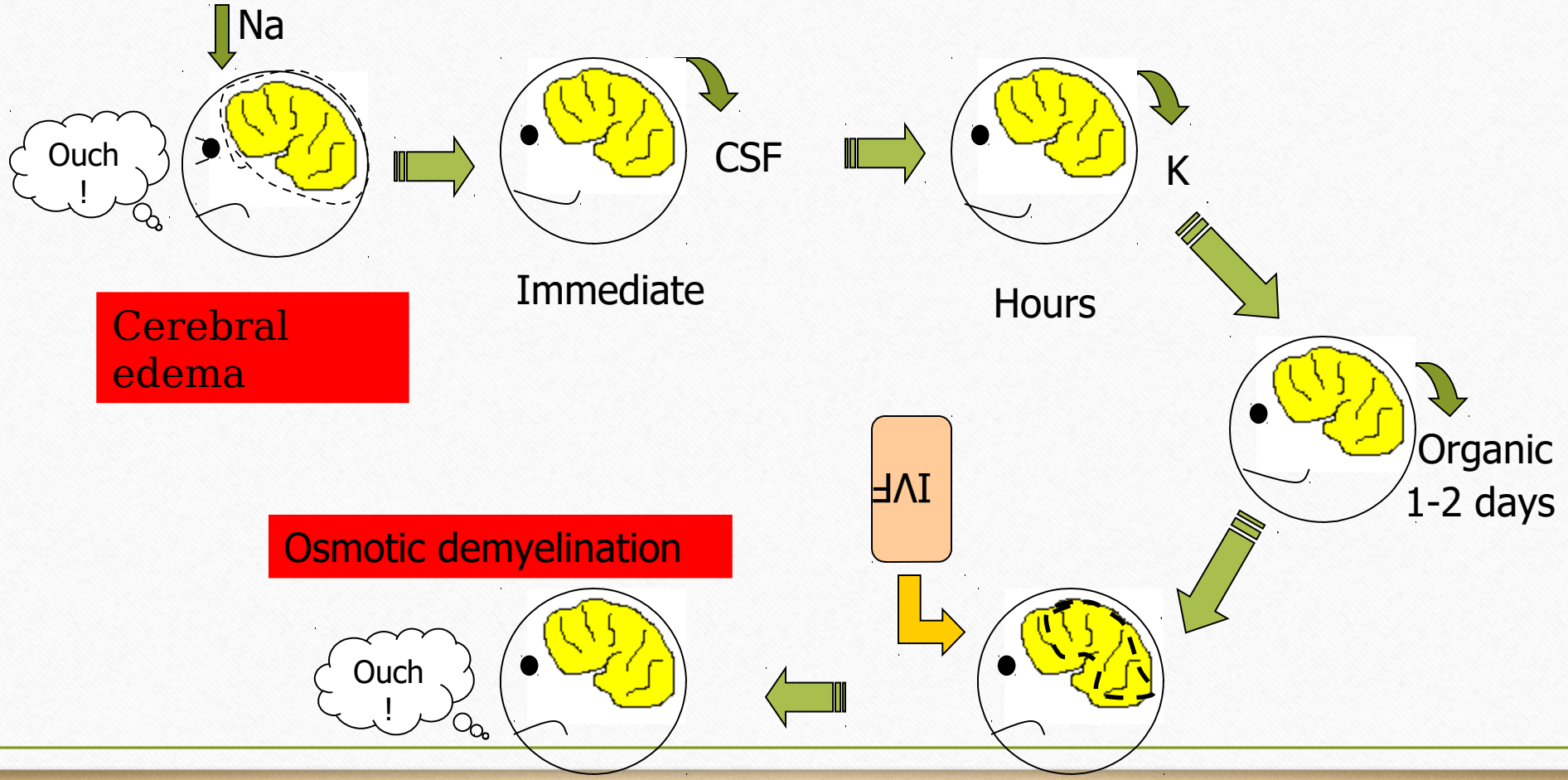


Adaptation



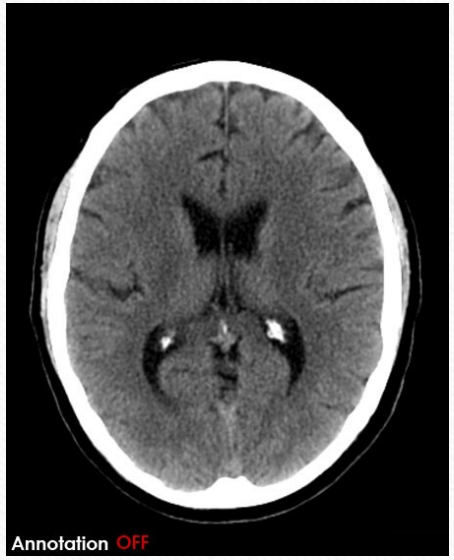
Overly aggressive Rx

Adaptations to hyponatremia

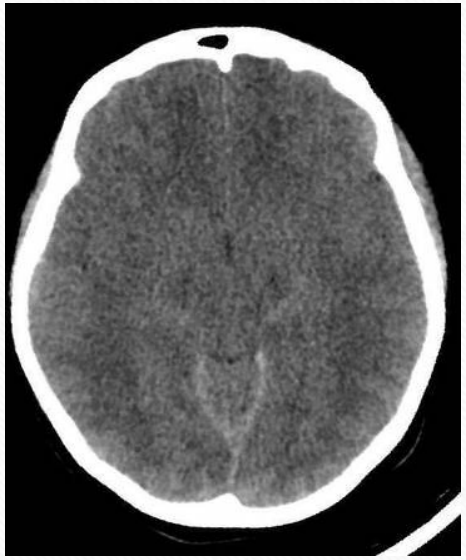


Acute complication of Hyponatremia

Normal CT Brain



Sever Hyponatremia



Classification Based on Severity of Hyponatremia

- **Mild:** Serum sodium concentration of 130-135 mEq/L
- **Moderate**: Serum sodium concentration of 120-129 mEq/L
- **Severe:** Serum sodium concentration of <120 mEq/L; may occur at <125 mEq/L

Classification Based on Tonicity

- **Hypotonic Hyponatremia** (True Hyponatremia)
  - Serum osmolality of <275 mOsm/kg H2O
- **Isotonic Hyponatremia**
  - Serum osmolality of 275-295 mOsm/kg H2O (Normal)
- **Hypertonic Hyponatremia**
  - Serum osmolality of >295 mOsm/kg H2O

