Electrolyte disorder

Division of Nephrology
St. Luke’s international hospital
Masahiko Nagahama. MD. FASN
Salt and Water balance

Salt imbalance

• Too much sodium – **EDEMA**
• Too little sodium – **VOLUME DEPLETION**

Water imbalance

• Too much water – **HYPONATREMIA**
• Too little water – **HYPERNATREMIA DEHYDRATION**
Hyponatremia is IMPORTANT

• Common problem
  – Prevalence in hospitalized : 2.5% - 42.6%
  – Prevalence in nursing home residents : 53%
    – Upadhyay A et al. AJM 2006
    – Shimasaki K et al. JASN 2012

• Related to poor prognosis
  – Among cardiac (CHF / MI) patients
  – Among liver cirrhotic patients
    – Biggins DM et al. Hepatology, 2005
    – Kim WR et al. NEJM 2008
  – Among CKD patients
    – Huang H et al NDT. 2016
However, hyponatremia is puzzling...

Most Frequently Accessed Topics in UpToDate: June 2008-June 2009

1. Causes of hyponatremia
2. Approach to the patient with abnormal liver function tests
3. Cellulites and erysipelas
4. Approach to the patient with anemia
5. Treatment of hyponatremia
6. Treatment of antibiotic-associated diarrhea caused by Clostridium difficile
7. Rhabdomyolysis
8. Treatment of diabetic ketoacidosis and hyperosmolar hypoglycemic state
9. Approach to the adults patient with thrombocytopenia
10. Diagnostic evaluation of a pleural effusion in adults
11. Diagnosis of hyponatremia
## Osmoregulation vs Volume Regulation

### What is sensed
- **Osmoregulation**: P-Osm
- **Volume regulation**: ECV (effective circulating volume)

### Sensors
- **Hypothalamus**
  - ① Carotid sinus
  - ② Atria
  - ③ G afferent arteriole

### Effectors
- **ADH**
  - ① Sympathetic N (norepinephrine)
  - ② ANP
  - ③ ADH
  - ④ Renin-Angiotensin-Aldosterone

### What is affected
- **Osmoregulation**: U-Osm, thirst
- **Volume regulation**: U-Na

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**Hypovolemic hyponatremia** is consistent with ↑ U-Osm and ↓ U-Na
A 50 y.o M came in severe watery diarrhea. He was slightly tachycardic and hypotensive. P–Na was 114meq/L on admission. Normal saline (N/S) was infused overnight. He received 1 L of N/S and P–Na was improved to 120meq/L next morning.

I/O : 1000mL / 200mL (No oral intake)  
TBW : 40L (weight 66kg)

Why was hyponatremia improved?

A: Higher sodium concentration of N/S (154meq/L) was given.
B: Low urine output makes free water clearance negligible.
C: No oral intake makes free water intake negligible.
D: Hypovolemia was corrected.
Normal saline infusion for hyponatremia

- Effective for Hypovolemic hyponatremia
- N/S is effective for hyponatremia not because N/S is hypertonic, but because hypovolemia induced ADH is suppressed due to the restoration of euvolemia.

Case: 1L of N/S (Na154mEq/l) was given to the pt with P-Na 114mEq/L. If TBW 40L, P-Na was increased by only 1mEq/L.


\[
\text{Change in serum Na}^+ = \frac{\text{infusate Na}^+ - \text{serum Na}^+}{\text{total body water} + 1}
\]

\[
\frac{154 - 114}{40 + 1} \div 1 \text{mEq/L}
\]
Estimation of the effect of 1L of any infusion*

\[ \triangle \text{Na} = \frac{\text{infused Na} - \text{P-Na}}{\text{TBW} + 1} \]

\( \triangle \text{Na} \) is after 1L of infusion

If infusion contains K, use “infused Na + K” for “infused Na”

**Osmolyte inside of body is unchanged**

\[
(\text{TBW} \times \text{P-Na}) \times 2 + (\text{infused Na} \times \text{infused fluid}) \times 2 = (\text{TBW} + \text{infused fluid}) \times (\text{P-Na} + \triangle \text{Na}) \times 2
\]

**Condition A**

**Condition B**

What defines urine volume?

\[
\text{Urine volume} = \frac{\text{Solute load}}{\text{Urine concentration}}
\]

- If solute load is 600mOsm/day,
  - Most diluted urine (50mOsm/kg) → 12L/day
  - Most concentrated urine (1200mOsm/kg) → 0.5L/day
Urine volume in different solute load and kidney function

