hyponatremia treatment guidelines: 2012 and beyond

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Joseph G. Verbalis: disclosures

consultant: Astellas, Ferring, Cardiokine, Otsuka
advisory board: Astellas, Otsuka
data safety board: Ferring
grant support: NHLBI, NIA, NCATS, Otsuka
**body fluid compartments**

Water is the largest component of our body; since the major determinant of body water is AVP-regulated water excretion by the kidneys, it follows logically that AVP must be the most important hormone in the body.

**AVP stimulation and effects**

- **Hyperosmolality, hypovolemia, angiotensin II**
- **Baroreceptors, natriuretic peptides**

AVP stimulates vasoconstriction and renal water reabsorption through V1a and V2 receptors, respectively.
Receptor-Mediated Effects of AVP

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>Site of Action</th>
<th>Activation Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>V&lt;sub&gt;1a&lt;/sub&gt;</td>
<td>Vascular smooth muscle cells, platelets, lymphocytes and monocytes, liver</td>
<td>Vasoconstriction, platelet aggregation, cytokine release, glycogenolysis</td>
</tr>
<tr>
<td>V&lt;sub&gt;1b&lt;/sub&gt;</td>
<td>Anterior pituitary</td>
<td>ACTH and β-endorphin release</td>
</tr>
<tr>
<td>V&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Renal collecting duct principal cells</td>
<td>Free water absorption</td>
</tr>
</tbody>
</table>

AVP Regulation of Water Reabsorption from Renal Tubular Cells
prevalence of dysnatremias at initial presentation to a health care provider
(data from 303,577 samples on 120,137 patients available for analysis)


relationship between hospital admission serum [Na⁺] and in-hospital mortality

Diabetes Insipidus and SIADH
Joseph G. Verbalis, MD

Chronic hyponatremia is also associated with increased adverse outcomes.

- Increased mortality over a 12-year period of outpatient follow-up
- Significantly increased risk of fracture


Hyponatremic disorders

- Hypovolemia/dehydration
- Polydipsia
- SIADH
- Extracellular fluid volume expansion
- Congestive heart failure
- Hepatic cirrhosis
- Bilateral ureteral obstruction
Hyponatremia can be caused by **dilution** from retained water, or by **depletion** from electrolyte losses in excess of water.
SIADH: essential criteria

- true plasma hypoosmolality
- urine concentration inappropriate for plasma osmolality ($U_{\text{osm}} > 100 \text{ mOsm/kg H}_2\text{O}$)
- clinical euvolemia, no diuretic therapy
- absent renal sodium conservation ($U_{\text{Na}} > 30 \text{ mmol/L}$)
- normal thyroid, adrenal and renal function


Diabetes Insipidus and SIADH

plasma AVP levels are inappropriately elevated in >95% of patients with SIADH


stimuli to AVP secretion

related to fluid homeostasis:
- hyperosmolality
- hypotension
- hypovolemia
- angiotensin II

independent of fluid homeostasis:
- nausea
- hypoxia
- hypercarbia
- hypoglycemia
- stress: cytokines
- physical activity
nephrogenic SIAD

caused by an activating mutation of the AVP V2R at the same site that also can cause DI via an inactivating mutation

Diabetes Insipidus and SIADH

Joseph G. Verbalis, MD

Arieff et al. Medicine 56:121, 1976 (hospital consults in one year; [Na+]<128 mmol/L)
Acute hyponatremia can cause death from cerebral edema and brain herniation.

**London marathon, April 22, 2007**

“A 22-year-old man died after completing his first London Marathon because he drank too much water. David Rogers collapsed at the end of the race and died yesterday in Charing Cross Hospital.”

