Workshop on Hyponatremia

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CSIM 2014
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Objectives

• Approach to diagnosis of hypoNa
  – Acute vs chronic
  – Etiology of hyponatremia

• Treating hypoNa safely
  – Acute vs chronic
  – Symptomatic vs asymptomatic
  – Addressing rapid correction (prevention and reversal)
    • In pts at highest risk for rapid correction
    • In pts at highest risk for osmotic demyelination (ODS)
  – ???Vaptans

• Cases
Why talk about hypoNa

• The most common electrolyte abnormality in hospitalized pts
• Associated with adverse outcomes in cirrhosis, CHF and inpatients
• ‘Asymptomatic’ chronic hypoNa (SIADH) in studies associated with gait abnormalities, increased falls and problems with mentation
• Lack of evidence in management
  – what guides our treatment
Hyponatremia

- Expert opinion ‘guidelines’ exist
- Case reports and literature reviews around harm of rapid correction
- No RCT to guide treatment strategies
- Very little evidence of managing rapid correction and trends towards rapid correction
  - Evidence around safety, not outcomes
  - Outcome evidence in rat models
Hyponatremia

• Most clinicians in agreement
  – Goals of Tx in chronic < 8-9 mEq/L/d (daily correction, not hourly)
  – Acute vs chronic
  – Tx chronic symptomatic hyponatremia emergently
  – Tx acute symptomatic emergently
  – Modify treatment based on etiology of hypoNa
Hyponatremia

- Patterns of practice differ in chronic hypoNa
  - Modifying Tx based on risk of ODS and risk of rapid progression
  - Using formulas
  - Starting with saline
  - Starting hypertonic saline and ddAVP upfront
  - Strategies to slow down rate of correction in pts trending to rapid correction
  - Reversing rapid correction
  - ???use of vaptans
Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations

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Georgetown University Medical Center, Washington, DC; University of Minnesota, Minneapolis, MN; Duke University Medical Center, Durham, NC; Tufts University School of Medicine, Boston, MA; University of Colorado, Denver, CO; University of Rochester, Rochester, NY; Royal College of Surgeons in Ireland School of Medicine, Dublin, Ireland.

The American Journal of Medicine, Vol 126, No 10A, October 2013
hyponatremia

- Workshop on hypoosmolar hyponatremia
- Defined as Na<135 mEq/L
- Temporal: Hyperacute, acute, chronic
- hypoNa severity: Mild (130-135), mod (120-129), severe (<120)
- Symptom severity: Asx, mild-mod sx, severe sx
Kidney Principles

• What determines urine output?
• Where is the concentrating and diluting segment of the kidney tubules?
• What is required to have a concentrated urine?
• What is required to have a dilute urine?
Urine Output

• Urine volume (L) = osmoles excreted (mosm) / osmolality (mosm/L)

• Obligate urine output determined by the # of osmoles being excreted and varies depending on the urine osmolality

• Typical western diet is 600-900mosm/d from protein and salt
  – 50mosm/L = 900mosm/x urine output x=18L
  – 600mosm/L=900mosm/x urine output x=1.5L
Concentrated urine

- Intact TAL and countercurrent mechanism to produce the osmotic gradient
- ADH
- Functional aquaporins
- Maximally concentrated urine 1200mosm/L
Dilute Urine

• Absence of ADH
• Kidneys ability to excrete the water
  – Thiazide diuretics, age, CKD effect the diluting segment
• Enough osmoles to drive the urine output
  – Low solute diets
  – Alcoholics (beer potomania)
• Maximally dilute urine 50 mosm/L
Quick look at approach to principles of management and approach to etiology
Approach to Management HypoNa

Acute

<48 hours
Story of acute illness
Story of H2O intoxication

3% saline 100 ml bolus
Repeat prn

Rapid correction with 3% saline
-especially if sx of cerebral edema

Chronic

>48 hours
Story of chronic illness
No story of acute illness

Sx
-sz, obtundation, coma

3% saline 1-2ml/kg/h
↑by 5-6 mmol/L in 3-6h

Asx

Consider etiology
<8mEq/L/d
<4mEq/L/d 4-6
**Na and K
Etiology

Principles to think about

Water to Solute threshold
Easily reversible ADH
Persistent ADH

Use of Urine Na and Urine osmolality
Etiology

Why are patients with poor solute intake at higher risk of developing hyponatremia?
Urine Output

