diagnosis and therapy of hyponatremia: what is new?

Joseph G. Verbalis, MD
Professor of Medicine and Physiology
Chief, Endocrinology and Metabolism
Director, Georgetown-Howard Universities
Center for Clinical and Translational Science
Georgetown University
Washington, DC USA
Joseph G. Verbalis: disclosures

consultant: Ferring, Otsuka

advisory board: Otsuka

data safety board: Ferring

grant support: NHLBI, NIDDK, NIA, NCATS, Otsuka
hyponatremia: what is new?

• success rates of therapies for hyponatremia
• predictors of failure of fluid restriction
• European hyponatremia “guidelines”
• exercise-associated hyponatremia
• use of 3% NaCl as bolus therapy
• hyponatremia-associated osteoporosis and bone fractures
• nephrogenic SIAD (V2R gain of function mutation)
A 75-year-old female was admitted for symptomatic hyponatremia with a serum $[Na^+] = 123$ mmol/L. She has a several year history of mild chronic hyponatremia, but recently has experienced confusion and dizziness. She was euvolemic on clinical exam, and was not taking antidepressants or diuretics. After 3 days on a confirmed 1,000 ml/d fluid restriction, serum $[Na^+] = 126$ mmol/L, but the patient is still symptomatic and complains of thirst. Laboratory data on day 3 are:

- $[Na^+]$, mEq/L 126
- $[K^+]$, mEq/L 4.0
- Posm, mOsm/kg H$_2$O 265
- BUN, mg/dL 6
- creatinine, mg/dL 0.8
- Uosm, mOsm/kg H$_2$O 335
- urine $[Na^+]$, mEq/L 45
- urine $[K^+]$, mEq/L 70
- TSH, µIU/L 3.5
- plasma cortisol, µg/dL 18

**Issues to be discussed:**

1. Diagnosis of SIADH
2. Appropriate selection of therapy in hyponatremic patients
3. When to use fluid restriction and predictors of failure of fluid restriction
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

plasma AVP levels are inappropriately elevated in >95% of patients with SIADH
<table>
<thead>
<tr>
<th>Test</th>
<th>All SIADH (%)</th>
<th>US SIADH (%)</th>
<th>EU SIADH (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Test Performed</td>
<td>175 (11)</td>
<td>116 (11)</td>
<td>52 (11)</td>
<td>0.793</td>
</tr>
<tr>
<td>All Bartter diagnostic criteria</td>
<td>732 (47)</td>
<td>506 (49)</td>
<td>215 (44)</td>
<td>0.070</td>
</tr>
<tr>
<td>• Serum osmolality</td>
<td>1034 (67)</td>
<td>685 (66)</td>
<td>327 (67)</td>
<td>0.862</td>
</tr>
<tr>
<td>• Urine osmolality</td>
<td>1063 (68)</td>
<td>749 (72)</td>
<td>294 (60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>• Urine sodium</td>
<td>975 (63)</td>
<td>688 (67)</td>
<td>274 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additional Labs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cortisol</td>
<td>506 (33)</td>
<td>356 (34)</td>
<td>141 (29)</td>
<td>0.030</td>
</tr>
<tr>
<td>• TSH</td>
<td>984 (63)</td>
<td>655 (63)</td>
<td>318 (65)</td>
<td>0.569</td>
</tr>
<tr>
<td>All of the above</td>
<td>329 (21)</td>
<td>222 (22)</td>
<td>102 (21)</td>
<td>0.789</td>
</tr>
<tr>
<td>Serum Uric Acid</td>
<td>422 (28)</td>
<td>262 (25)</td>
<td>160 (33)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

treatments for hyponatremia

- isotonic saline infusion
- hypertonic saline infusion
- vaptan (conivaptan, tolvaptan)

short-term

- fluid restriction
- demeclocycline
- furosemide + NaCl
- mineralocorticoids
- urea
- vaptan (tolvaptan)

long-term
hyponatremia: symptom-based treatment recommendations
hyponatremia treatment algorithm based on neurological symptoms

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

LEVEL 2 – MODERATE SYMPTOMS: altered mental status, disorientation, confusion, unexplained nausea, gait instability

LEVEL 1 – NO OR MINIMAL SYMPTOMS: difficulty concentrating, irritability, altered mood, depression, unexplained headache

ALL: fluid restriction, but consider pharmacologic therapy (vaptan, urea) under select circumstances:
- inability to tolerate fluid restriction or predicted failure of fluid restriction (see table)
- very low [Na⁺] (<125 mmol/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
- unstable gait and/or high fracture risk
- prevention of worsened hyponatremia with increased fluid administration
- therapeutic trial for symptom improvement