“Today it emerged the fitness instructor from Milton Keynes died from hyponatraemia, or water intoxication. This is when there is so much water in the body that it dilutes vital minerals such as sodium down to dangerous levels. It can lead to confusion, headaches and a fatal swelling of the brain.”

p[Na⁺] = 122 mmol/L

Drank Lucozade

http://www.dailymail.co.uk/news/article-450341/Marathon-victim-died-drinking-MUCH-water.html
Diabetes Insipidus and SIADH
Joseph G. Verbalis, MD

**chronic hyponatremia is associated with much less severe symptomatology**

<table>
<thead>
<tr>
<th></th>
<th>acute</th>
<th>chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients</td>
<td>14</td>
<td>52</td>
</tr>
<tr>
<td>duration</td>
<td>&lt; 12 hrs</td>
<td>3 days</td>
</tr>
<tr>
<td>serum [Na⁺]</td>
<td>112 ± 2</td>
<td>118 ± 1</td>
</tr>
<tr>
<td>stupor or coma</td>
<td>100%</td>
<td>6%</td>
</tr>
<tr>
<td>seizures</td>
<td>29%</td>
<td>4%</td>
</tr>
<tr>
<td>mortality</td>
<td>50%</td>
<td>6%</td>
</tr>
<tr>
<td>low [Na⁺] deaths</td>
<td>36%</td>
<td>0%</td>
</tr>
</tbody>
</table>


**brain volume regulation**

1. true loss of brain solute
2. can reduce or eliminate brain edema despite severe hypoosmolality
3. time dependent process


THIS IS NOT A NORMAL BRAIN!
symptomatic hyponatremia: neurological manifestations

- headache
- irritability
- nausea / vomiting
- mental slowing
- unstable gait / falls
- confusion / delerium
- disorientation

- stupor / coma
- convulsions
- respiratory arrest

symptomatic but less impaired; usually chronic

life-threatening; usually acute

the degree of symptomatology is a surrogate for the duration of hyponatraemia

pontine and extrapontine myelinolysis: clinical manifestations

- tremor
- incontinence
- hyperreflexia, pathological reflexes
- quadripareisis, quadriplegia
- dysarthria, dysphagia
- cranial nerve palsies
- mutism, locked-in syndrome
**central pontine myelinolysis:**

white areas in the middle of the pons indicate massive demyelination of descending axons (corticobulbar and corticospinal tracts)

Wright, Laureno & Victor

*Brain* 102:361-385, 1979

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safe correction of hyponatremia entails balancing the risks of the hyponatremia versus the risks of the correction; these, in turn, depend on the degree of brain volume regulation that has occurred

Verbalis

*Trends Endocrinol Metab* 3:1-7, 1992
managing the rate of correction of hyponatremia

1. maximum correction for chronic hyponatremia:
   \[ \leq 12 \text{ mmol/L in the first 24 h} \]
   \[ \leq 18 \text{ mmol/L in the first 48 h} \]

2. even lower (\(\leq 8 \text{ mmol/L in any 24h period}\)) if any of the following are present:
   - serum Na \(\leq 105 \text{ mEq/L}\)
   - hypokalemia
   - alcoholism and/or malnutrition
   - liver disease

3. maximum correction for acute hyponatremia:
   not ascertained, but much lower risk

treatments for hyponatremia

- isotonic saline infusion
- hypertonic saline infusion
- vaptan (conivaptan, tolvaptan)  \(\text{short-term}\)
- fluid restriction
- demeclocycline
- furosemide + NaCl
- mineralocorticoids
- urea
- vaptan (tolvaptan)  \(\text{long-term}\)
hypertonic saline correction

- choose desired correction rate of plasma [Na⁺] (e.g., 1.0 mEq/L/h)
- obtain or estimate patient’s weight (e.g., 70 kg)
- multiply weight X desired correction rate and infuse as ml/h of 3% NaCl (e.g., 70 kg X 1.0 mEq/L/h = 70 ml/h infusion)
Diabetes Insipidus and SIADH

Nielsen et al., JASN 10:647-663, 1999
**diuresis:**
increased excretion of urine by the kidney; includes water and typically increased solute excretion as well

**aquaresis:**
increased excretion of water by the kidney without increased solute, i.e., electrolyte-sparing excretion of free water by the kidney

what aquaresis really looks like!

courtesy nephology fellows, Lenox Hill Hospital, New York, NY
**tolvaptan: SALT studies and SALT-WATER open label extension study**