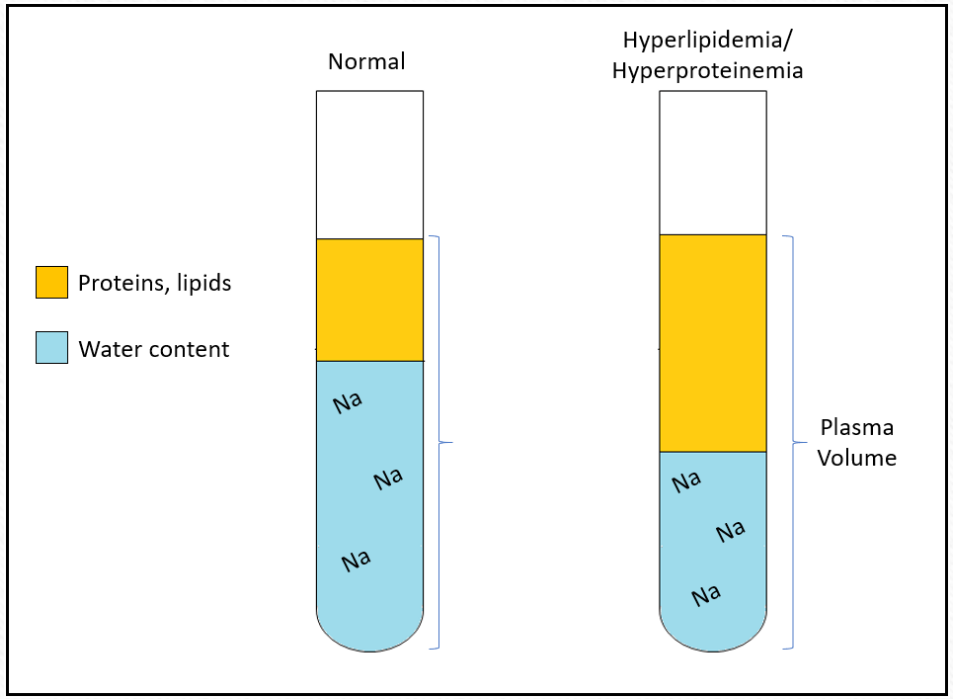
Classification Based on Duration

- **Acute:**
  - Hyponatremia that has developed over a period of <48 hours
- **Chronic**
  - Hyponatremia that has been present for ≥48 hours or the duration is unclear

Symptoms and signs of hyponatremia

- Symptoms of hyponatremia are often nonspecific
- Headache
- Lethargy
- Dizziness and ataxia
- Confusion
- Psychosis
- Seizure
- Coma

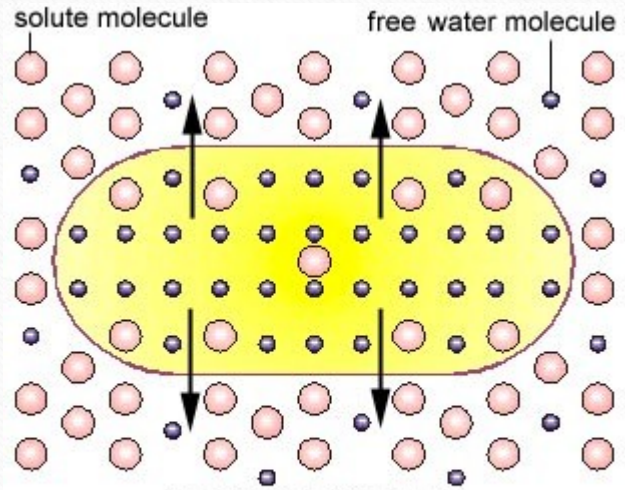
Isotonic hyponatremia or Pseudo-hyponatremia



- Serum multianalyzers measure [Na+] using indirect potentiometry and specimen dilution.
- Assumes that water constitutes 93% of plasma.
- High plasma lipid or protein conc. will lower the aqueous contribution to plasma volume, leading to a falsely decreased calculated [Na+] value.

