Sodium & Water Assessment & Therapeutics

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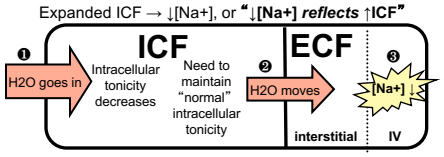
Assessing and managing Na/H2O disorders is complicated and requires a systematic approach.

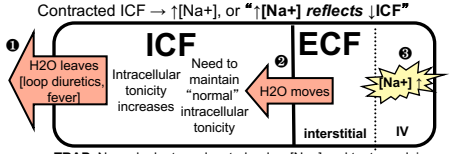
My patient's serum [Na+] is abnormal and/or they seem to be "dehydrated"!

Serum [Na+] is the best reflection of ICF status.
Why does serum [Na+] *reflect* ICF and what does it mean?

Expanded ICF → ↓[Na+], or **"↓[Na+] *reflects* ↑ICF"**



Contracted ICF → ↑[Na+], or **"↑[Na+] *reflects* ↓ICF"**



TRAP: Never look at an elevated or low [Na+] and try to explain how that might *cause* ↑ or ↓ ICF. It doesn't, and it reinforces a misconception. Serum [Na+] REFLECTS what's happening in the ICF. The ICF will look after itself, with consequences for the ECF.

assess the ICF

START HERE!

assess the ECF (~volume + interstitial water)

Serum [Na+]
Ⓝ135-145 mmol/L

Signs & Symptoms:
↓[Na+]: Cerebral edema, nausea/malaise, headache, lethargy, seizures, coma, noncardiogenic pulmonary edema
↑[Na+]: Rupture of cerebral veins, lethargy, weakness, irritability, twitching, seizures, coma

↑ hypernatremia (↓ ICF)

↓ hyponatremia (↑ ICF)

~38% incidence in hospitalized patients [Arch Intern Med. 2010;170(3):294-302; Am J Med 2006;117:S30-5]. Most vulnerable: post-op, elderly, ICU, gen med. 67% of cases are ACQUIRED in hospital. RR death ~2, 64% increase in LOS. Chronic: increased risk of falls and fractures.

Pseudohyponatremia: caused by high concentrations of active osmoles: hyperglycemia, lipemia/severe hyperlipidemia, mannitol. Plasma osmolality can be high, normal.

Causes: insufficient H2O intake (H2O restriction, lack of access to H2O, NPO, altered mental status, babies, loss of thirst response) +/- increased H2O loss (diarrhea, vomiting, diabetes insipidus, acute loop diuretic, hyperglycemia, extensive burns

Hypovolemia/contracted ECF:
[JAMA. 1999;281:1022-1029]
1. **Postural changes** (lying→standing): severe dizziness or HR ↑ ≥30bpm or SBP↓ ≥20mmHg
2. ↓JVP (<2cm ASA)
3. SCr/BUN <12 (or <10)
4. Urine [Na+] <20-30 mmol/L (if available)
5. ↓Urine output (<0.5 ml/kg/h)
6. Orbital depression
7. Skin tenting
8. Cool extremities
9. Dry mucous membranes
10. ↓capillary refill

Hypervolemia/excess ECF:
Edema (peripheral, pulmonary), ascites, ↑JVP, ↑BNP

Additional approaches to assessing hypovolemia vs. euvolemia:
Possibly greater diagnostic precision for detecting hypovolemia than clinical assessment alone:
(1) If NOT on diuretics: measure **fractional excretion of Na**: <1% = hypovolemia. [Arch Intern Med 1984;144:981-2]
(2) If on diuretics or not: **fractional excretion of UREA** (<35% = hypovolemia. [Kidney Int 2002;;62:2223-9]) or **fractional excretion of URIC ACID** (<12% = hypovolemia [(J Clin Endocrinol Metab 2008;93: 2991–7])

ADH (arginine vasopressin, AVP) facts:
- manufactured and released by the ***posterior pituitary*** (the "neurohypophysis")
- ADH's **purpose** is to (1) help *maintain blood pressure* by retaining H2O during hypovolemia (inefficient mechanism) and vasoconstriction (V1 receptors), (2) *prevent hyperosmolality* during dehydration (efficient mechanism)
- causes free H2O reabsorption from distal tubule via V2 receptors. Similar effect to exogenous free H2O administration (i.e., can result in hyponatremia d/t expanded ICF). "ADH=D5W"
- **two stimuli for release: (1)↑serum osmolality (the "osmotic stimulus" - most sensitive stimulus), (2) significant ↓volume (the "non-osmotic stimulus" - less sensitive stimulus)**
- ADH release turns off when serum osmolality is normal or low and pt is euvolemic or hypervolemic. If it's ON during these states, it's *inappropriate* (SIADH/SIAD)
- loss of ADH secretion ability = *neurogenic diabetes insipidus (DI)*; blocked ADH activity at the site of action (eg, by lithium, demeclocycline) = *nephrogenic DI*.
- when ADH is present, urine osmolality will be >100 mosm/kg
- ADH does NOT make you thirsty (only ↑ plasma osmolality makes you thirsty)

ECF STATUS?