![Graph showing changes in serum sodium levels over time with tolvaptan and placebo.](image1)


**SALT: mean increases in serum [Na⁺] after 30 d in patients with cirrhosis, HF, and SIADH**

![Bar graph showing delta increase in serum sodium with tolvaptan and control.](image2)

tolvaptan: SALT trials, SIADH patients
changes in SF-12 general health survey scores after 30 days of oral administration

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=39)</th>
<th>Tolvaptan (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(physical function, body pain, general health, physically limited accomplishment)</td>
<td>-0.16</td>
<td>3.64</td>
</tr>
<tr>
<td>Mental Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(vitality, social function, calmness, sadness, emotionally limited accomplishment)</td>
<td>-0.45</td>
<td>5.47</td>
</tr>
</tbody>
</table>

*p = 0.019
p = 0.051


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treatment of hyponatremia results in an improvement of the MCS to the mean of average U.S. adults

SF-12 Mental Component Summary (MCS)
**fluid restriction**

**general guidelines:**
- restrict all intake that is consumed by drinking, not just water
- aim for a fluid restriction that is 500 ml/d below the 24-hour urine output
- do not restrict sodium unless indicated

**predictors of failure of fluid restriction:**
- high urine osmolality (>500 mOsm/kg H₂O)
- urine Na⁺ + K⁺ greater than the serum [Na⁺]
- 24-hour urine output <1,500 ml/d
- increase in serum [Na⁺] <2 mmol/L in 24h
**Urinary/plasma electrolyte ratio**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Recommended fluid consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.0</td>
<td>0 mL</td>
</tr>
<tr>
<td>0.5–1.0</td>
<td>Up to 500 mL</td>
</tr>
<tr>
<td>&lt;0.50</td>
<td>Up to 1 L</td>
</tr>
</tbody>
</table>


**Hyponatremia treatment algorithm**

**Euvolemic hyponatremia (SIADH)**

**LEVEL 3 – SEVERE SYMPTOMS:** vomiting, seizures, obtundation, respiratory distress, coma

- Hypertonic NaCl, followed by fluid restriction ± vaptan

**LEVEL 2 – MODERATE SYMPTOMS:** nausea, confusion, disorientation, altered mental status

- Vaptan, followed by fluid restriction
**osmotic demyelination syndrome (ODS)**

No cases of CPM have been reported following correction of hyponatremia with vaptans in >5,000 patients to date.

Wright, Laureno & Victor
*Brain*
102:361-365, 1979

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**hyponatremia treatment algorithm**

**euvolemic hyponatremia (SIADH)**

**LEVEL 3 – SEVERE SYMPTOMS:**
- vomiting, seizures, obtundation, respiratory distress, coma

- hypertonic NaCl, followed by fluid restriction ± vaptan

**LEVEL 2 – MODERATE SYMPTOMS:**
- nausea, confusion, disorientation, altered mental status

- vaptan, followed by fluid restriction

**LEVEL 1 – NO OR MINIMAL SYMPTOMS:**
- headache, irritability, inability to concentrate, altered mood, depression

- fluid restriction, but vaptan under select circumstances:
  - inability to tolerate fluid restriction or failure of fluid restriction
  - unstable gait and/or high fracture risk
  - very low sodium level (<125 mEq/L) with increased risk of developing symptomatic hyponatremia
  - need to correct serum [Na⁺] to safer levels for surgery or procedures, or for ICU/hospital discharge
  - prevention of worsened hyponatremia with increased fluid administration
  - therapeutic trial for symptom relief

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hyponatremia increased the risk of fracture in CKD independently of osteoporosis