Hypertonic hyponatremia (Translocational hyponatremia)

- Hyponatremia combined with plasma tonicity > 295
- Most commonly observed in hyperglycemia
- The correction factor is a 1.6 mmol/L decrease in serum Na for every 5.6 mmol per L increase in glucose.
- Other causes: Mannitol and radiocontrast.



Hypertonic Environment:
The solute concentration is greater outside the cell; the free water concentration is greater inside. Free water flows out of the cell.

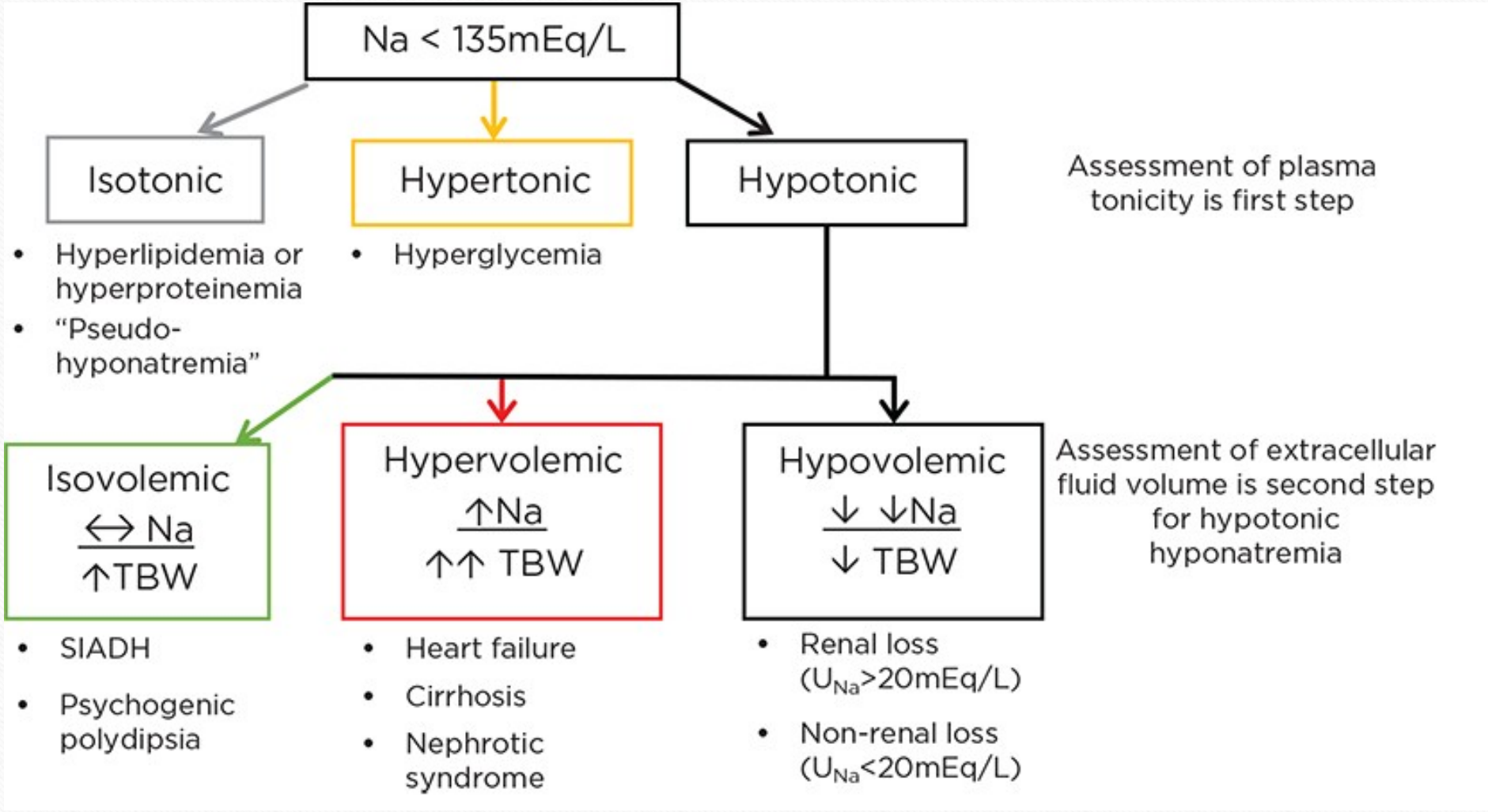
Hypotonic hyponatremia (True Hyponatremia)

- **Serum osmolality < 275 mOsm/kg H2O**

Hypotonic Hyponatremia and Preserved Urinary Dilution (i.e. Low Urine Osmolality)

- Low Uosm indicative of maximally dilute urine—typically <100 mOsm/kg H2O
- Vasopressin is appropriately suppress.
- Causes:
  - Primary polydipsia
  - “tea-and-toast” diet
  - Beer potomania: excessive intake of alcohol, particularly beer, together with poor dietary solute intake that leads to fatigue, dizziness, and muscular weakness.