MANAGEMENT:
1. Calculate total free water or "fluid" deficit (the amount of H2O that would lower the patient's Na to 140 or 145 mmol/L.
2. **ASSESS THE ECF**
3. Assess whether ICF, ECF, or both need to be repleted and the relative urgency of each.
4. Choose a form of H2O for repletion: **Use GI tract (PO H2O) whenever possible**. If IV replacement needed, choose a free-water-containing crystalloid for replacement of ICF +/- NS for ECF repletion. D5W is most efficient Na-lowering crystalloid. Infuse at 50-200 ml/h.
5. Choose RATE of administration: GOAL: reduce serum [Na+] by *no more than* ~0.5 mmol/L/h (i.e., ~12 mmol/L/day) to prevent ODS, though there is no evidence of cerebral harm from rapid (>0.5) vs. slower (<0.5 mmol/L/h) correction of hypernatremia. *[CJASN 2019;14:656-63]*
6. Reassess [Na+] at least once daily depending on severity).

Free water or "fluid" deficit (L):
[([Na+] actual / [Na+] desired) -1] x TBW

Change in serum [Na+] per L of crystalloid administered (Adrogue-Madias formula)

$$\text{Change in serum Na}^+ = \frac{(\text{infusate Na}^+ + \text{infusate K}^+) - \text{serum Na}^+}{\text{total body water} + 1}$$

where infusate [Na+] = 154 for NS. 513 for 3%NaCl. 855 for 5%NaCl. 130 for LR. Tells you what 1L will do to serum [Na+]

Diabetes Insipidus (DI) – central or nephrogenic
Causes: idiopathic 30%, **Central**: malignant/benign brain/pituitary tumors 25%, head trauma 16%, post cranial surgery 20%, ICH, CNS infection. **Nephrogenic**: pyelonephritis, renal amyloidosis, sickle cell anemia, hypokalemia, hypercalcemia, **drugs**: lithium, demeclocycline, corticosteroids, etOH, amhoB, vaptans, aminoglycosides, cisplatin, foscarnet, cidofovir
Diagnosis: Clinical suspicion + urine>2L/day + serum osmolality>urine osmolality in a hypernatremic patient + urine specific gravity <1.005. Serum vasopressin normal or elevated in nephrogenic DI with modest H2O restriction. *Vasopressin challenge test* to evaluate central DI.
Goal of Therapy: Maintain urine volume <1 mL/kg/h and/or urine osmolality >500mosm/L.
Therapy: *Central* **1.** Drink lots of water. **2.** DDAVP/desmopressin 1-4 ug/d SC/IM/IV over 30 mins in 50ml NS (10-20 mcg IN q12-24h) [binds only V2 receptors, so doesn't cause HTN response]. **3.** Thiazides ↓ urine volume (↑ urine osmolality, ↓ urine output by causing volume depletion → ↑ H2O retention via aldosterone & proximal Na reabsorption). **4.** Restrict Na intake (to ↑ Na & H2O retention in proximal tubule). **5.** Induce SIADH (chlorpropamide 250 – 500mg daily, carbamazepine 400 –1200 mg/d, clofibrate 500mg tid/qid)
Nephrogenic **#1**, **3**, and **4** above + remove cause if possible. DDAVP won't help. If Li-induced, amiloride 10mg/d can cure and prevent DI [Nat Rev Nephrol 2009;5, 270–276], and case reports suggest acetazolamide may help [e.g. NEJM 2016;375:2008-9].

hypervolemic hyponatremia
Causes: HF, ascites, CKD, iatrogenic, primary polydipsia

MANAGEMENT:
-treat the underlying cause -often DIURESIS is required -know ascites vs. CHF management principles

euvolemic hyponatremia
Causes: adrenal [cortisol] insufficiency (look for ↑[K+]), **SIADH/SIAD**

DIAGNOSIS of SIADH/SIAD:
Plasma osmolality <275 mOsmol/kg + urine osmolality >100 mosm/kg + urine [Na+] >20mEq/L + absence of thiazide diuretic [SMJ 2009;102:380-4, *Am J Med 2013;126(10):S1–42*]. If on diuretic, add fractional excretion of Uric Acid (>12%) to rule in SIADH. [JClinEndocrinolMetab 2008;93: 2991–7], though definitive diagnosis can't be made until thiazide stopped. If uncertain about euvolemia, give 500mL IV NS & remeasure serum Na+.

