Hyponatremia

Background

- Definition: [Na] <136
- Usually due to ↓ water excretion and rarely solely from ↑ free water intake
- Classification
  Mild (130–135); moderate (125–130); severe/profound (<125)
  Acute (<24 hr); chronic (>48 hr)
  Symptomatic; asymptomatic
  Hypotonic; pseudohyponatremia (or isotonic); hypertonic
  Hypovolemic; euvolemic; hypervolemic

Clinical Manifestations

- Water movement into the brain leading to brain edema acutely
- Related to the degree and the rapidity of establishment of the hyponatremia
- Symptoms in acute hyponatremia can be nonspecific like malaise, nausea progressing to headache, lethargy, gait imbalance and in extreme cases seizures and coma
- Chronic hyponatremia <130 is associated with subtle neurologic symptoms leading to fall, general malaise, and decrease attention span
- Severe acute hyponatremia can rarely lead to brain edema–induced brain herniation especially in premenopausal women and young children

Workup of Hyponatremia (*JASN* 2017; 28:1340)

Step1: Differentiate Hypotonic from Nonhypotonic Hyponatremia

- Measure P_{osm} to rule out nonhypotonic hyponatremia
- Calculated P_{osm} = 2 × [Na] + [Glucose]/18 + BUN/2.8 (normal: 275–290 mOsmol/Kg)
- Measured P_{osm} (done in the lab) reflects the total of all osmolytes in plasma
  - Hypertonic hyponatremia: osmotically active compounds (eg, glucose, mannitol, alcohols) drawing water out of cells
  - Isotonic hyponatremia: water-insoluble substances (eg, protein and lipid) may interfere with the measurement of sodium. The osmolar gap (Measured-Calculate P_{osm}) is helpful in these circumstances: a difference of more than 10 is in favor of an additional osmolar substance
- Treatment of nonhypotonic hyponatremia is centered around the underlying etiology, eg, hyperglycemia where indicated

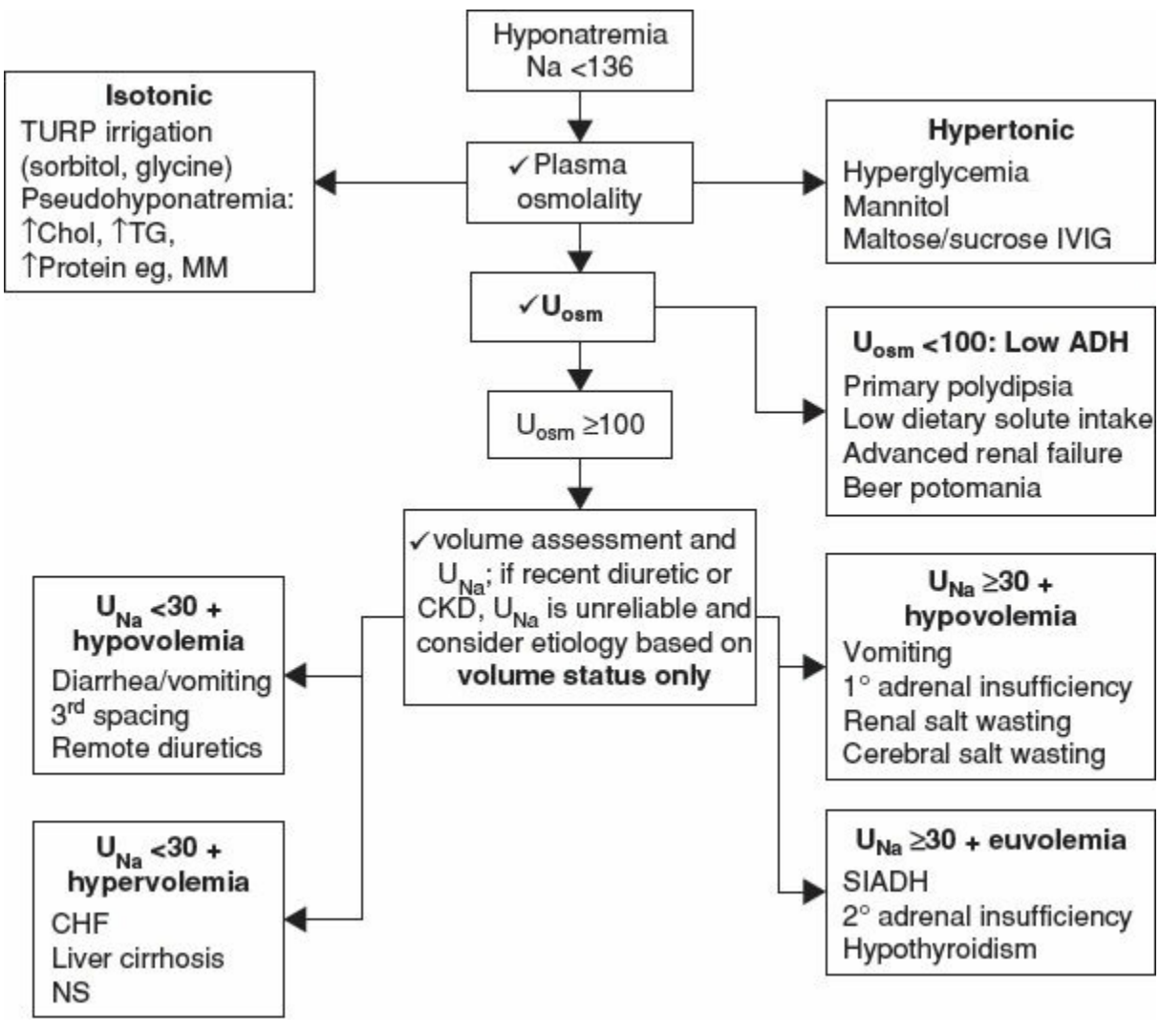
Step 2: U_{osm} and GFR to Assess the Role of the Kidney