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<tr>
<th>Solute load</th>
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<th>Normal Min U-Osm 50(mOsm/kg)</th>
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</tr>
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<td>12</td>
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<td>1200 mOsm</td>
<td></td>
<td>24</td>
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- If U-Osm is constant, Low solute load decreases U volume.
- If solute load is constant, Impaired kidney function decreases U volume.
Isotonic fluids are safer than hypotonic fluids in hospitalized children requiring maintenance IV fluid therapy in terms of hospital acquired hyponatremia.
P-Na between hospitalized patients and normal subjects

hospitalized patients (n=9428)

normal subjects (n=792)

St. Luke’s Int Hosp
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A healthy, 25 year-old, male volunteer entered a study involving an infusion of a diuretic hormone. Before being given the drug, a water diuresis was initiated by infusing D5W and replacing urine volume ml/ml as oral water. After 3 hours, his iv had to be replaced. He did not void for 9 hours. What happened?
Suddenly

①↑U-Osm
②↓U volume
Q1: What happened (↑U-Osm / ↓U volume)?

A: AKI is developed due to volume overload.

B: ADH is secreted due to hypernatremia (Osm related).

C: ADH is secreted due to hypervolemia (volume related).

D: ADH is secreted due to IV replacement.
ADH is secreted by

- ↑ Plasma osmolality ← Osm regulation
- ↓ Blood volume ← Volume regulation
- nausea / vomit / pain / stress, etc.

Sickness induced ADH secretion
ADH secretion by vomit
40 times more intense than P-Osm!!

Robertson GL. Recent Prog Horm Res 1977
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Clinical Practice Guidelines of Hyponatremia

- 2003: Consensus document on the treatment of ascites, dilutional hyponatremia and hepatorenal syndrome in liver cirrhosis (Spain)
- 2007: Hyponatremia treatment guidelines 2007: expert panel recommendations (United States)
- 2010: Hyponatremia in Adults (Ireland)
- 2011: Prodigy Topic on Hyponatremia (United Kingdom)
- 2012: Electrolytstoornissen (Netherlands)
- 2013: Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations (United States)
- 2013: Royal Children's Hospital Melbourne Australia: Clinical Practice Guideline on Hyponatremia (Australia)
- 2014: European Clinical Practice Guideline (Europe)
- 2014: The treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (Spain)
Review and analysis of differing regulatory indications and expert panel guidelines for the treatment of hyponatremia

Diagnosis and Treatment of Hyponatremia: Compilation of the Guidelines

Ewout J. Hoorn and Robert Zietse
Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus Medical Center, Rotterdam, The Netherlands

Diagnosis and treatment of hyponatremia: a systematic review of clinical practice guidelines and consensus statements

Evi V Nagler, Jill Vanmassenhove, Sabine N van der Veer, Ionut Nistor, Wim Van Biesen, Angela C Webster, and Raymond Vanholder
Among 10 guidance documents (5 clinical practice guidelines and 5 consensus statements), 2 clinical practice guidelines attained an average AGREE scores of > 50% for all of the domains.
Clinical practice guideline on diagnosis and treatment of hyponatraemia

Goce Spasovski, Raymond Vanholder¹, Bruno Allolio², Djillali Annane³, Steve Ball⁴, Daniel Bichet⁵, Guy Decaux⁶, Wiebke Fenske², Ewout Hoorn⁷, Carole Ichai⁸, Michael Joannidis⁹, Alain Soupart⁶, Robert Zietse⁷, Maria Haller¹⁰, Sabine van der Veer¹¹, Wim Van Biesen¹ and Evi Nagler¹ on behalf of the Hyponatraemia Guideline Development Group

ESICM : European Society of Intensive Care Medicine
ESE : European Society of Endocrinology
ERA-EDTA : European Renal Association
- European Dialysis and Transplant Association
ERBP : European Renal Best Practice
Summary of European Clinical Practice Guideline

- Treat the patient (symptom), not the number
  - Do NOT panic unless the patient is symptomatic
  - First approach to the patient is symptom based
- Distinguish between “target” and “limit”
  - A target is a goal one is aiming for
    - Target $\Delta 5$ mEq/L for severely symptomatic pts
  - A limit is a change one does not want to exceed
    - Limit $\Delta 10$ mEq/L/24hrs, $\Delta 8$ mEq/L/24hrs thereafter for all pts
- Be aware of overcorrection
  - UNINTENTIONAL shut down of ADH is frequently happened
  - DDAVP use is reasonable to prevent overcorrection
Treat the patient(sympptom), not the number

Table 1  Hierarchy of outcomes.