Hypotonic Hyponatremia With Impaired Urinary Dilution (i.e. High Urine Osmolality)


Na < 135mEq/L
Isotonic
Hypertonic
Hypotonic
Assessment of plasma tonicity is first step
• Hyperlipidemia or hyperproteinemia
• "Pseudo-hyponatremia"
• Hyperglycemia
Isovolemic
↔ Na
↑TBW
Hypervolemic
↑Na
↑↑ TBW
Hypovolemic
↓ ↓Na
↓ TBW
Assessment of extracellular fluid volume is second step for hypotonic hyponatremia
• SIADH
• Psychogenic polydipsia
• Heart failure
• Cirrhosis
• Nephrotic syndrome
• Renal loss (U_{Na}>20mEq/L)
• Non-renal loss (U_{Na}<20mEq/L)

Classification Based on Extracellular Volume Status

- Hypovolemic hyponatremia
- Euvolemic hyponatremia
- Hypervolemic hyponatremia

Hypovolemic Hyponatremia

- Decreased total body water with greater decrease in sodium level
- Extracellular fluid losses can occur from kidney, gastrointestinal tract or the skin
- Most common cause is thiazide diuretic therapy; other causes are Addison’s disease
- Signs and symptoms associated with volume depletion:
  - Dry mucous membranes, . Decreased skin turgor . Vomiting . Diarrhea
  - Tachycardia . Hypotension
- Elevated blood urea nitrogen and uric acid level
- Urinary sodium usually <20 mEq/L unless the kidney is the site of sodium loss

Hypervolemic Hyponatremia

- Increased total body water compared with sodium that occurs when kidneys cannot excrete water efficiently
- Common causes include heart failure, liver cirrhosis and kidney injury
- Clinical signs include:
  - Peripheral edema
  - Ascites
  - Raised jugular venous pressure
  - Pulmonary edema
  - Underlying illness
- Useful diagnostic lab findings are elevated plasma levels of brain natriuretic peptide and spot urine of <20-30 mEq/L

Euvolemic Hyponatremia

- Increased total body water with normal sodium level
- Accounts for the majority of hyponatremia cases
- Most commonly caused by syndrome of inappropriate antidiuretic hormone (SIADH)
- Other causes are hypothyroidism and glucocorticoid deficiency
- Clinical signs depend on the underlying illness

Diagnostic criteria for SIADH

Essential features

- Decreased serum osmolality (<275 mOsm/kg)
- Urinary osmolality >100 mOsm/kg
- Clinical euvolaemia
- Urinary sodium >40 mmol/L with normal dietary salt intake
- Normal thyroid and adrenal function
- No recent use of diuretics

Supplemental features

- Low Serum uric acid
- Low normal Serum urea serum creatinine
- Fractional sodium excretion >1%, fractional urea excretion >55%
- Failure to correct hyponatraemia after 0.9% saline infusion
- Correction of hyponatraemia through fluid restriction
- Abnormal water loading test (excretion <80% of a 20 mL/kg water load in 4 h)
- Elevated vasopressin levels despite hypotonicity and clinical euvolaemiaa

Etiology of SIADH

Medical Conditions	Drugs
Acute illness, emotional stress, psychosis, pain, and nausea	Antidepressants & antipsychotics: Selective serotonin reuptake inhibitors, tricyclics, venlafaxine, phenothiazines, butyrophenones, monoamine oxidase inhibitors
Exercise-associated hyponatremia	
Pulmonary diseases: Any form of pneumonia, acute respiratory failure, pneumothorax, and acute respiratory distress syndrome	Anticonvulsants: Carbamazepine, sodium valproate, lamotrigine
HIV infection, adrenal insufficiency, hypothyroidism	
Central nervous system (CNS) disorders: Stroke, hemorrhage, infection, trauma, and psychosis	Anticancer drugs: Vinca alkaloids, ifosfamide, melphalan, cyclophosphamide, methotrexate
Surgical procedures: Orthopedic surgeries (e.g., hip & knee replacement) and trans-sphenoidal pituitary surgery	Vasopressin analogues: Desmopressin, oxytocin, terlipressin, vasopressin
Ectopic production of ADH: Most often due to small cell carcinoma of the lung (extrapulmonary small cell carcinoma in a few cases). Other causes include head and neck cancer, olfactory neuroblastoma, C-cell carcinomas of the thyroid, and pancreatic cancer	Miscellaneous: Opiates, nonsteroidal anti-inflammatory drugs, MDMA (ecstasy), levamisole, clofibrate, interferon, amiodarone, bromocriptine, angiotensin-converting enzyme inhibitors
Hereditary and idiopathic causes	