HYPO: solute repletion (isotonic NaCl iv or oral sodium replacement)

EU: vaptan, limited hypertonic NaCl, or urea, followed by fluid restriction

HYPER: vaptan, followed by fluid restriction

ALL: hypertonic NaCl¹, followed by fluid restriction ± vaptan²

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

LEVEL 2 – MODERATE SYMPTOMS:
- altered mental status
- disorientation
- confusion
- unexplained nausea
- gait instability

LEVEL 1 – NO OR MINIMAL SYMPTOMS:
- difficulty concentrating
- irritability
- altered mood
- depression
- unexplained headache

³ Hypertonic NaCl may cause osmotic demyelination syndrome (ODS), especially if rapid correction is attempted.
### Table 5  General Recommendations for Employment of Fluid Restriction and Predictors of the Increased Likelihood of Failure of Fluid Restriction

**General recommendations:**
- 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 volume.
- Do not restrict sodium or protein intake unless indicated.

**Predictors of the likely failure of fluid restriction:**
- High urine osmolality (>500 mOsm/kg H$_2$O).
- Sum of the urine Na$^+$ and K$^+$ concentrations exceeds the serum Na$^+$ concentration.
- 24-hour urine volume <1500 mL/d.
- Increase in serum Na$^+$ concentration <2 mmol/L/d in 24-48 hours on a fluid restriction of ≤1 L/d.

D = day; H$_2$O = water; K = potassium; kg = kilogram; L = liter; mL = milliliter; mmol = millimole; mOsm = milliosmole; Na = sodium.

*Verbalis et al, Am J Med 126:S1-42, 2013*
use of urine electrolytes to predict stringency of fluid restriction

<table>
<thead>
<tr>
<th>urine/plasma electrolyte ratio</th>
<th>recommended fluid consumption</th>
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<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>

case #1: U/P electrolyte ratio = \(\frac{85+50}{120} = 1.12\)
fluid restriction

- fluid restriction in patients with SIADH corrects hyponatremia by only 1-2 mmol/L/day, even when severe (<500 ml/day)

- in addition, fluid restriction is poorly tolerated because of increased thirst, with subsequent poor compliance

## Success Rates in Treating Hyponatremia by Physicians in the HN Registry

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<th>Diagnosis &amp; Treatment</th>
<th>$\Delta [Na^+] \geq 5$ mmol/L</th>
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<th>$[Na^+] \geq 135$ mmol/L</th>
</tr>
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<td>SIADH, no rx (n=168)</td>
<td>41%</td>
<td>45%</td>
<td>20%</td>
</tr>
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<td>44%</td>
<td>29%</td>
<td>10%</td>
</tr>
<tr>
<td>SIADH, NS (n=384)</td>
<td>36%</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td>SIADH, tolvaptan (n=183)</td>
<td>78%</td>
<td>74%</td>
<td>40%</td>
</tr>
<tr>
<td>SIADH, 3% NaCl (n=78)</td>
<td>60%</td>
<td>25%</td>
<td>13%</td>
</tr>
</tbody>
</table>

At discharge, serum $[Na^+]$ was $<135$ mmol/L in 75% of patients, and $\leq 130$ mmol/L in 43% of patients.

decreases in serum [Na⁺] with fluid restriction and isotonic saline infusion
diuresis:
increased excretion of urine by the kidney; includes water and typically increased solute excretion as well

aquareasis:
increased excretion of water by the kidney without increased solute, i.e., electrolyte-sparing excretion of free water by the kidney
tolvaptan: salt-water open label extension study

what aquaresis really looks like!

courtesy nephology fellows, Lenox Hill Hospital, New York, NY
SALT: mean increases in serum [Na\(^+\)] after 30 d in patients with cirrhosis, HF, and SIADH

hyponatremia: osmotic demyelination syndrome
osmotic demyelination syndrome: clinical manifestations

- tremor
- incontinence
- hyperreflexia, pathological reflexes
- quadriparesis, 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
differentiating goals from limits of correction of hyponatremia

re-lowering of serum $[\text{Na}^+]$ is only recommended in patients with high risk of ODS.

