Sodium & Water Assessment & Therapeutics

by Peter Loewen, B.Sc.(Pharm), ACPR, Pharm.D., R.Ph., FCSHP
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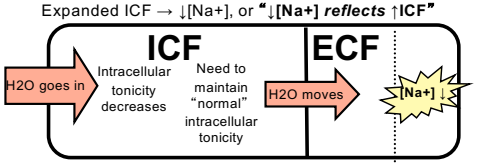
Assessing and managing Na/H2O disorders is complicated and requires a systematic approach.

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

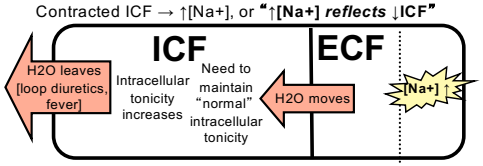
Serum [Na+] is the best reflection of ICF status.

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)

Common causes: water restriction (lack of access to water, loss of thirst response), diarrhea, vomiting, diabetes insipidus, acute diuresis with loop diuretic PLUS lack of or insufficient water intake.

↓ 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.

Hypovolemia/contracted ECF:
[JAMA. 1999;281:1022-1029]
1. **Postural changes** (lying→standing): severe dizziness, HR ↑ ≥30bpm, 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])

ECF STATUS?

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

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

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

Diabetes Insipidus (DI)

Causes: idiopathic 30%, malignant/benign brain/piiituitary tumors 25%, head trauma 16%, post cranial surgery 20%. **Drugs (always nephrogenic DI)**: Lithium, demeclocycline. etOH, amho B, vaptans, aminoglycosides, cisplatin, foscarnet, cidofovir [Saifan C, et al. ISRN Nephrol 2013;2013:1–7].

Diagnosis: Clinical suspicion + urine specific gravity <1.005 + uOsm<200 mOsm/kg in a hypernatremic patient. More elaborately: water deprivation test (Miller-Moses test)

Goal of Therapy: Maintain urine volume <1 mL/kg/h and/or urine osmolality >500 mosm/L.

Therapy:

Neurogenic

1. Drink lots of water. **2.** DDAVP 1-4 ug/d SC/IM/IV over 30 mins in 50ml NS (10-20 mcg IN q12-24h). **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.** Cause SIADH (chlorpropamide 250 – 500 qd. carbamazepine 400 –1200 /d, clofibrate 500 tid/qid)

Nephrogenic **#1**, **3**, and **4** above. If Li-induced, AMILORIDE 10mg/d can cure and prevent DI [Nat Rev Nephrol 2009;5, 270–276]

MANAGEMENT:
1. Calculate total H2O deficit (the amount of H2O that would lower the patient's Na to 140 or 145 mmol/L. ("free water deficit")

2. ASSESS THE ECF

3. Assess whether ICF, ECF, or both need to be repleted and the relative urgency of each.
4. 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 a ROUTE and 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 this is rare when correcting hypernatremia.
6. Reassess frequently (at least once daily depending on severity).

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+.

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 of SIADH/SIAD:
1. Identify & remove cause
2. H2O restriction (<1000 or <500 mL/day)
3. Urea 0.25-0.5 g/kg/day
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.

hypovolemic hyponatremia
Causes: volume depletion (millions of causes) with continued intake of hypotonic fluid (e.g. water)

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

VOLUME REPLACEMENT

IV-adults: NS 250-1000ml over 15-60mins depending on severity, pt weight, age. **REASSESS ECF**. Caution if underlying heart failure. If necessary, follow with NS 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 hypovolemia normally 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+].

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), (2) *prevent hyperosmolality* during dehydration (efficient mechanism)
- causes free H2O reabsorption from distal tubule. 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/SIAH)
- 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)

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 >25mmo/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.

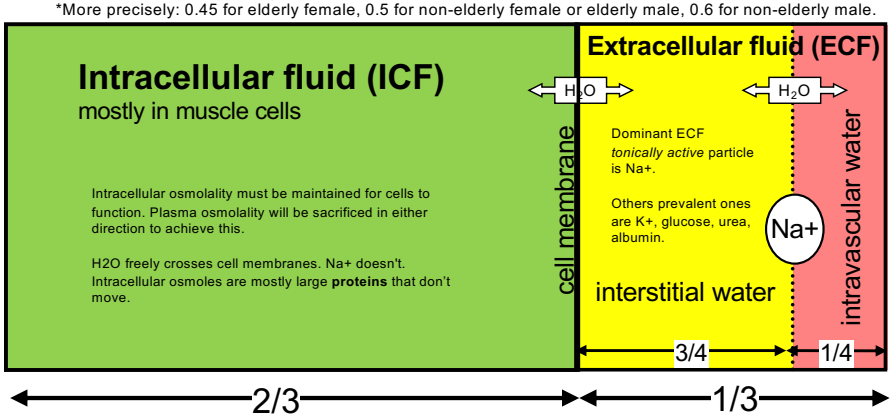
Treating severe hyponatremia (<120 mmol/L) or hyponatremia with severe symptoms (N&V, headache, CV distress, deep somnolence, seizures, coma (GCS<9)): *[Eur J Endocrinol 2014 Feb 4;170(3):G1–G47].* Adrogue's formula underpredicts rise in [Na+] in 74% of cases [ClinJAmSocNephrol 2007;2:1110–7].

TREATMENT: (based on 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/L/d 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]

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 male.



Where does 1L of exogenous fluid end up?

Crystalloid / Colloid	ICF	ECF (intravascular)
Tap water, D5W	666mL	333mL (84mL)
NS (0.9% NaCl)	0	1000mL (250mL)
D5-1/2NS, 1/2NS	333mL	666mL (166ml)
2/3D5-1/3NS	445mL	555mL (139mL)
3% NaCl*	-2000mL	+3000mL (750mL)
Albumin 5%, blood	0	1000mL (1000mL)
hetastarch, pentaspan	0	1000mL (1000mL)

*giving 1L of this would surely KILL a patient. These values are given for illustration/comparison purposes only.