Approach to hyponatremia

Approach to hyponatremia

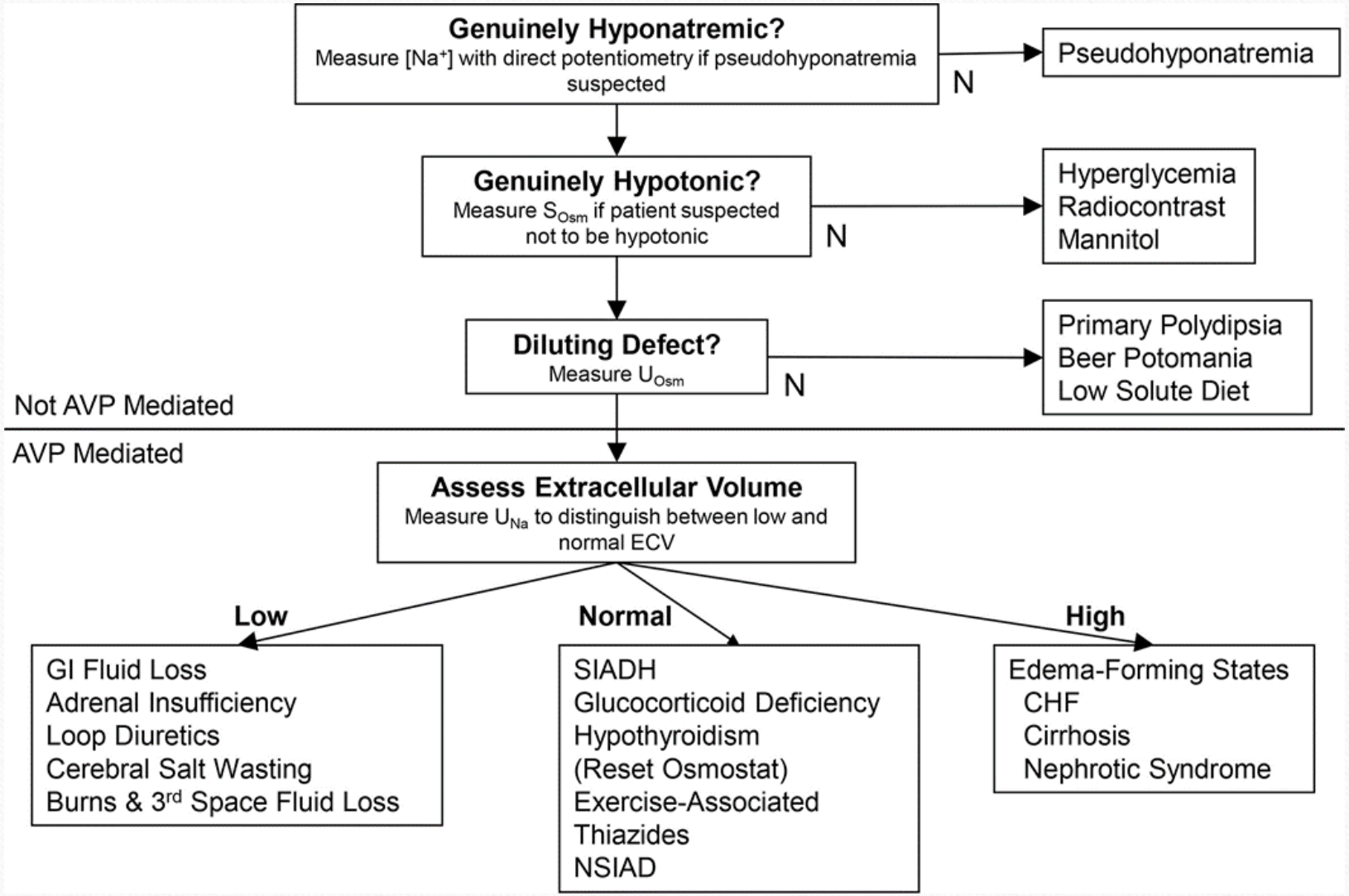
1. Confirm the patient truly has a hypo-osmolar state by checking serum osmolality
2. Assess for serious signs or symptoms suggesting cerebral edema
3. Determine the duration of development of hyponatremia (less or more than 48 hours)
4. Assess the patient’s extracellular fluid volume status using clinical examination and laboratory testing
5. Check the urine osmolality to see if the urine is appropriately dilute (< 100 mOsm/kg) or inappropriately concentrated (≥ 100 mOsm/kg)
6. Assess for underlying causes of hyponatremia
7. Look for drugs the patient is taking that potentiate antidiuretic hormone action (e.g., selective serotonin uptake inhibitors)

History

- Inquire from patient’s history possible causes of hyponatremia
- History of cardiac, cancer, pulmonary, endocrine, gastrointestinal, neurologic and renal diseases
- History of electrolyte-rich fluid loss (eg vomiting, diarrhea or diuretic therapy)
- History of low protein intake and/or high fluid intake
- Medications used (eg diuretics, Carbamazepine, selective serotonin reuptake inhibitors)
- Alcohol and illicit drug use (eg beer, 3,4-methylenedioxymethamphetamine/”Ecstasy”)
- For athletes, training regimens because high-endurance activities can cause hyponatremia
- History of very recent surgery

Physical Examination

- The patient should be examined to determine volume status, looking for signs of dehydration or volume overload.
- Polyuria is most common in primary polydipsia
- Signs of volume depletion include:
  - Low urine output . Weight loss . Orthostatic hypotension . Decreased jugular venous pressure
  - Poor skin turgor, Dry mucus membranes . Absence of axillary sweat . Absence of edema.
- Signs of volume overload include:
  - Edema and/or ascites . Rales or crackles on lung auscultation
  - Significant weight gain . Raised jugular venous pressure.