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**Figure 3** Recommendations for relowering of serum sodium concentration ($[\text{Na}^+]$) to goals (green) for patients presenting with serum $[\text{Na}^+] < 120$ mmol/L who exceed the recommended limits of correction (red) in the first 24 hours. Abbreviations: L = liter; mmol = millimole; ODS = osmotic demyelination syndrome.

patients at high risk of ODS

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Factors That Place Patients at High Risk of Developing the Osmotic Demyelination Syndrome with Correction of Chronic Hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk of Osmotic Demyelination Syndrome</td>
<td></td>
</tr>
<tr>
<td>• Serum sodium concentration $\leq 105$ mmol/L</td>
<td></td>
</tr>
<tr>
<td>• Hypokalemia*</td>
<td></td>
</tr>
<tr>
<td>• Alcoholism*</td>
<td></td>
</tr>
<tr>
<td>• Malnutrition*</td>
<td></td>
</tr>
<tr>
<td>• Advanced liver disease*</td>
<td></td>
</tr>
</tbody>
</table>

$L$ = liter; mmol = millimole.  
*Unlike the rate of increase in serum sodium concentration, neither the precise level of the serum potassium concentration nor the degree of alcoholism, malnutrition, or liver disease that alters the brain’s tolerance to an acute osmotic stress have been rigorously defined.

osmotic demyelination syndrome (ODS)

one case of CPM has been reported following correction of hyponatremia using a vaptan as monotherapy in >5,000 patients to date; two cases of ODS have been reported with combined use of tolvaptan and hypertonic (3%) NaCl

reported case of ODS using a vaptan as monotherapy

<table>
<thead>
<tr>
<th>Day</th>
<th>Sodium (mEq/L)</th>
<th>Urine output (mL)</th>
<th>Tolvaptan (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>122</td>
<td>2250</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>123</td>
<td>2300</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>124</td>
<td>2300</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>123</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>121</td>
<td>2200</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>126</td>
<td>7460</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>142</td>
<td>11950</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>167</td>
<td>10500</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>187</td>
<td>4500</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>181</td>
<td>3800</td>
<td></td>
</tr>
</tbody>
</table>

Malhotra I et al. Case Rep Endocrinol. Epub 2014 Jan 8
hyponatremia: European recommendations
2014 European clinical practice guideline

- joint venture of 3 societies representing specialists with interest in hyponatremia

Societies sponsored production of guideline

**Table 3. Recommendations for the Use of Vaptans in the Treatment of Hyponatremia.**

<table>
<thead>
<tr>
<th>Hyponatremia Classification</th>
<th>Expert Panel Recommendation*</th>
<th>European Clinical Practice Guideline†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic hyponatremia</td>
<td>Vaptan is not a treatment option.</td>
<td>Vaptan is not a treatment option.</td>
</tr>
<tr>
<td>Euvolemic hyponatremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Vaptan is a treatment option.</td>
<td>Vaptan is not a treatment option.</td>
</tr>
<tr>
<td>Moderate-to-severe central nervous system symptoms</td>
<td>Vaptan is not a treatment option.</td>
<td>Vaptan is not a treatment option.</td>
</tr>
<tr>
<td>Hypervolemic hyponatremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Vaptan is a treatment option, except in patients with liver disease.</td>
<td>Vaptan is not a treatment option.</td>
</tr>
<tr>
<td>Moderate-to-severe central nervous system symptoms</td>
<td>Vaptan is not a treatment option.</td>
<td>Vaptan is not a treatment option.</td>
</tr>
</tbody>
</table>

* Data are adapted from Verbalis et al.\textsuperscript{53}
† Data are adapted from Spasovski et al.\textsuperscript{32} These guidelines were developed by members of three medical societies: the European Society of Intensive Care Medicine, the European Society of Endocrinology, and the European Renal Association–European Dialysis and Transplant Association.
7.4.3 Patients with SIAD

7.4.3.1. In moderate or profound hyponatraemia, we suggest restricting fluid intake as first-line treatment (2D).

7.4.3.2. In moderate or profound hyponatraemia, we suggest the following can be considered equal second-line treatments: increasing solute intake with 0.25–0.50 g/kg per day of urea or a combination of low-dose loop diuretics and oral sodium chloride (2D).