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

- Biochemical severity
  - Mild: Na 130-135 mEq/L
  - Moderate: Na 125-130 mEq/L
  - Profound: Na < 125 mEq/L

- Time-based
  - Acute: duration < 48 hours
  - Chronic: duration ≥ 48 hours

- Symptom based
  - Moderately symptomatic
  - Severely symptomatic

<table>
<thead>
<tr>
<th>Severity</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderately severe</td>
<td>Nausea without vomiting</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td>Severe</td>
<td>Cardiorespiratory distress</td>
</tr>
<tr>
<td></td>
<td>Abnormal and deep somnolence</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Coma (Glasgow Coma Scale ≤ 8)</td>
</tr>
</tbody>
</table>
Algorithm for the management of hyponatraemia

Severe symptoms?

Yes

Go to Section 7.1
Hyponatraemia with severe symptoms

No

Moderately severe symptoms?

Yes

Go to Section 7.2
Hyponatraemia with moderately severe symptoms

No

Acute hyponatraemia?

Yes

Go to Section 7.3
Acute hyponatraemia without severe or moderately severe symptoms

No

Go to Section 7.4
Chronic hyponatraemia

Reduced circulating volume?

Yes

No
Osmotic Demyelination Syndrome

• Delayed onset
  – Typically 2 to 6 days after excessive correction of P-Na

• Varied symptoms
  – Pontine symptoms classic
    • Swallowing dysfunction
    • Quadriparesis
    • Locked syndrome
  – Extrapontine syndrome common
    • Seizures
    • Behavioral disturbances
    • Movement disorders
Summary of European Clinical Practice Guideline

• Treat the patient (symptom), not the number
  • Do NOT panic in asymptomatic hyponatremia!!
  • First approach to the patient is symptom based
• Distinguish between “target” and “limit”
  • A target is a goal one is aiming for
    • Target $\Delta 5$ mEq/L for severely symptomatic pts
  • A limit is a change one does not want to exceed
    • Limit $\Delta 10$ mEq/L/24hrs, $\Delta 8$ mEq/L/24hrs thereafter for all pts
• Be aware of overcorrection
  • UNINTENTIONAL shut down of ADH is frequently happened
  • DDAVP use is reasonable to prevent overcorrection
## Unintentional shut down of ADH

<table>
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<tr>
<th>Cause of Hyponatremia</th>
<th>Mechanism of Escape From Antidiuresis</th>
</tr>
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<tbody>
<tr>
<td><strong>Hypovolemia</strong></td>
<td>Volume repletion reverses baroreceptor-mediated vasopressin secretion</td>
</tr>
<tr>
<td><strong>Beer potomania, tea and toast diet</strong></td>
<td>Increased solute intake enhances delivery of glomerular filtrate to distal diluting sites</td>
</tr>
<tr>
<td><strong>Thiazide diuretics</strong></td>
<td>Discontinuation of diuretic restores diluting function of the distal tubule</td>
</tr>
<tr>
<td><strong>SSRI</strong></td>
<td>Discontinuation of antidepressant eliminates drug-induced SIADH</td>
</tr>
<tr>
<td><strong>Desmopressin</strong></td>
<td>Discontinuation of synthetic vasopressin eliminates antidiuretic state</td>
</tr>
<tr>
<td><strong>Hypopituitarism</strong></td>
<td>Cortisol replacement restores ability to suppress vasopressin secretion</td>
</tr>
<tr>
<td><strong>Addison disease</strong></td>
<td>Volume and cortisol replacement</td>
</tr>
<tr>
<td><strong>Nausea, surgery, pain, or stress</strong></td>
<td>Spontaneous resolution of ADH secretion</td>
</tr>
</tbody>
</table>

*Sterns RH et al. Am J Kidney Dis. 2010*
Overcorrection is underrecognized

- ≤12mEq/L/day: 76%
- >12mEq/L/day: 24%

P-Na ≤ 120mEq
N=255

Literatures of DDAVP use for hyponatremia


- **Sterns** RH, Hix JK: Overcorrection of hyponatremia is a medical emergency. Kidney Int. 2009


- **Sterns** RH, Hix JK, Silver S. Treatment of hyponatremia. Curr Opin Nephrol Hypertens. 2010

Take home messages

• Osm R vs Volume R are essentially separated except for ADH
• The urine volume is the quotient of solute load over urine concentration
• Recognize “Sickness induced ADH secretion”
  – Hosp acquired hypo Na
• Watch for unintentional shut down of ADH
  – Consider DDAVP if needed
• Do NOT panic in asymptomatic hyponatremia!!