- U_{osm} is expected to decrease in response to hyponatremia. If hypotonic hyponatremia coexist with low U_{osm} (<100), this can be explained by:

1. 1° polydipsia (usually >12 L): overwhelming the excretion of dilute urine
2. Low dietary solute intake (eg, malnutrition, alcoholism): the low total solute excretion limits the amount of maximal daily urinary water excretion due to reduce delivery of fluid in the diluting segment and creates an environment where even a mild increase of hypotonic intake leads to hyponatremia

Step 3: Volume Status Assessment for Patient with High U_{osm} (>100) and U_{Na}

- U_{osm} >100 in a hyponatremia (elevated ADH levels): true hypovolemia, effective hypovolemia, SIADH, hypothyroidism, and Addison disease
- It is sometimes difficult to differentiate clinically hypovolemic hyponatremia from euvolemic hyponatremia (sensitivity and specificity ≈ 50%) (*Am J Med* 1995;99:348)
- U_{Na} <30 can be used as a supplement to assess volemia (using a cutoff of 30)
- U_{Na} diagnostic value is limited in CKD, recent diuretics use, dietary Na restriction
- ↑ [Na] with isotonic saline infusion trial is favor of hypovolemic hyponatremia (in SIADH with U_{osm} <500, [Na] improves with isotonic saline infusion)
- Since ADH is a uricosuric hormone, fraction of excretion of uric acid (FE_{UA}) is a helpful diagnostic tool: FE_{UA} >12% is sensitive and specific for SIADH



Diagnostic approach for hyponatremia based on P_{osm}, U_{osm}, U_{Na}, and volume status.

Treatment of Hyponatremia (*NDT* 2014;29:i1; *Am J Med* 2013;126:S1)

- When hypokalemia is concomitant with hyponatremia, the correction of hypokalemia may contribute to the correction of the hyponatremia (the repletion of K helps restore plasma osmolarity by ↑ total body osmoles)
- For acute or severely symptomatic hyponatremia, a bolus of hypertonic saline 3% (100 mL over 10 min ×3 as needed to relieve symptoms or the [Na] increases by 6)
- In hypovolemic hyponatremia, patients will start autocorrecting as soon and the volume is expanded; to avoid rapid correction, it is recommended to combine volume expansion with desmopressin
- The limit for correction is 8 mmol/L/d; Hypotonic fluids and/or DDAVP can be used to relower [Na] if overcorrection occurs
- Restrict fluid intake (both PO and IV) to 500 mL/d below the 24-hr urine volume in low U_{osm}, hypervolemic hyponatremia and **Syndrome of Inappropriate Antidiuresis (SIAD)**
- If U_{osm} >300–500, consider furosemide to lower U_{osm}
- Urea: induces osmotic diuresis → free water excretion; used as second line to fluid restriction; safe and effective (*CJASN* 2018;13:1627); Even if overcorrection occurs with urea, the risk of ODS and demyelination lesions is less
- Salt tablets increase urine solute load; Usual doses for NaCl tablets are 6–9 g daily