Genuinely Hyponatremic?
Measure [Na+] with direct potentiometry if pseudohyponatremia suspected
N
Pseudohyponatremia
Genuinely Hypotonic?
Measure SOsm if patient suspected not to be hypotonic
N
Hyperglycemia
Radiocontrast
Mannitol
Diluting Defect?
Measure UOsm
N
Primary Polydipsia
Beer Potomania
Low Solute Diet
Not AVP Mediated
AVP Mediated
Assess Extracellular Volume
Measure UNa to distinguish between low and normal ECV
Low
GI Fluid Loss
Adrenal Insufficiency
Loop Diuretics
Cerebral Salt Wasting
Burns & 3rd Space Fluid Loss
Normal
SIADH
Glucocorticoid Deficiency
Hypothyroidism
(Reset Osmostat)
Exercise-Associated
Thiazides
NSIAD
High
Edema-Forming States
CHF
Cirrhosis
Nephrotic Syndrome

Management of hyponatremia

How to manage hyponatremia?

1. Treat neurologic emergencies related to hyponatremia
2. Evaluate and defend intravascular volume
3. Prevent worsening hyponatremia
4. Prevent rapid overcorrection
5. Treat the Underling cause

Acute symptomatic hyponatremia

- Supportive care: ICU admission and close monitoring
- Correct acute, severe hyponatremia with bolus(es) of hypertonic saline or sodium bicarbonate.
- Goal: Raise sodium by 4–6 mmol/L and stop.
- 3% NaCl: 2mL/kg over 10min. If persistent symptoms, may repeat 2X until symptoms resolve.
- NaHCO3: 100 cc of 8.4% sodium bicarbonate (2 “ampules” of crash cart bicarb) over 10 minutes (=200 ml of 3% Saline).

Try Not to Make It Worse!

- Prevent worsening of hyponatremia: strict fluid restriction and saline locking the IV; applied to all hyponatremic patients.

Euvolemic Hyponatremia

- Careful monitoring during treatment
- Fluid restriction
- Loop diuretics plus salt tablets to replace urinary sodium losses
- Urea tablets or Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors
- Vasopressin receptor antagonists
- Enhance solute intake if poor nutrition
- Discontinue medications associated with SIADH
- Treatment of underlying condition associated with SIADH (eg, antibiotics for pneumonia)
- Treatment of endocrinopathy (eg, hypothyroidism)

Chronic (>48hours)

1. Hypovolemic Hyponatremia
   - 1st isotonic fluid infusion
   - plus treat underlying cause
2. Hypervolemic Hyponatremia
   - Fluid restriction
   - plus treat underlying cause
   - adjunct loop diuretic or spironolactone
   - Vasopressin receptor antagonist +

Prevent Rapid Overcorrection

- Target rates of sodium correction: Rule of 6s. Six in six hours for severe symptoms, then stop. Six a day makes sense for safety.”
- Prevent overcorrection: Rule of 100s.
- Insert a foley catheter and monitor intake and outputs.
- If urine output >100cc/hour, send STAT urine osmolarity and urine sodium.
- If urine osmolarity<100, consider administering DDAVP IV. Consider DDAVP for appropriate candidates.

Hypernatremia

Hypernatremia

Hypernatremia, serum sodium concentration of 145 mmol/L a state of total body water deficiency absolute or relative to total body sodium.

It can result from:

1. water loss (e.g., diabetes insipidus [DI])
2. hypotonic fluid loss (e.g., Osmotic diarrhea),
3. hypertonic fluid gain (Sodium containing fluids e.g., IV Fluid)

Pathophysiology

- Hypernatremia is caused by:
  - Net water loss (increased loss or decreased intake)
  - Rarely, sodium gain.
- Patients at increased risk:
  - Impaired thirst mechanism or
  - Restricted access to water (e.g., those with altered mental status, intubated patients, infants, older adults).

Hypernatremia

- Hypernatremia is common in ICU, the older nursing home resident, usually with dementia and infant.
  - Inpatient (1%)
  - Outpatient (2%)