- Urine volume (L) = \textbf{osmoles excreted (mosm)} \over \textbf{osmolality (mosm/L)}
- Obligate urine output determined by the # of osmoles being excreted and varies depending on the urine osmolality
- Typical western diet is 600-900mosm/d from protein and salt
  - \(50\text{mosm/L} = 900\text{mosm/x urine output} \ x=18\text{L}\)
  - \(600\text{mosm/L}=900\text{mosm/x urine output} \ x=1.5\text{L}\)
Low vs Western solute diet

**Low Solute diet**

\[
\begin{align*}
50 \text{mosm} & \quad = & \quad \frac{250 \text{ mosm diet}}{5L} \\
\text{Stimulus for ADH} & \quad = & \quad \frac{300 \text{mosm}}{0.83L}
\end{align*}
\]

**Western Solute diet**

\[
\begin{align*}
50 \text{mosm} & \quad = & \quad \frac{900 \text{ mosm diet}}{18L} \\
\text{Stimulus for ADH} & \quad = & \quad \frac{300 \text{mosm}}{3L}
\end{align*}
\]

Caution with Tx: as soon as take away stimulus for ADH with NS, the kidney will have solute (NaCl) to excrete and will now be able to increase the urine output and the [Na] will increase rapidly.

Pts with psychogenic polydipsia are usually ok as long as they drink less than their solute threshold and have no stimulus for ADH.
Why do patients with SIADH have high urine Na vs patients with volume depletion with low urine Na?

Why are patients with SIADH euvoletic?
Urine Na and Urine osmolality

- **SIADH**
  - High urine osm >100 mosm/L
  - Urine Na > 40 mEq/L, unless volume depleted or very low salt diet

- **Glucocorticoid deficiency and hypothyroidism**
  - High urine osm, Urine Na >40 mEq/L

- **Volume depletion (true and effective)**
  - High urine osm > 300mosm/L
  - Urine Na <20 mEq/L unless on diuretics, low mineralcorticoid state, or cerebral/renal salt wasting

- **Low solute state**
  - Low urine osmolality (<200mosm/L)
  - Urine Na depends on diet

- **Water intoxication**
  - Low urine osmolality 50 mosm/L
  - Low Urine Na
• In SIADH pt has increased water across TBW
  – Defect in water handling
  – No problems with salt handling in the tubules
  – Increased fluid $\rightarrow$ high ANP and BNP levels $\rightarrow$
    increased salt in the urine
• If give a pt with SIADH 0.9% NS and their urine osmolality $>$ the osmolality of NS, the pt will
  excrete the NaCl but hold onto some of the water and the serum $[\text{Na}]$ will drop
SIADH example

Urine osmolality fixed at 600 mosm/L
0.9% NS osmolality = 154 x 2 = 308

\[
\frac{600 \text{ mosm}}{L} = \frac{308 \text{ mosm}}{xL}
\]

\(X\) = obligatory urinary losses driven by the salt excretion

\(X = 0.5L\) of 1 L of NS excreted and 0.5L of NS distributed across TBW as free water leading to decreased serum Na

**no defect in salt excretion**

**defect in H2O excretion**

Treatment Options for SIADH
Low Na

ADH
- Appropriate
  - ↑ tonicity
  - ↓ ECFV
    - true
    - effective
- Inappropriate
  - SIADH
  - drugs
  - CNS
  - pulmonary
  - cancer
  - endurance
  - exercise
  - nausea
  - pain
  - stress
  - low cortisol
  - hypothyroidism

WATER
- Exogenous
  - po or IV
- Endogenous
  - cell metabolism

SOLUTE threshold
- Low salt diet
- Low prtn diet
- Beer potomania

FREE H2O EXCRETION
- Increasing age
- Decreased GFR
- Thiazide diuretic
- PG inhibitors
- Low solute