7.4.3.3. In moderate or profound hyponatraemia, we recommend against lithium or demeclocycline (1D).

7.4.3.4. In moderate hyponatraemia, we do not recommend vasopressin receptor antagonists (1C).

7.4.3.5. In profound hyponatraemia, we recommend against vasopressin receptor antagonists (1C).

### Quality of evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Patients</th>
<th>Clinicians</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Strong</td>
<td>Most people in your situation would want the recommended course of action, only a small proportion would not</td>
<td>Most patients should receive the recommended course of action</td>
<td>The recommendation can be adopted as policy in most situations</td>
</tr>
<tr>
<td>2. Weak</td>
<td>Most people in your situation would want the recommended course of action, but many would not</td>
<td>You should recognise that different choices will be appropriate for different patients You must help each patient to arrive at a management decision consistent with her or his values and preferences</td>
<td>Policy making will require substantial debate and involvement of many stakeholders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Quality level</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>We are confident that the true effects lie close to that of the estimates of the effect</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>The true effects are likely to be close to the estimates of the effects, but there is a possibility that they are substantially different</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The true effects might be substantially different from the estimates of the effects</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>The estimates are very uncertain and often will be far from the truth</td>
</tr>
</tbody>
</table>
2014 ERBP clinical practice guideline: no recommendation for vaptans

Although vasopressin receptor antagonists do increase serum sodium, the guideline development group judged that based on current evidence, these drugs cannot be recommended. Indeed, the risk benefit ratio seems to be negative: there is no proven outcome benefit aside from increase in serum sodium concentrations, while there are increasing concerns on safety. The most prominent safety-related factor is the increased risk for overly rapid correction of hyponatraemia. As this risk is greatest in patients with profound hyponatraemia, the guideline development group wanted to recommend against the use of vasopressin receptor antagonists in this specific patient group. In addition, our concern around the toxicity profile of these compounds was increased by reports from the U.S. Food and Drug Administration warning for hepatotoxicity associated with the use of high tolvaptan doses in autosomal dominant polycystic kidney disease.

2014 clinical practice guideline: guideline development

- Systematic reviews of specific research questions
- Outcomes ranked according to relative importance in decision-making process

<table>
<thead>
<tr>
<th>Hierarchy</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critically important</td>
<td>Patient survival</td>
</tr>
<tr>
<td></td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td>Brain damage/brain oedema</td>
</tr>
<tr>
<td></td>
<td>Epileptic seizures</td>
</tr>
<tr>
<td></td>
<td>Osmotic demyelinating syndrome</td>
</tr>
<tr>
<td></td>
<td>Respiratory arrest</td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td>Cognitive function</td>
</tr>
<tr>
<td>Highly important</td>
<td>Bone fractures</td>
</tr>
<tr>
<td></td>
<td>Falls</td>
</tr>
<tr>
<td></td>
<td>Length of hospital stay</td>
</tr>
<tr>
<td>Moderately important</td>
<td>Serum sodium concentration</td>
</tr>
</tbody>
</table>

Serum [Na\(^+\)] ranked least important outcome

low frequency of overly rapid correction in SALT studies (SIADH subgroup analysis)

5.9% (3 out of 51 patients) had overly rapid correction:
- 13 mmol/L/24 h (n=1)
- 14 mmol/L/24 h (n=2)

without neurological symptoms suggestive of osmotic demyelination

The EU guideline group quoted higher incidences of overly rapid correction (10-12%) because they used a definition of >10 mmol/L/24h rather than >12 mmol/L/24h

<table>
<thead>
<tr>
<th></th>
<th>Fluid restriction</th>
<th>Vaptans (tolvaptan)</th>
<th>Urea</th>
<th>Loop diuretic</th>
<th>Demeclocycline</th>
<th>Lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>International</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERBP guideline</td>
<td>First-line treatment in moderate or profound hyponatraemia</td>
<td>Not recommended in moderate hyponatraemia Recommended against in profound hyponatraemia</td>
<td>Equal second-line treatment</td>
<td>Equal second-line treatment (combined with oral NaCl)</td>
<td>Recommended against in moderate or profound hyponatraemia</td>
<td>Recommended against in moderate or profound hyponatraemia</td>
</tr>
<tr>
<td>Expert Panel</td>
<td>Generally first-line treatment</td>
<td>Recommended “Have the potential to replace water restriction as first-line treatment”</td>
<td>Recommended as an alternative oral treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommendations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>National</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>First-line treatment</td>
<td>Recommended in patients not suitable for fluid restriction or furosemide</td>
<td>Recommended as an option Could be therapy of choice in children with SIADH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>First-line treatment Calculate electrolyte-free water clearance prior to initiation</td>
<td>First-line treatment in patients not suitable for fluid restriction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>First-line treatment Calculate electrolyte-free water clearance prior to initiation</td>
<td>Consider if fluid restriction is not advised, or has a poor response</td>
<td></td>
<td></td>
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success rates in treating hyponatremia by physicians in the HN Registry

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At discharge, serum $[Na^+]$ was <135 mmol/L in 75% of patients, and $\leq 130$ mmol/L in 43% of patients