MANAGEMENT of SIADH/SIAD:
1. Identify & remove cause
2. H2O restriction (<1000 or <500 mL/day)
3. Urea 0.25-0.5 g/kg/day PO
4. Furosemide +/- NaCl liberalization (eg, >10g/d)
5. Fludrocortisone
6. Other: lithium, demeclocycline, tolvaptan (PO) [2014 Euro guidelines (Eur J Endocrinol 2014;170(3):G1–G47)] recommend *against* all of these.
Spasovski et al. Eur J Endocrinol 2014 Feb 4;170(3):G1–G47. See also Verbalis et al. Am J Med 2013;126(10):S1–42.

Common Causes of SIADH/SIAD:
pain, vomiting, CNS injury / inflammation / tumor, pituitary tumors, any lung injury / inflammation / tumor, porphyria.

Drugs: carbamazepine, chlorpropamide, clofibrate, cyclophosphamide, interferons, ecstasy, opioids, oxytocin, PTZs, SSRIs, NSAIDs, TCAs, mirtazapine, venlafaxine, vincristine, vasopressin, desmopressin, nicotine. **SIADH usually resolves when culprit drug is cleared.**

MANAGEMENT:
1. Manage cause (vomiting, diarrhea, etc.)
2. Shut down ADH secretion by restoring VOLUME to the intravascular space.

VOLUME REPLACEMENT
IV-adults: NS (or equivalent) 250-1000ml over 15-60mins depending on severity, pt weight, age.
REASSESS ECF. Caution if underlying heart failure. If necessary, follow with NS (or equivalent) IV infusion @ 50-250 ml/h. D5-1/2NS requires 1.5x the volume as NS. Reassess frequently (≥ once daily) until hypovolemia +/- hyponatremia resolved.
ORAL: Water, WHO-ORS, water+salt, sports drinks, Rehydralyte (310 mOsm/kg), Pedialyte (250 mOsm/kg) [Contain 2-3 g/dL glucose, 45-90 mEq/L Na+, 30 mEq/L of base, and 20-25 mEq/L K+].

Hypovolemic Hyponatremia
If hyponatremia is severe (<125 mmol/L) see "Treating severe hyponatremia" box!
If hyponatremia not severe, treat the hypovolemia and hyponatremia will resolve naturally via ADH shutdown → produce dilute urine → ICF depletion → raises serum [Na+].
Tip: When correcting hypovolemic hyponatremia (almost always caused by ADH secretion), it's not the Na+ in the crystalloid that raises the serum [Na+]. It's the crystalloid staying in the ECF (IV space specifically) → shuts off ADH secretion → produce dilute urine → deplete ICF → raises serum [Na+].

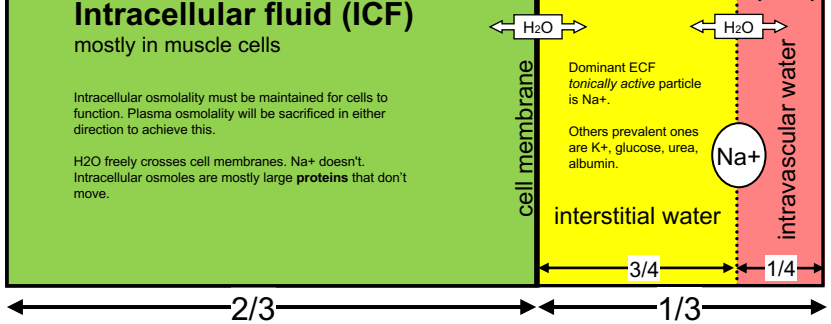
Balanced Crystalloids (e.g. PlasmaLyte, PlasmaLyte 148, BMES):
Have physiologic [Na+] (140), [Cl-] (98), osmolality (294) + buffers (acetate, gluconate). Invented to cause less hyperchloremic metabolic acidosis than NS in patients needing large volume replacement. **Outcomes**: May cause slightly less hyperchloremia (~2 points less on average) than NS, but no difference in mortality, need for renal replacement therapy, SCr, or any other clinical outcome. PLUS trial: NEJM 2022;386:815-26; MA od 6 trials N=34,000: Hammond et al. NEJM Evid. 2022;1(2). **Lactated Ringers**: same idea. [Na+] 130, [Cl-] 109. lactate buffer.