Check serum osmolality, Urine osmolality and urine Na

Approach to etiology
SIADH example

Urine osmolality fixed at 600 mosm/L
0.9% NS osmolality = 154 x2 = 308

\[
\frac{600 \text{ mosm}}{1 \text{ L}} = \frac{308 \text{ mosm}}{x \text{ L}}
\]

\[X = \text{obligate urinary losses driven by the salt excretion}\]

\[X = 0.5 \text{ L of 1 L of NS excreted and 0.5 L of NS distributed across TBW as free water}\]

**no defect in salt excretion**

**defect in H2O excretion**

SIADH Treatment Options

Assess if acute/chronic or Sx

1) Treat/remove offending cause
2) Water restrict

3) Try and modify the equation
   a) 3% saline osmolality = 512 x2 = 1024

\[
\frac{600 \text{ mosm}}{1 \text{ L}} = \frac{1024 \text{ mosm}}{x \text{ L}}
\]

\[X = 1.7 \text{ L}\]

High solute diet/Salt tablets/oral Urea as outpt approach to drive the urine outpt

b) Lasix can interfere with the [ ] ability

\[
\frac{300 \text{ mosm}}{1 \text{ L}} = \frac{1024 \text{ mosm}}{x \text{ L}}
\]

\[x = 3.4 \text{ L}\]

4) Demeclocycline

5) ADH receptor antagonists (Vaptans)
Cases: hypoNa

• Things to think about:
  – Timeline of acute vs chronic
  – Consequence of acute hypoNa and of chronic hypoNa
    • Who is at risk

• Consequence of rapid correction
  – Who is at risk
  – How rapidly should we correct
Case 1

• 23 year old female brought to ER by her friend with a headache.
  – Rave
  – Ecstasy
  – 2-3L of water

• Stat bloodwork Na 130 mEq/L
  – What are her risks?
  – How should she be managed?
  – What would her urine osmolality be?
NEJM;342:1584

Diagram showing the cyclic process of brain osmolality changes and their effects:

1. **Normal brain** (normal osmolality)
2. **Osmotic demyelination**
3. **Loss of organic osmolytes** (low osmolality)
4. **Loss of sodium, potassium, and chloride** (low osmolality)
5. **Water gain** (low osmolality)
6. **Immediate effect of hypotonic state**
7. **Rapid adaptation**
8. **Proper therapy** (slow correction of the hypotonic state)
9. **Improper therapy** (rapid correction of the hypotonic state)
10. **Slow adaptation**

The cycle continues with water entering the brain, inducing osmotic demyelination, and the process repeats.
Case 1

- Pt kept in ER with persistent H/A, became drowsy. Free water restricted, urine osmolality 400 mosm/L
- 1 hour into admission pt started seizing, stat Na 124
- Given 100 cc of hypertonic (3%) saline over 15 minutes, benzos. Pt stopped seizing
  - Repeat Na 130 mEq/L
- 30 minutes later, foley bag filling up with urine. Repeat urine osmolality 50 mosm/L
Case Review:

- Acute and hyperacute hypoNa:
  - Water loading/ectasy/postop scenarios
- Could be symptomatic at any level but usually when Na<130
- Nausea/malaise 125-130 mEq/l
- H/A, N/V, muscle cramps, restlessness, disorientation <125 mEq/L
- Obtundation, seizure, coma, ARDS, brainstem herniation (< 120, but could happen earlier)

**sx of cerebral edema
Case Review

• Pts at risk for cerebral edema:
  – Young menstruating females at highest risk as they can’t shed the elytes in the acute brain adaptation due to estrogen blocking the Na/K pump
  – postop scenarios
  – Water loading
  – Symptomatic

• Can correct quickly as not at risk for ODS
  – Risk of ODS if didn’t recognize that there’s a chronic problem or its acute on chronic hypoNa
Case review

- Ecstasy (MDMA) leads to hypoNa
  - Causes excess thirst
  - Induces ADH secretion
  - Water readily available
- If asx and Na above 130, could observe but could also treat
  - Monitor urine output and osmolality, No Normal saline
  - Will likely spontaneously recover when ADH shuts off
- If sx or Na decreasing then Tx
  - Hypertonic saline **100ml bolus and repeat q10 min as needed**
  - Water restrict
  - Wait until ADH wears off (half life of 10-15min)
Approach to Management
HypoNa