ADH Antagonist (Vaptans) (*NEJM* 2015;372:2207)

- Block V2-receptors in collecting duct principal cells → aquaresis
- Tolvaptan (PO): start with 15 mg qd; up to 60 mg, 30 days
- Conivaptan (IV): start with 20 mg over 30 min then 20 mg/24 hr; up to 40 mg/24 hr, 4 days
- NOT indicated in the treatment of acute or severely symptomatic hyponatremia
- s/e: overcorrection, liver toxicity
- On initiation, fluid restriction should be stopped and patient should be allowed access to free water intake to avoid overcorrection; if the target Na is not achieved after 24 hr of vaptan initiation, fluid restriction will be resumed

Treatment of Hyponatremia		
Correction limit	8–10 mEq/L/24 hr	
Correction rate	4–6 mEq/L/24 hr	
Overcorrection	Hypotonic solution DDAVP 2–4 µg IV	Only if baseline <120 mEq/L
Treatment of ODS	Hypotonic solution DDAVP 2–4 µg IV	Lower [Na] by 16 mEq/L
Severe symptomatic hyponatremia	NaCl 3% (100 mL over 10 min) ×3 as needed	Symptoms improve or ↑ Na by 6 mEq/L
SIAD	1st line: address the stimulus of ADH secretion + Fluid restriction[a] 2nd line: urea, salt tablets 3rd line: lithium, demeclocycline	Fluid restriction calculation $(U_{Na} + U_K)/S_{Na}$ >1 → <500 mL/d ≈1 → 500–700 mL/d <1 → <1 L/d
Hypovolemic hyponatremia	Isotonic volume expansion	DDAVP concomitant in patients with high risk of ODS (hypokalemic, alcoholic, malnutrition) 4–8 µg IV q6-8h
Hypervolemic hyponatremia	1st line: fluid restriction 2nd line: vaptan[b] or hypertonic saline + loop diuretics	High risk of overcorrection with Vaptan

[a]Risk of nonresponders: U_{Na} ≥130 mmol/L; U_{osm} ≥500 mOsm/kg; UOP <1,500 mL/d

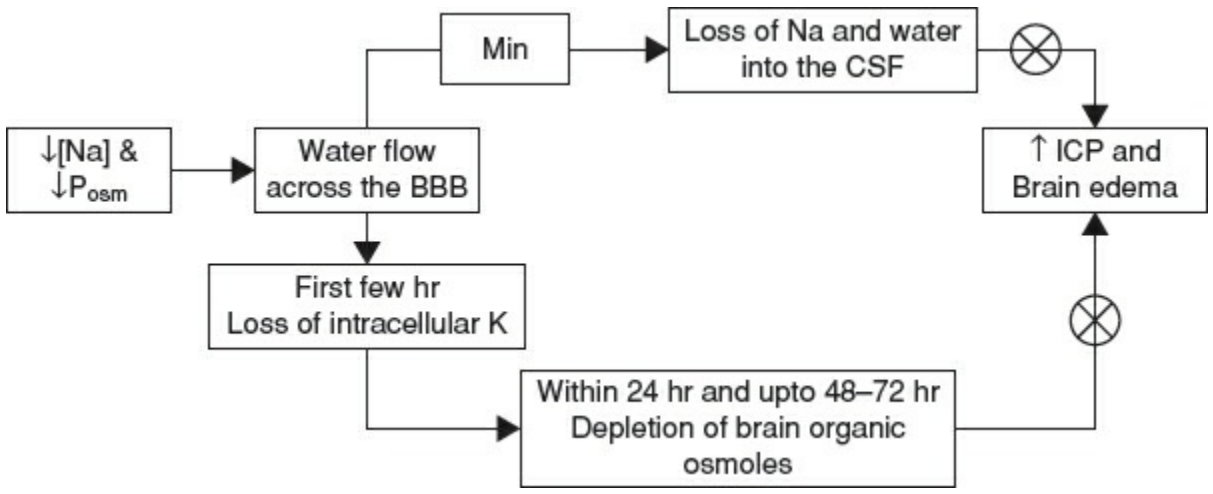
[b]Avoid Vaptan in patients with liver disease