A healthy 25-year-old female just completed her first marathon race. She felt ill toward the end of the race, but was able to walk back to her hotel unassisted. Six hours later, her roommate noticed that she was not making sense. She was taken to the nearby ER where she was found to be disoriented and confused but without focal neurological deficits. Vital signs were stable except for an increased respiratory rate to 32 and the patient was euvolemic by clinical exam. Laboratory data from the ER are:

- $[\text{Na}^+]$, mEq/L 122
- $[\text{K}^+]$, mEq/L 3.5
- Posm, mOsm/kg H$_2$O 254
- BUN, mg/dL 12
- creatinine, mg/dL 0.8
- Uosm, mOsm/kg H$_2$O 412
- urine $[\text{Na}^+]$, mEq/L 50
- urine $[\text{K}^+]$, mEq/L 20
- glucose, mg/dL 140

**Issues to be discussed:**

1. Exercise-associated hyponatremia
2. Time course and symptoms of EAH
3. Therapy of acute hyponatremias
EAH: definition

EAH is the occurrence of hyponatremia in individuals engaged in prolonged physical activity and is defined by a serum or plasma sodium concentration ([Na\(^+\)]) below the normal reference range of the laboratory performing the test; for most laboratories, this is a [Na\(^+\)] < 135 mmol/L.

EAH can occur during or after physical activity, and most commonly occurs in events lasting longer than four hours, although a few cases have been reported during shorter duration events.
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.”

\[ p[Na^+] = 122 \text{ mmol/L} \]
drank Lucozade
fatal EAH: cerebral edema

normal brain

hyponatremic brain

brain volume regulation:

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

- >100 reported cases, 9 documented deaths

**runners requiring medical assistance:**
- 6-40% (Cape town, Houston, San Diego, Pittsburgh)

**prospective studies:**
- Hawaii ironman triathlon, 1991: 9/30 (30%)
- New Zealand ironman triathlon, 1997: 43/330 (18%; 45% of females)
- Houston marathon, 2000: 33/117 (28%; 39% of females)
- Boston marathon, 2002: 62/488 (13%; 22% of females)

**ALL PROSPECTIVE STUDIES: 15.2%**
hyponatremia can be caused by dilution from retained water, or by depletion from electrolyte losses in excess of water.
relation between weight changes and post-race serum [Na⁺] in 2154 endurance athletes

Collaborative study: Auckland; Boston; Cape Town; Christchurch; Houston.
Almond et al, *NEJM* 352:1550-1556, 2005
AVP and copeptin level elevations at the end of a 100 mile endurance run

<table>
<thead>
<tr>
<th>TRIAL MEASUREMENT (N)</th>
<th>[AVP]ₚ Mean ± SD (min – max)</th>
<th>[Copeptin]ₚ Mean ± SD (min – max)</th>
<th>[Na⁺]ₚ Mean ± SD (min – max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WSER Sodium Balance Trial Pre-race (6 normonatremic)</td>
<td>0.7 ± 0.4 (0.2-1.1)</td>
<td>10.3 ± 12.5 (2.1-34.9)</td>
<td>138.7 ± 2.3 (136-142)</td>
</tr>
<tr>
<td>WSER Sodium Balance Trial Post-race (6 normonatremic)</td>
<td>2.7 ± 1.9 (1.4-6.4)</td>
<td>28.2 ± 16.2 (3.6-52.1)</td>
<td>136.7 ± 1.6 (135-139)</td>
</tr>
<tr>
<td>WSER Hyponatremia Trial Pre-3% NaCl Treatment (6 hyponatremic)</td>
<td>3.2 ± 2.9 (0.3-6.9)</td>
<td>22.5 ± 27.5 (2.9-73.0)</td>
<td>130.3 ± 2.6 (126-133)</td>
</tr>
<tr>
<td>WSER Hyponatremia Trial Post-3% NaCl Treatment (6 hyponatremic)</td>
<td>2.1 ± 2.5 (0.5-7.1)</td>
<td>24.9 ± 39.7 (2.8-105)</td>
<td>133.5 ± 3.4 (127-136)</td>
</tr>
</tbody>
</table>

1. **DRINK BIG.** Drink, drink and drink some more. Not just on race day but every day.

2. **TIMING’S EVERYTHING.** About four hours before the race drink 80-100 oz of fluid.