Acute
<48 hours
Story of acute illness
Story of H2O intoxication

- 3% saline 100 ml bolus q10 min repeat prn
- Rapid correction with 3% saline especially if sx of cerebral edema

Chronic
>48 hours
Story of chronic illness
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Sx
-sz, obtundation, coma

Asx
3% saline 1-2ml/kg/h
↑ by 4-6 mmol/L in 3-6
Case 2: hypoNa

• Things to think about:
  – Timeline of acute vs chronic
  – Consequence of acute hypoNa and of chronic hypoNa
    • Who is at risk

• Consequence of rapid correction
  – Who is at risk
  – How rapidly should we correct
Case 2

- 75 yo female 6 day hx of N/V and SOB, 2 day hx of fever and pleuritic CP, 1 day of confusion. PMHx HTN, COPD, chronic poor intake. HCTZ for 10 years, puffers. O/E: looks sick, BP 120/80, HR 96 reg, RR 24, O2 sats 88%RA, T 37.2, JVP ASA, no edema

- BW: Na 110, K2.8, HCO3 28, Cr 105, Hgb 137, WBC 9

- Urine osmolality: 400 mosm/L, Una 20 mEq/L

- CXR: LLL infiltrate
• How should she be managed:
  – Acute vs chronic
  – Sx vs Asx
• What are goals of treatment
  – Rate of correction
  – Is she at risk of ODS
• How should she be treated
• What’s the etiology
Symptoms of chronic hyoNa

• Asymptomatic
  – Studies show when Na < 130 chronically, pts may have some subtle neurological findings (gait, cognition)

• Mild-moderate (nonspecific)
  – H/A, N/V, muscle cramps, fatigue, gait abn, confusion

• Severe sx
  – Seizures, obtundation, coma, respiratory failure
• How should she be managed:
  – Acute vs **chronic**
  – Sx vs Asx:
    • Pt has severe hyponatremia (<120) with mild-moderate sx
• What are goals of treatment
  – Rate of correction: **4-6 mEq/L/day, in her <4 mEq** given high risk for ODS
• What’s the etiology
  – **Multifactorial: volume depletion, lung pathology, pain, HCTZ, possible tea and toaster**
Approach to Management
HypoNa

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3% saline 1-2ml/kg/h
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  - low cortisol
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WATER
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FREE H2O EXCRETION
- Increasing age
- Decreased GFR
- Thiazide diuretic
- PG inhibitors
- Low solute

Check serum osmolality,
Urine osmolality and urine Na

Approach to etiology
Case 2: Review

• Goal given chronic >48 h and asymptomatic should be slow
  – 8mEq/day upper limit, aim for 4-6 mEq
  – **Aim for <4mEq if at increased risk for ODS**
  – **An increase in serum K by 1 mEq/L has the same effect on the ICF cells as 1 mEq/L increase in Na**
Case 2: Review

• Risk factors for ODS
  – Rapid correction (>10-12mEq/L/d or >18mEq/L in 48h)
    Case reports with increase of 9mEq/l/d
  – Hypoxemia
  – Severe liver disease
  – Alcoholism
  – **Malnutrition**
  – **Hypokalemia**
  – **Na<120mEq/L**
  – **Chronic hypoNa**
Back to Case 2

• Pt was given 1L of Normal Saline in ER, hemodynamically stable
• A formula was used to calculate the IV solution to bring up the Na
Correction

- Formulas:
- Free water excess = TBW x (140-[Na])/140
  - TBW = 0.6 x body wt (0.5 in females)
- Androguéé and Madias formula
  - $\Delta$Na= (infusate Na + infusate K) – serum Na/TBW +1
  - Estimates the effect of 1 L of any infusate on [Na]
- Many other formulas
Case 2

- Androgué formula was used
  - Goal Na 118, TBW 50kg x 0.5=25l
  - ΔNa =154-110/25+1= 1.69
  - 1 L of NS will change the [Na] by 1.69, therefore 4 L of NS over 24 hrs will increase the Na by 6.7
  - the pt was already given 1 L, the decision was for 3 L over 24 hrs at a rate of 125ml/h
  - Pt was started on antibiotics and gravol for nausea
  - HCTZ was held, tylenol for pain
Case 2

• 4 hours into treatment
  – Foley bag filled with urine
  – Urine osmolality was 75mosm/L
  – Repeat serum Na 116 (6 hours after initial Na was drawn)

• What happened to our patient?