Diuretics and Na/H2O balance:
Thiazide: depletes a lot of Na, but not much H2O. Makes you pee roughly NS, but not much of it.
Loop: makes you pee roughly 1/2NS.
Spironolactone: Makes you pee NS, but not much of it. Doesn't usually disturb Na balance.
Metolazone: a thiazide that makes you pee a LOT of NS.
Trick: To remove volume while lowering Na (eg, hypervolemic hypernatremia): give metolazone + D5W, or furosemide + LOTS of D5W.

CPM/ODS (central pontine myelinolysis/osmotic demyelination syndrome):
spastic quadriparesis and pseudobulbar palsy/paralysis (dysphagia, dysarthria, weakness of the tongue, emotional lability). Consciousness may be impaired. Lesions visible on CT or MRI. Outcomes vary from death to complete recovery, regardless of severity. No specific therapy except to avoid causing it. [Eur Neurol 2009;61:59-62, Eur J Intern Med 2008;19:29-31.] Incidence unknown, but associated with initial Na+<120 PLUS rise in serum Na+ by >25mmol/L or achieving normonatremia within first 48h [NEJM 1987; 317:1190-1195]. Cause presumed to be cell death d/t rate of correction of hyponatremia overwhelming cells' ability to restore lost intracellular organic osmolytes ejected during hyponatremia. Very rarely caused by overcorrection of HYPERnatremia.

Where's your water?

Total body water (TBW) = 0.6* x total body weight
*More precisely: 0.45 for elderly female, 0.5 for non-elderly female or elderly male, 0.6 for non-elderly lean male.



Where does 1L of exogenous fluid end up?

Crystalloid / Colloid	ICF	ECF (intravascular)
Tap water, D5W	666mL	333mL (84mL)
NS (0.9% NaCl), PlasmaLyte, "balanced crystalloids", BMES, Lactated Ringer's (Hartmann's)*	0	1000mL (250mL)
D5-1/2NS, 1/2NS	333mL	666mL (166ml)
2/3D5-1/3NS	445mL	555mL (139mL)
3% NaCl giving 1L of this would be LETHAL. These values are given for illustration/comparison purposes only.	-2000mL	+3000mL (750mL)
Albumin 5%, blood	0	1000mL (1000mL)
hetastarch, pentaspan	0	1000mL (1000mL)

*some favor over NS in trauma, shock, prolonged surgery d/t lower risk of hyperchloremic metabolic acidosis. **Not superior to NS** in terms of patient outcomes [PLUS trial. NEJM 2022;386(9):815–26, Hammond NE, et al. NEJM Evid. 2022;1(2)]

Treating severe hyponatremia (<120 mmol/L) or hyponatremia with severe symptoms (N&V, headache, CV distress, deep somnolence, seizures, coma (GCS<9)]: *[Eur J Endocrinol 2014 Feb 4;170(3):G1–G47]*. Adrogue's formula underpredicts rise in [Na+] in 74% of cases [CJASN 2007;2:1110–7].
TREATMENT: (based on SLASA trial JAMA Intern Med. 2021;181(1):81-92, Verbalis JG et al. AmJMed 2013;126:S1-S42 consensus guidelines)
ACUTE severe hyponatremia (<24h duration) with severe symptoms (minimal risk of ODS):
- GOAL: rapid 4-6 mmol/L increase in serum [Na+]
- 100mL 3%NaCl IV over 10 mins, repeated twice at 30min intervals as needed
- then allow serum [Na+] to correct to normal spontaneously (low risk of ODS), or if not correcting, move to approach below starting with Day2.

CHRONIC severe hyponatremia (>24h duration) with severe symptoms (risk of ODS): Usually caused by SIADH. *Especially high risk of ODS in patients with serum Na+<105 mmol/L, alcoholism, hypokalemia, malnutrition, advanced liver disease.*
- Day1 goal: 4-6 mmol/Ld increase in serum [Na+] in first 6 hours. ("Rule of Sixes": *"six a day makes sense for safety: so six in six hours for severe sx's and stop."* [AmJKidneyDis 2010;56:774-779] using 100mL 3% NaCl IV over 10 mins, repeated twice at 30min intervals as needed.
- Day2+: max 8-12 mmol/L/day increases in serum [Na+] (or 4-6 mmol/L/d if especially high-risk of ODS) using 3% NaCl IV infused at 0.5-2 mL/kg/h
- max 10-12 mmol/L/24h increase in serum [Na+] (max 8 mmol/L/24h if especially high risk of ODS)
- measure serum [Na+] q4-6h until serum [Na+] >125 mmol/L
- implement standard SIADH treatment measures
- excessive H2O diuresis can occur, but role of concurrent desmopressin + IV D5W is unclear. If used, stop when serum [Na+] exceeds ~128 mmol/L [Am J Kidney Dis 2013;61:571-578]