3. **Don’t skip the sports drink at the aid stations even if you are not thirsty.**

4. **Get down as much sports drink at every aid station along the way.**

5. **10-PRACTICE, PRACTICE.** Like training for your big race you need to train yourself to drink lots of fluids before, during and after the race. Remember, practice makes perfect.
Hyponatremia treatment algorithm based on neurological symptoms

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

- **ALL:** hypertonic NaCl\(^1\), followed by fluid restriction ± vaptan\(^2\)

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

- **HYPO:** solute repletion (isotonic NaCl iv or oral sodium replacement)\(^3\)
- **EU:** vaptan, limited hypertonic NaCl, or urea, followed by fluid restriction
- **HYPER:** vaptan, followed by fluid restriction

**LEVEL 1 – NO OR MINIMAL SYMPTOMS:** difficulty concentrating, irritability, altered mood, depression, unexplained headache

- **ALL:** fluid restriction, but consider pharmacologic therapy (vaptan, urea) under select circumstances:
  - inability to tolerate fluid restriction or predicted failure of fluid restriction (see table)
  - very low [Na\(^+\)] (<125 mmol/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
  - unstable gait and/or high fracture risk
  - prevention of worsened hyponatremia with increased fluid administration
  - therapeutic trial for symptom improvement
hypertonic saline correction

- choose desired correction rate of plasma $[\text{Na}^+]$ (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)

OR:

- 100-200 ml bolus infusion (5-10 min) of 3% NaCl, repeat every 30 min until goal reached

FOR ALL SALINE CORRECTIONS:

- follow serum $[\text{Na}^+]$ and urine output every 2-4 hrs during the active correction
SUMMARY STATEMENT

For those athletes presenting with signs and symptoms consistent with EAHE, emergent intravenous treatment therapy with hypertonic saline is indicated and should not be delayed pending laboratory measurement or other diagnostic testing (Grade 1B).

differentiating goals from limits of correction of hyponatremia

re-lowering of serum $[\text{Na}^+]$ is only recommended in patients with high risk of ODS

**Figure 3** Recommendations for re-lowering of serum sodium concentration ($[\text{Na}^+]$) to goals (green) for patients presenting with serum $[\text{Na}^+] < 120$ mmol/L who exceed the recommended limits of correction (red) in the first 24 hours. Abbreviations: L = liter; mmol = millimole; ODS = osmotic demyelination syndrome.

An 80-year-old female was seen as an outpatient for chronic hyponatremia with a serum [Na\(^+\)] that ranged from 125-129 mmol/L. Her main complaint was feeling unsteady on her feet, and she had a history of several falls in the past 2 years. Her only medication is HCTZ 25 mg/d for systolic hypertension. A recent DXA scan confirmed a diagnosis of osteoporosis in the LSS (T-score=-3.3) and hip (T-score=-2.7). Laboratory data:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Na(^+)], mEq/L</td>
<td>127</td>
</tr>
<tr>
<td>[K(^+)], mEq/L</td>
<td>3.9</td>
</tr>
<tr>
<td>Posm, mOsm/kg H(_2)O</td>
<td>263</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>10</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.2</td>
</tr>
<tr>
<td>Uosm, mOsm/kg H(_2)O</td>
<td>480</td>
</tr>
<tr>
<td>Urine [Na(^+)], mEq/L</td>
<td>75</td>
</tr>
<tr>
<td>Urine [K(^+)], mEq/L</td>
<td>52</td>
</tr>
<tr>
<td>TSH, µIU/L</td>
<td>2.9</td>
</tr>
<tr>
<td>Plasma cortisol, µg/dL</td>
<td>18</td>
</tr>
</tbody>
</table>

**Issues to be discussed:**

1. Is chronic “asymptomatic” hyponatremia benign?
2. Gait instability and falls in chronic hyponatremia
3. Hyponatremia-induced osteoporosis
4. Other possible adverse effects of chronic hyponatremia
hyponatremia:
association with adverse clinical outcomes
relationship between hospital admission serum $[\text{Na}^+]$ and in-hospital mortality

correcting hyponatremia improves mortality

![Graph showing odds ratio for overall mortality](image)

Corona et al. PLOSone, 10(4) Apr 23, 2015
hyponatremia: association with fractures
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

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

six independent international studies have shown increased fracture rates in patients with hyponatremia – there seems little question about this – the real question now is: **why does this occur and via what mechanisms?**
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 (2.64–34.09)</td>
<td>67.43 (7.48–607.42)</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

correction of hyponatremia normalizes gait stability in “asymptomatic” hyponatremia

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

Impact of hyponatremia on nerve conduction and muscle strength

Frédéric Vandergheynst*,1, Yannick Gombeir*,1, Flavio Bellante†, Gaetano Perrotta†, Gauthier Remiche†, Christian Mélot‡, Nicolas Mavroudakis† and Guy Decaux∗

*Internal Medicine, †Neurology, ‡Emergency Medicine Departments, Erasme University Hospital, Université Libre de Bruxelles, Brussel, Belgium


[Graph showing TUG results with different [Na] values and corresponding seconds for Hypo and Normo conditions.]