• What is the circulating half life of ADH
• What happened to our pt?
• ADH was turned off

• What is the circulating half life of ADH?
• Circulating half life of ADH is 10 minutes and once remove the stimulus for ADH, the pt who has been holding onto to H2O for days will now have a brisk water diuresis
Rapid correction

• Scenarios of turning off ADH
  – Repleting volume
  – Steroids in adrenal insufficiency
  – Stopping drugs that cause ADH
  – Stopping thiazide
  – Use of aquaporin antagonists

• Cause of hypoNa often multifactorial
• Caution about formulas
  – Based on closed box, not accounting for what the urine output will do and when ADH will turn off
  – Assumes the main cause of hypoNa is low total body salt (only true if pt has true volume depletion)
  – Giving NS in SIADH states will often lower serum Na
  – Giving NS in low solute states will lead to a diuresis and rapid correction of Na
  – Giving NS in hypervolemic states will lead to further volume OL
  – Need to understand the etiology of hypoNa before can manage appropriately
  – Studies show that Andrograde formula overcorrected the Na on many occasions
Back to Case 2

- Could we have anticipated that the pt was at high risk of rapid correction?
- Is the pt at high risk of ODS?
• Could we have anticipated that the pt was at high risk of rapid correction?
  – Multifactorial triggers for ADH all being treated at the same time

• Is the pt at high risk of ODS?
  – Malnutrition
  – Hypokalemia
  – very low Na 110
  – hypoNa likely chronic (>48h)
• If we saw this pt initially in ER what treatment strategies could we use to try and stay within target Na correction
  – <8 mEq/L/d
Prevention: Safety

• Common Prevention Strategies
  – Target Na 4-6 mEq/L/d: buffer
  – Attempts to not fully shut off ADH
  – Close monitoring of Na (q2-4h), urine output and osmolality
  – Administer free water if trajectory of rapid correction or if hit target prior to 24 hours
  – ?? Giving ddAVP +/- D5W if need to slow down correction rate or reverse rate
Prevention

• Some patterns of practice
  – Once target reached, if reached early → ddAVP to prevent an aquaresis and further correction with ongoing monitoring of Na
  – Sood’s group advocates for pts with high likelihood of turning off ADH and high ODS risk, preemptive ddAVP (2-4 mcg IV q6-8h) and slow infusion of 3% saline targeting a controlled increase of 4-6 mEq/L/d and stop ddAVP when Na 128
    • Iatrogenic state of SIADH

Regimen: If above target

- D5W 3 ml/kg over 1 hour (should lower by 1 mEq/l), repeated until goal Na achieved
- ddAVP 2-4 mcg IV q6hours, continue until Na appropriately increases to 125-130
- Measure Na after every D5W infusion to see if need more D5W (stop D5W when reach goal as below)

• Goal
  - Lower by 1 mEq/l/h
  - overall rate of <8-9 mEq/L for 24 hours and <18 for 48h

Relowering not validated in human trials but shown to be safe
Relowering prevents ODS in rat models

ODS

• Delayed by 2-6 days
• Sx include dysarthria, dysphagia, para/quadraparesis, behavioral changes, confusion, obtundation, coma
  – Partially reversible, irreversible
• MRI may take weeks to be positive
• ?earlier imaging detection with newer modalities
Pattern of Practice

- be safe
- if no good evidence: weigh risk and benefits in each individual case
Case 3