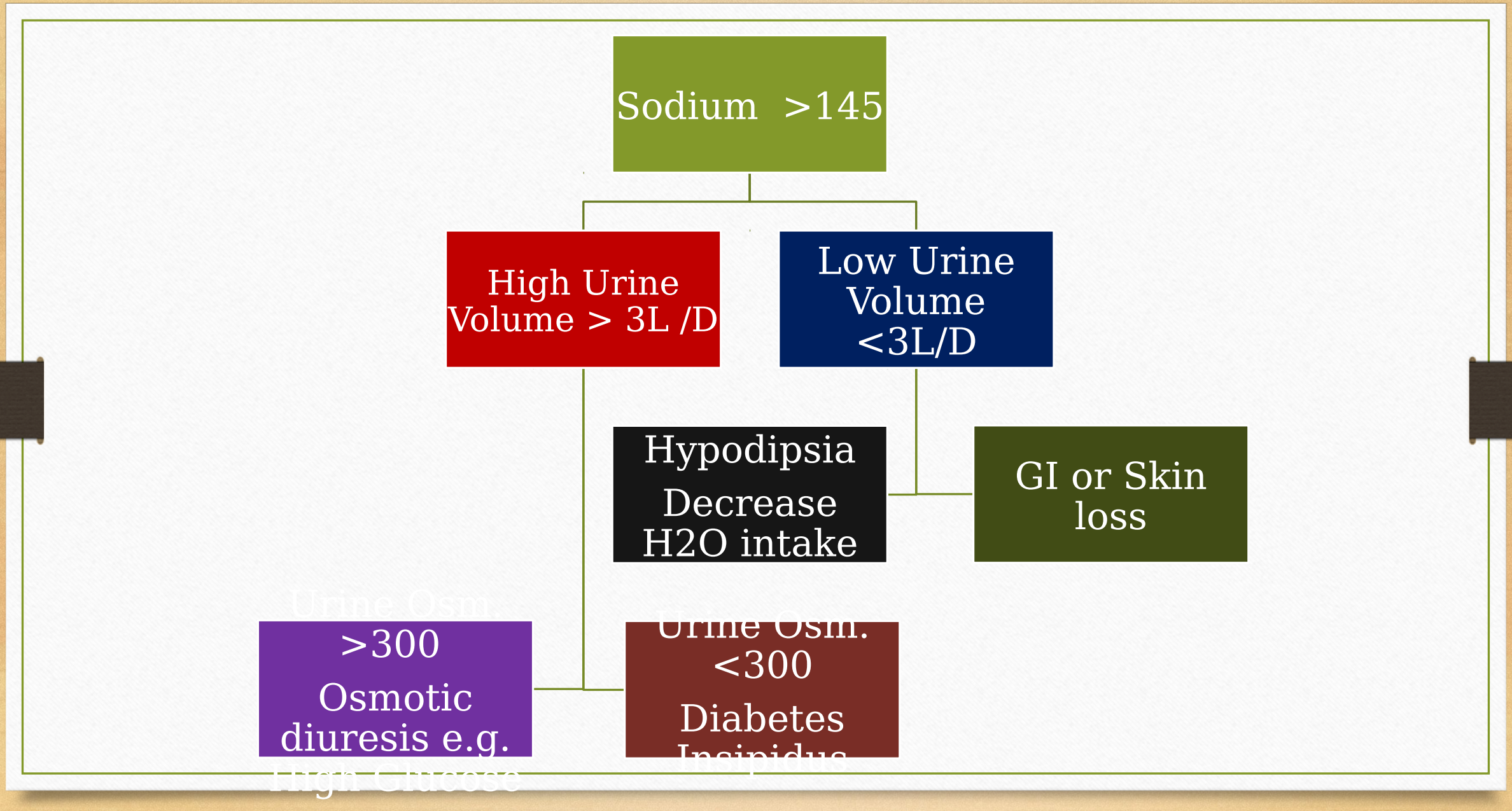
- Clinical presentation:
  - Often asymptomatic
  - Irritability, nausea, weakness, altered mental status
  - Brain shrinkage, resulting in vascular rupture and intracranial bleeding.

Approach

- Detailed History AND Urine Osmolaity can reveal most of the cases:
  - Water loss (GI loss or Insensible loss or Polyuria)