14.94 ± 5.1 vs. 12.5 ± 4.68  

P = 0.006
reductions of brain organic osmolytes after 14 days of sustained hyponatremia

the hyponatremic brain is NOT a normal brain, but rather represents a state of allostasis as a result of solute losses

chronic hyponatremia induced marked bone loss in rats


normonatremic

\[ [\text{Na}^+] = 140 \]

hyponatremic

\[ [\text{Na}^+] = 115 \]
bone micro-CT of rat femurs after chronic hyponatremia

[Na$^+$] = 140 mmol/L

[Na$^+$] = 114 mmol/L

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

lowering extracellular sodium increases osteoclastogenesis in RAW264.7 cells

Barsony et al. JBC 286(12):10864-75, 2011
lowering extracellular sodium increases osteoclastogenesis in rat bone marrow derived macrophages

normonatremic \([\text{Na}^+] = 136 \text{ mmol/L}\)

hyponatremic \([\text{Na}^+] = 117 \text{ mmol/L}\)

Barsony et al. JBC 286(12):10864-75, 2011
lowering extracellular sodium increases bone resorption from whale dentin by bone marrow derived macrophages

Barsony et al. JBC 286(12):10864-75, 2011
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 $[\text{Na}^+] = 133.0 \pm 0.2 \text{ mmol/L}$

36-yr-old male was diagnosed with SIADH at age 22
sodium levels remained low from 111–130 mmol/L
diagnosed with osteoporosis at age of 34 after a MRI scan showed compression fractures at T9–11 and L2
DXA scan showed Z-scores of −3.9 at the lumbar spine (L3–L4) and −1.3 in the total hip
no other known risk factors for osteoporosis
urinary excretion of calcium and sodium elevated
plasma AVP level was inappropriately elevated

Recovery From SIADH-Associated Osteoporosis: A Case Report

Anne-Sophie Sejiling, Anne-Luise Thorsteinsson, Ulrik Pedersen-Bjergaard, and Pia Eiken

Department of Cardiology, Nephrology, and Endocrinology (A.-S.S., A.-L.T., U.P.-B., P.E.), Nordsjællands Hospital, DK-3400 Hillerød, Denmark; Faculty of Health Sciences (A.-S.S.), University of Southern Denmark, DK-5000 Odense, Denmark; and Faculty of Health Sciences (U.P.-B., P.E.), University of Copenhagen, DK-2200 Copenhagen, Denmark
Osteoporosis and fractures are both 2.6-fold increased in a large U.S. hospital system (MedStar, Washington DC).

chronic hyponatremia is associated with a 3.987 O.R. of osteoporosis

Usala et al.  
*J Clin Endocrinol Metab*  
100:3021-31, 2015
Recent hyponatremia is associated with a 3.079 O.R. for fragility fractures.
Results: Osteoporosis Multivariate Analysis

Results: Fragility Fracture
Multivariate Analysis


<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent HN</td>
<td>3.047 (2.826-3.286)</td>
</tr>
<tr>
<td>Chronic HN</td>
<td>4.608 (4.153-5.114)</td>
</tr>
<tr>
<td>Prior HN</td>
<td>1.339 (1.297-1.402)</td>
</tr>
<tr>
<td>Chronic and Recent HN</td>
<td>11.211 (8.812-14.263)</td>
</tr>
<tr>
<td>Only Recent HN</td>
<td>2.545 (2.349-2.757)</td>
</tr>
<tr>
<td>Only Chronic HN</td>
<td>3.670 (3.269-4.121)</td>
</tr>
</tbody>
</table>
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


lowering extracellular sodium increases osteoclastogenesis in RAW264.7 cells despite correcting to normal osmolality

Barsony et al. JBC 286(12):10864-75, 2011
hyponatremia causes loss of both calcium and sodium from bones

Table 2 Bone ash analyses in bones from hyponatremic rats

<table>
<thead>
<tr>
<th></th>
<th>L1–L2 vertebrae</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normonatremic</td>
<td>Hyponatremic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet weight (g)</td>
<td>1.9980±0.1609</td>
<td>1.6638±0.0513**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry weight (g)</td>
<td>0.8178±0.0986</td>
<td>0.7462±0.0266</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ash weight (mg/bone)</td>
<td>307.8±27.8</td>
<td>270.0±16.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium mass (mg)</td>
<td>121.78±7.4</td>
<td>113.38±10.06*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium mass (mg)</td>
<td>22.2±0.56</td>
<td>19.07±1.54**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05 compared to normonatremic group values