• 45 yo female with a GBM brain tumor
• On carbamazepine for seizures, neurology says can’t stop
• Euvolemic
• Urine Na 70 mEq/L, urine Osm 600 mosm/L
• Na persistently 125 mEq/L despite fluid restriction 1.2L/d
• Going for neurosurgery, consult for preop Na management
Table 1. Causes of the Syndrome of Inappropriate Antidiuresis (SIAD). *

<table>
<thead>
<tr>
<th>Malignant Diseases</th>
<th>Pulmonary Disorders</th>
<th>Disorders of the Central Nervous System</th>
<th>Drugs</th>
<th>Other Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>Infections</td>
<td>Infection</td>
<td>Drugs that stimulate release of AVP or enhance its action</td>
<td>Hereditary (gain-of-function mutations in the vasoressin V2 receptor)</td>
</tr>
<tr>
<td>Lung</td>
<td>Bacterial pneumonia</td>
<td>Encephalitis</td>
<td>Chlorpropamide</td>
<td>Idiopathic</td>
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<tr>
<td>Smaller cell</td>
<td>Viral pneumonia</td>
<td>Meningitis</td>
<td>SSRI</td>
<td>Transient</td>
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<tr>
<td>Mesothelioma</td>
<td>Pulmonary abscess</td>
<td>Brain abscess</td>
<td>Tricyclic antidepressants</td>
<td>Endurance exercise</td>
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<tr>
<td>Oropharynx</td>
<td>Tuberculosis</td>
<td>Rocky Mountain spotted fever</td>
<td>Clofibrate (Atromid-S, Wyeth–Ayerst)</td>
<td>General anesthesia</td>
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<td>Gastrointestinal tract</td>
<td>Aspergillosis</td>
<td>AIDS</td>
<td>Carbamazepine (Epitol, Lemmon; Tegretol, Ciba–Geigy)</td>
<td>Nausea</td>
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<tr>
<td>Stomach</td>
<td>Asthma</td>
<td>Bleeding and masses</td>
<td>Vincristine (Oncovin, Lilly; Vincasar, Pharmaica and Upjohn)</td>
<td>Pain</td>
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<tr>
<td>Duodenum</td>
<td>Cystic fibrosis</td>
<td>Subdural hematoma</td>
<td>Nicotine</td>
<td>Stress</td>
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<td>Pancreas</td>
<td>Respiratory failure associated with positive-pressure breathing</td>
<td>Subarachnoid hemorrhage</td>
<td>Narcotics</td>
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<td>Genitourinary tract</td>
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<td>Cerebrovascular accident</td>
<td>Antipsychotic drugs</td>
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<td>Ureter</td>
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<td>Brain tumors</td>
<td>Ifosfamide (Ifex, Bristol-Myers Squibb)</td>
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<td>Bladder</td>
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<td>Head trauma</td>
<td>Cyclophosphamide (Cytoxan, Bristol-Myers Squibb; Neosar, Pharmaica and Upjohn)</td>
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<td>Prostate</td>
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<td>Hydrocephalus</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
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<td>Endometrium</td>
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<td>Cavernous sinus thrombosis</td>
<td>MDMA (&quot;ecstasy&quot;)</td>
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<td>Endocrine thymoma</td>
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<td>Other</td>
<td>AVP analogues</td>
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<tr>
<td>Lymphomas</td>
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<td>Multiple sclerosis</td>
<td>Desmopressin (DDAVP, Rhone–Poulenc Rorer; Stimate, Centeon)</td>
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<td>Sarcomas</td>
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<td>Guillain–Barré syndrome</td>
<td>Oxytocin (Pitocin, Parke–Davis; Syntocinon, Novartis)</td>
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<td>Ewing’s sarcoma</td>
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<td>Shy–Drager syndrome</td>
<td>Vasopressin</td>
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<td>Delirium tremens</td>
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<td>Acute intermittent porphyria</td>
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</table>

* AIDS denotes the acquired immunodeficiency syndrome, AVP arginine vasopressin, SSRI selective serotonin-reuptake inhibitor, and MDMA 3,4-methylenedioxymethamphetamine.
<table>
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<th>Etiology of SIADH</th>
<th>Likely duration of SIADH</th>
<th>Relative risk of chronic SIADH</th>
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<td>Tumors 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, SSRI)</td>
<td>Duration of drug therapy</td>
<td></td>
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<td>Brain tumors</td>
<td>Indefinite</td>
<td></td>
</tr>
<tr>
<td>Idiopathic (senile)</td>
<td>Indefinite</td>
<td></td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</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>Medium</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>Postoperative hyponatremia</td>
<td>2-3 days postoperatively</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: SIADH, syndrome of inappropriate antidiuretic hormone secretion; HIV, human Immunodeficiency virus.