+

  - Lack of access to water or Primary neurological disease

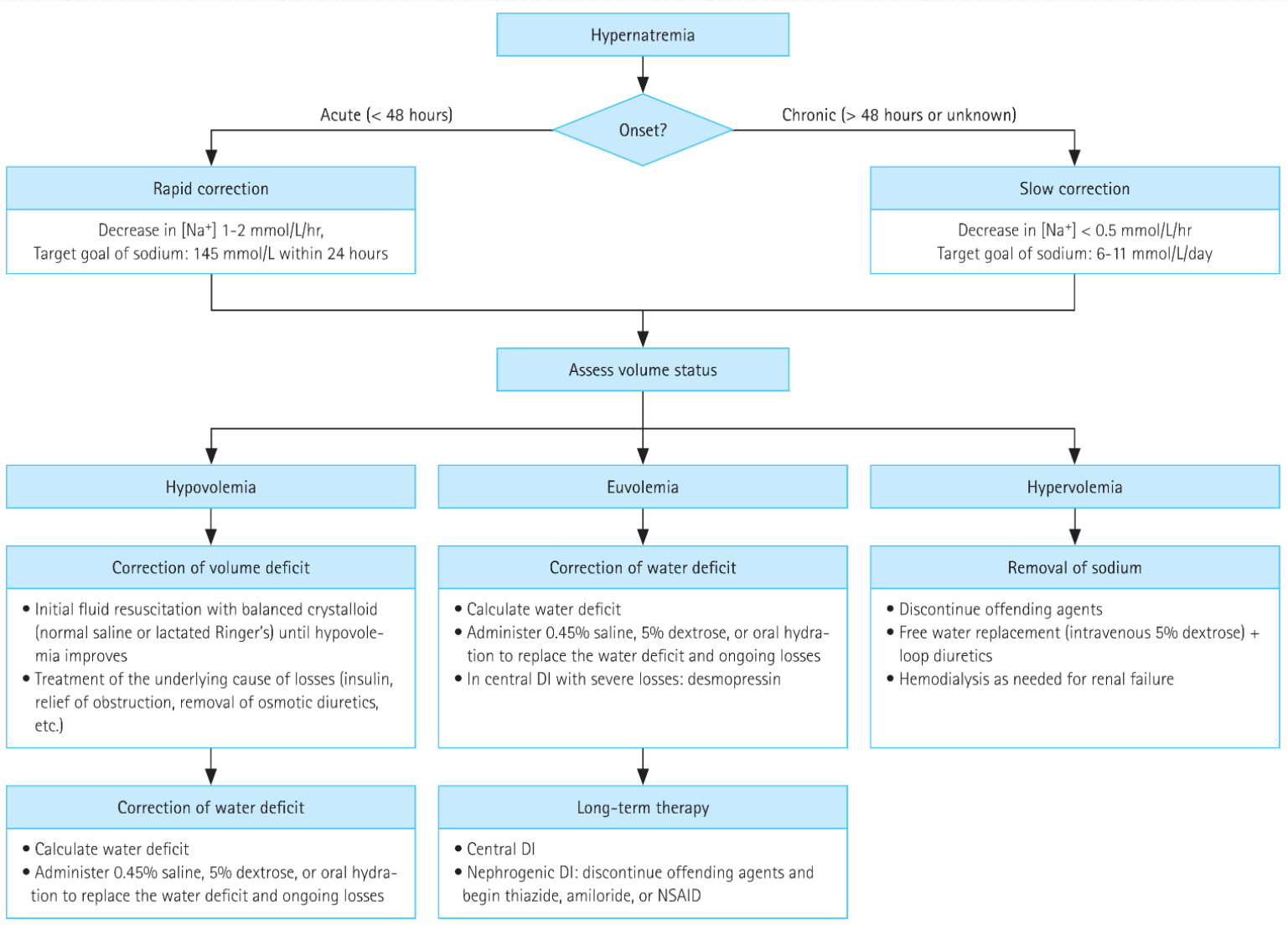

Sodium >145
High Urine Volume > 3L /D
Low Urine Volume <3L/D
Hypodipsia
Decrease H2O intake
GI or Skin loss
Urine Osm.
>300
Osmotic diuresis e.g.
High Glucose
Urine Osm.
<300
Diabetes Insipidus

How to approach?

- Determine whether the extracellular volume is hypovolemic, euvolemic, or hypervolemic using the history and physical examinations
- Measure urine sodium
  - Volume depletion exhibit decreased sodium excretion in the urine (< 20 mmol/L).
  - Elevated urine sodium concentration (> 20 mmol/L):
    - Osmotic diuresis, the use of diuretics, postobstructive nephropathy, or the recovery phase from acute tubular necrosis

How to approach?

- Measure urine volume and Urine osmolality:
  - A Uosm < 300 mOsm/kg and polyuria (> 3 L/day or > 40 mL/kg/day) suggest the presence of diabetes insipidus.
    - Administration of exogenous AVP enables the distinction between central and nephrogenic diabetes insipidus
  - If Uosm is between 300 and 800 mOsm/kg, this may reflect a process of osmotic diuresis


Hypernatremia
Onset?
Acute (< 48 hours)
Chronic (> 48 hours or unknown)
Rapid correction
Decrease in [Na+] 1-2 mmol/L/hr,
Target goal of sodium: 145 mmol/L within 24 hours
Slow correction
Decrease in [Na+] < 0.5 mmol/L/hr
Target goal of sodium: 6-11 mmol/L/day
Assess volume status
Hypovolemia
Euvolemia
Hypervolemia
Correction of volume deficit
• Initial fluid resuscitation with balanced crystalloid (normal saline or lactated Ringer's) until hypovolemia improves
• Treatment of the underlying cause of losses (insulin, relief of obstruction, removal of osmotic diuretics, etc.)
Correction of water deficit
• Calculate water deficit
• Administer 0.45% saline, 5% dextrose, or oral hydration to replace the water deficit and ongoing losses
• In central DI with severe losses: desmopressin
Removal of sodium
• Discontinue offending agents
• Free water replacement (intravenous 5% dextrose) + loop diuretics
• Hemodialysis as needed for renal failure
Correction of water deficit
• Calculate water deficit
• Administer 0.45% saline, 5% dextrose, or oral hydration to replace the water deficit and ongoing losses
Long-term therapy
• Central DI
• Nephrogenic DI: discontinue offending agents and begin thiazide, amiloride, or NSAID

Case Presentation

Case Discussion

- Mr. P is a 66-year-old man who comes to the emergency department with a chief complaint of headache. Shortly after arrival he has a generalized seizure. Initial labs reveal a serum sodium concentration of 122 mEq/L.

- What would you do?

Case Discussion

- Due to Mr. P.’s seizure and subsequent postictal state, Mr. P cannot give a medical history. His vital signs are BP, 140/95 mm Hg; pulse, 90 bpm; temperature, 36.0°C; RR, 18 breaths per minute. His neck veins are flat. His lungs are clear to auscultation. Cardiac exam reveals a regular rate and rhythm. There is no jugular venous distention (JVD), S3 gallop, or murmur. His abdomen is obese with no clear mass. No ascites is appreciated. Extremity exam reveals no edema.
- What other investigations you would order?

Case Discussion

- Mr. P’s laboratory studies reveal a glucose of 7.8 mmol/l; K+, 3.9 mEq/L; BUN, 3 mmol/l; creatinine, 70 umol/l; and a serum osmolality of 254 mOsm/L. Urine osmolality is 80 mOsm/L.

- what is the most likely diagnosis?

Questions