1,408 female patients from Cork, Ireland adjusted for age, T-score, amenorrhea, steroid use, liver disease, smoking and EtOH use, liver disease, and osteoporosis treatments


correction of hyponatremia normalizes gait stability in “asymptomatic” hyponatremia

serum \([Na^+]=130 \text{ mEq/L}\)

serum \([Na^+]=139 \text{ mEq/L}\)

serum \([Na^+]=124 \text{ mEq/L}\)

serum \([Na^+]=135 \text{ mEq/L}\)

increased risk of falls with “asymptomatic” hyponatremia

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>% Falls</th>
<th>Odds ratio</th>
<th>Adjusted odds ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>“asymptomatic” chronic hyponatremia</td>
<td>122</td>
<td>21.3%</td>
<td>9.45</td>
<td>67.43 (7.48–607.42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2.64–34.09)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>normonatremic controls</td>
<td>244</td>
<td>5.35%</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*adjusted for age, sex and covariates


hyponatremia induces marked bone loss in rats

normonatremic
[Na⁺] = 140

hyponatremic
[Na⁺] = 115

Verbalis, Barsony, et al. JBMR 25:554-663, 2010
Hyponatremia induces a 5-fold increase in osteoclasts compared to normonatremic controls by TRAP staining.

Odds ratio for hyponatremia as a predictor of osteoporosis in NHANES III database.

Bone mineral density by of hip measured by DEXA; results adjusted for age, sex, BMI, physical activity, serum vitamin D (ng/mL) and diuretic use.

Mean serum [Na^+] = 133.0 ± 0.2 mmol/L.
why does hyponatremia cause osteoporosis???

one-third of total body sodium is stored in bone, and mobilization of this sodium from bone during prolonged deprivation requires the resorption of bone matrix, similar to the release of stored calcium to compensate for calcium deprivation.


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hyponatremia-induced activation of ROS pathways in serum and in osteoclasts differentiated from RAW264.7 cells

Chronic hyponatremia exacerbates multiple manifestations of senescence in male rats

Julia Barsony, Michaele B. Manigrasso, Qin Xu, Helen Tam & Joseph G. Verbalis

1. osteoporosis
2. hypogonadism
3. cardiac fibrosis
4. sarcopenia
5. decreased body fat

Barsony et al. AGE, Jan 5 2012 [Epub ahead of print]
the Japanese eat a low fat diet and have lower rates of cardiovascular disease than the English and Americans.

the French eat a high fat diet and have lower rates of cardiovascular disease than the English and Americans.

the Chinese drink little alcohol and have lower rates of cardiovascular disease than the English and Americans.

the Italians drink much alcohol and have lower rates of cardiovascular disease than the English and Americans.

evidence-based conclusions?

eat and drink whatever you want

it’s speaking English that kills you

courtesy of Dr. Peter Liu, University of Toronto
tolvaptan: need to continue therapy after discharge depends on the etiology of the SIADH

<table>
<thead>
<tr>
<th>Aetiology of SIADH</th>
<th>Likely duration of SIADH</th>
<th>Relative risk of chronic SIADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumours producing vasopressin ectopically (small-cell lung carcinoma, head and neck carcinoma)</td>
<td>Indefinite</td>
<td>High</td>
</tr>
<tr>
<td>Drug-induced, with continuation of offending agent (carbamazepine, SSRIs)</td>
<td>Duration of drug therapy</td>
<td></td>
</tr>
<tr>
<td>Brain tumours</td>
<td>Indefinite</td>
<td></td>
</tr>
<tr>
<td>Idiopathic (benign)</td>
<td>Indefinite</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>1–4 weeks</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1–2 weeks</td>
<td></td>
</tr>
<tr>
<td>Inflammatory brain lesions</td>
<td>Dependent on response to therapy</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure (chronic obstructive lung disease)</td>
<td>Dependent on response to therapy</td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>Dependent on response to therapy</td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>2–7 days to indefinite</td>
<td></td>
</tr>
<tr>
<td>Drug-induced, with cessation of offending agent</td>
<td>Duration of drug therapy</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2–5 days</td>
<td></td>
</tr>
<tr>
<td>Nausea, pain, prolonged exercise</td>
<td>Variable depending on cause</td>
<td></td>
</tr>
<tr>
<td>Post-operative hyponatraemia</td>
<td>2–3 days postoperatively</td>
<td></td>
</tr>
</tbody>
</table>

*Time frames are based on clinical experience.