Hyponatremia Formulas

- Effective P_{osm} = 2 × [Na] + [glucose]/18; (normal value: 270–285 mOsmol/kg)
- Since Na and K is the main extracellular and intracellular solutes, respectively:
  Plasma [Na] = (total body Na + total body K)/TBW
  This formula explain why correcting hypokalemia could improve hyponatremia
- Plasma volume: 93% aqueous (water), 7% nonaqueous (fat and protein)
  Physiologic [Na] = reported [Na]/0.93 (eg, 143/0.93 ≈ 154 [Na] in 0.9% isotonic saline fluid)

Brain Adaptation to Hyponatremia

- Hyponatremia and ↓ P_{osm} → water flow across the blood–brain barrier → ↑ ICP → loss of Na and water into the CSF → improving ICP within min (acute adaptation)
- Chronic adaptation starts within hours through intracellular K loss (cell swelling sensitive cationic channels) followed by loss of brain organic osmolytes (glutamine, glutamate, taurine, and myoinositol) that needs up to 72 hr to be complete



Brain adaptation to hyponatremia.

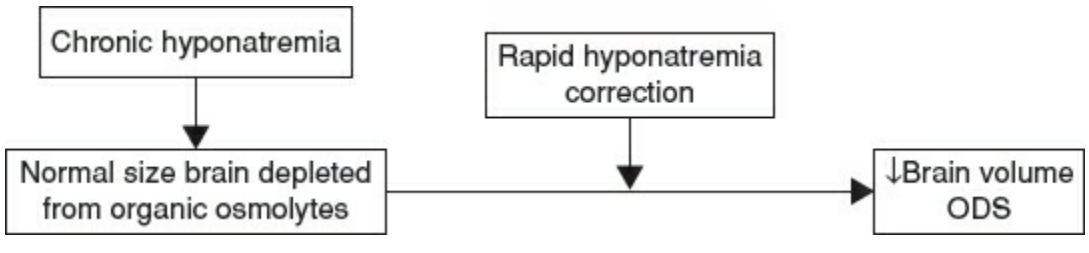
- The rate of correction of hyponatremia is important whenever the brain has adapted to hypotonicity (after 48–72 hr of established hyponatremia)

Osmotic Demyelination Syndrome (ODS)

- a/w rapid correction of hyponatremia (>8 mEq/L in 24 hr; >16 mEq/L in 48 hr)
- The hourly rate is not a risk factor of ODS unless the daily rate threshold is exceeded
- Prevention: target a rate of correction of 4–6 mEq/L/d in chronic "asymptomatic" hyponatremia

Risk Factors for ODS	
Admission plasma Na	• [Na] ≤120 mEq/L (mainly for ≤105 mEq/L) • [Na] >120 postliver transplant or CDI after dDAVP discontinuation
Therapy	• Hypertonic saline • Vasopressin antagonists
Autocorrection following therapy (rapid renal free water loss)	• Hypovolemic hyponatremia treated with volume expansion • Adrenal insufficiency treated with glucocorticoids • Holding DDAVP in overtreated Central DI; Holding thiazide diuretics • ESRD on HD
Patient related	• Alcoholism; malnutrition; liver disease; pregnancy • Hypokalemia

- In hyponatremic ESRD, during dialysis, the rapid ↑ P_{osm} induced by the correction of hyponatremia is counterbalanced by HD-induced ↓ of potassium, uremic toxins including urea (urea does not cross the BBB as fast as water and act as an effective osmole relative to the brain compartment)



Mechanism of osmotic demyelination syndrome (ODS).