**p<0.01 compared to normonatremic group values

Barsony et al. JBC 286(12):10864-75, 2011
sodium deficiency states:

• low plasma $[\text{Na}^+]$ due to low ECF sodium
• sodium resorbed from bone is retained by the kidney due to activation of the RAAS
• Internal sodium stores help to stabilize ECF volume and blood pressure
• evolutionarily protective

syndrome of inappropriate antidiuretic hormone secretion (SIADH):

• low plasma sodium due to excess water, not sodium deficiency
• sodium resorbed from bone is excreted by the kidney since RAAS is down-regulated
• pathological “misinterpretation” of low plasma $[\text{Na}^+]$
• no brake, since plasma $[\text{Na}^+]$ remains low
A 3-month-old male was admitted for irritability, generalized seizures and failure to thrive. An MRI scan of the brain was read as WNL, and a general work-up was unrevealing for any underlying abnormality. There is no family history of metabolic or electrolyte abnormalities. Laboratory data on admission are:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Na(^+)], mEq/L</td>
<td>118</td>
<td>Uosm, mOsm/kg H(_2)O</td>
<td>720</td>
</tr>
<tr>
<td>[K(^+)], mEq/L</td>
<td>3.7</td>
<td>urine [Na(^+)], mEq/L</td>
<td>75</td>
</tr>
<tr>
<td>Posm, mOsm/kg H(_2)O</td>
<td>247</td>
<td>urine [K(^+)], mEq/L</td>
<td>50</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>3</td>
<td>TSH, µIU/L</td>
<td>2.0</td>
</tr>
<tr>
<td>glucose, mg/dL</td>
<td>90</td>
<td>plasma cortisol, µg/dL</td>
<td>22</td>
</tr>
</tbody>
</table>

**Issues to be discussed:**

1. Diagnosis of nephrogenic syndrome of inappropriate antidiuresis (NSIAD)
2. Treatment of NSIAD
3. Prevalence of NSIAD in adults as a potential cause of SIADH with low plasma AVP levels
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

plasma AVP levels are inappropriately elevated in most patients with SIADH.
nephrogenic SIAD

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

Feldman et al.  
*New Engl J Med*  
352:1884-90, 2005
treatment of NSIAD with oral urea

Table II. Blood and urine studies in 4 patients with chronic SIAD treated with oral urea

<table>
<thead>
<tr>
<th>Patient</th>
<th>Oral Urea Dose g/kg/day</th>
<th>Serum Sodium mEq/L</th>
<th>Osmolality mOsm/kg H₂O</th>
<th>BUN mg/dL</th>
<th>Urine Creatinine mg/dL</th>
<th>Sodium mEq/L</th>
<th>Osmolality mOsm/kg H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>137-146</td>
<td>283</td>
<td>25-39</td>
<td>&lt;0.3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>137-145</td>
<td>295</td>
<td>31-44</td>
<td>0.4</td>
<td>31</td>
<td>514</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>137-143</td>
<td>284</td>
<td>17-23</td>
<td>&lt;0.3</td>
<td>37</td>
<td>508</td>
</tr>
<tr>
<td>4</td>
<td>0.7</td>
<td>134-143</td>
<td>287</td>
<td>22-46</td>
<td>0.3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Normal Range</td>
<td>NA</td>
<td>134-143</td>
<td>285-293</td>
<td>8-23</td>
<td>0.3-0.7</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*ND = not done; NA = not applicable; BUN = blood urea nitrogen.*

family tree illustrating transmission of the mutated vasopressin receptor type 2 (AVPR2) gene responsible for nephrogenic syndrome of inappropriate antidiuresis (NSIAD) over five generations

Decaux et al. JASN 18:606-612, 2007
Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations

Joseph G. Verbalis, MD, a Steven R. Goldsmith, MD, b Arthur Greenberg, MD, c Cynthia Korzelius, MD, d Robert W. Schrier, MD, e Richard H. Sterns, MD, f Christopher J. Thompson, MD, FRCPI g

aGeorgetown University Medical Center, Washington, DC; bUniversity of Minnesota, Minneapolis, MN; cDuke University Medical Center, Durham, NC; dTufts University School of Medicine, Boston, MA; eUniversity of Colorado, Denver, CO; fUniversity of Rochester, Rochester, NY; gRoyal College of Surgeons in Ireland School of Medicine, Dublin, Ireland.