- Clinical manifestation are delayed (2–6 d), irreversible, or partially reversible: dysarthria, dysphagia, paraparesis, quadriparesis, and locked in Sd; behavioral disturbances, tremors, catatonia and seizures; lethargy, confusion, disorientation, obtundation, and coma
- MRI could show the demyelination lesions (delayed finding up to 4 wk) which can affect any part of the brain and spinal cord
- Some proposed preventive measures:
  - In pts likely to overcorrect (hypovolemic hyponatremia): DDAVP (1–2 μg IV or SC q6–8h) is given at the start of onset volume expansion (NS or hypertonic saline)
  - In pts on therapy where the goal is likely to be exceeded or overcorrected → stop therapy + D5W (6 mL/kg) or dDAVP
- Relowering [Na] to the daily correction limit of 8 mEq/L can ↓ the severity of ODS and even after the onset of neurologic, it is recommended to relower [Na] by 16 mEq/L
- For patient with baseline [Na] ≥120, it is probably unnecessary to relower Na in case of overcorrection, slowing the correction rate is enough in these cases

Specific Etiologies of Hyponatremia

Diuretics-induced Hyponatremia

- More common with thiazides than loop diuretics because loop diuretics prevent the generation of a corticomedullary interstitial osmotic gradient which limits the ability of the collecting tubule to reabsorb free water even if ADH is elevated
- Thiazide-induced hyponatremia is due to several mechanisms: (1) reduction in diluting function of the distal tubule; (2) an underlying tendency to increased water intake (polydipsia); (3) impaired urea-mediated water excretion

Hypervolemic Hyponatremia

- Hyponatremia is an important prognostic factor in CHF and cirrhosis

Syndrome of Inappropriate Antidiuresis (SIAD) (*NEJM* 2007;356:2064)

- Desalination: since volume expansion does not affect U_{osm} in SIAD, an expansion with isotonic solution results in a net electrolyte-free water gain in patients with SIAD (especially if U_{osm} >500) leading to worsening of the hyponatremia
- Etiologies: drugs, cancer (small cell lung cancer), pulmonary disorders, CNS disorders, hereditary nephrogenic SIAD (GOF mtation of V2 receptor; treated with urea; vaptan are ineffective therapy), idiopathic and transient (nausea, pain, anesthesia)
- Copeptin is produced during the cleavage of the vasopressin prohormone, it can be used as an indirect measurement tool for vasopressin levels
- U_{osm} is an indirect measurement for the ADH concentration, using copeptin in hyponatremia is of limited utility (beyond distinguishing primary polydipsia from the other etiologies of hyponatremia) (*Endocrine* 2018;60:384)
- SIAD has 5 subtypes:
  Type A: vasopressin/copeptin secretion is not related to S_{osm}; erratic ADH secretion
  Type B: relationship between S_{osm} and Vasopressin/copeptin is intact but lower threshold (reset osmostat)
  Type C: vasopressin/copeptin secretion is not related to S_{osm}; constant ADH secretion
  Type D: undetectable vasopressin/copeptin (nephrogenic SIAD)
  Type E: reverse relationship between S_{osm} and copeptin/vasopressin (barostat reset) due to increased sensitivity of baroreceptors to increased vasopressin release

Cerebral (or Renal) Salt Wasting

- The same lab profile as SIAD (hyponatremia, concentrated urine, high U_{Na}, hypouricemia, and ↑ FE_{UA} >11%). The FE_{UA} does not decrease after correction of the hyponatremia: stays >11%; in SIAD the FE_{UA} decreases to less than 11% with the correction of the hyponatremia (Am J Med Sci 2016;352:385)

Adrenal Insufficiency

- Cortisol deficiency disrupts the negative feedback loop that inhibits ADH release. The increase of corticotropin-releasing hormone production in response to cortisol deficiency promotes hypothalamic ADH release leading to hyponatremia (*PNAS* 2000;97:483)

Acute Hyponatremia

- Etiologies always involve a high free water intake with additional pathogenesis: postop, exercise, the use of 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”), haloperidol, thiazide diuretics, desmopressin, oxytocin, TURP/hysterectomy irrigants (glycine, sorbitol, mannitol, and IV cyclophosphamide)
- Glycine and sorbitol cause cerebral edema; mannitol does not cause cerebral edema (hypertonic hyponatremia)
- MDMA ↑ ADH release and free water intake in an effort to prevent hyperthermia
- Hypertonic saline 3% is an effective and life-saving for hyponatremia-induced cerebral edema

Mild Chronic Hyponatremia (*CJASN* 2015;10:2268)

- Asymptomatic, >72 hr and [Na] between 125 and 135 mEq/L
- Hyponatremia is a/w higher mortality and morbidities in outpatient, inpatient, and ICU settings (neurocognitive deficits, gait disturbances, falls, bone fractures, osteoporosis)

- It is not clear if correction of hyponatremia improves outcomes