Figure 4  Estimated probability of the need for long-term treatment of hyponatremia depending on the underlying etiology of the syndrome of inappropriate antidiuretic hormone secretion. Abbreviations: HIV = human immunodeficiency virus.
Dx of SIADH

**Essential features**
- Decreased effective osmolality (<275 mOsm/kg of water)
- Urinary osmolality >100 mOsm/kg of water during hypotonicity
- Clinical euvolesma
  - No clinical signs of volume depletion of extracellular fluid
  - No orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes
  - No clinical signs of excessive volume of extracellular fluid
  - No edema or ascites
- Urinary sodium >40 mmol/liter with normal dietary salt intake
- Normal thyroid and adrenal function
- No recent use of diuretic agents

**Supplemental features**
- Plasma uric acid <4 mg/dl
- Blood urea nitrogen <10 mg/dl
- Fractional sodium excretion >1%; fractional urea excretion >55%
- Failure to correct hyponatremia after 0.9% saline infusion
- Correction of hyponatremia through fluid restriction
- Abnormal result on test of water load (<80% excretion of 20 ml of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution (<100 mOsm/kg of water)
- Elevated plasma AVP levels, despite the presence of hypotonicity and clinical euvolesma
Low Na

ADH
- Appropriate
  - $\uparrow$ tonicity
  - $\downarrow$ ECFV
    - true
    - effective
- Inappropriate
  - SIADH
  - drugs
  - CNS
  - pulmonary
  - cancer
  - endurance
  - exercise
  - nausea
  - pain
  - stress
  - low cortisol
  - hypothyroidism

WATER
- Exogenous
  - po or IV
- Endogenous
  - cell metabolism

SOLUTE threshold
- Low salt diet
- Low prtn diet
- Beer potomania

FREE H2O EXCRETION
- Increasing age
- Decreased GFR
- Thiazide diuretic
- PG inhibitors
- Low solute

Check serum osmolality, Urine osmolality and urine Na

Approach to etiology
**Fluid restriction**

(Usually not adequate if urine osmolality > 500mosm/l)

**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.

*The American Journal of Medicine, Vol 126, No 10A, October 2013*
SIADH example

Urine osmolality fixed at 600 mosm/L
0.9% NS osmolality = 154 x 2 = 308

\[
\frac{600 \text{mosm}}{L} = \frac{308 \text{mosm}}{xL}
\]

X = obligatory urinary losses driven by the salt excretion

X = 0.5L of 1 L of NS excreted and 0.5L of NS distributed across TBW as free water leading to decreased serum Na

**no defect in salt excretion

**defect in H2O excretion
SIADH example

Urine osmolality fixed at 600 mosm/L
0.9% NS osmolality = 154 x 2 = 308

600 mosm
----- = 308 mosm
L xL

X = obligatory urinary losses driven by salt excretion

X = 0.5 L of 1 L of NS excreted and 0.5 L of NS distributed across TBW as free water leading to decreased serum Na

**no defect in salt excretion

**defect in H2O excretion

SIADH Treatment Options

Assess if acute/chronic or Sx

1) Treat/remove offending cause
2) Water restrict

3) Try and modify the equation
   a) 3% saline osmolality = 512 x 2 = 1024

   600 mosm
   ----- = 1024 mosm
   L xL

   X = 1.7 L

   High solute diet/Salt tablets/oral Urea as outpt approach to drive the urine output

   b) Lasix can interfere with the [] ability

   300 mosm
   ----- = 1024 mosm
   L xL

   x = 3.4 L

4) Demeclocycline
5) ADH receptor antagonists (Vaptans)
Vaptans

- CHF
- SIADH
  - In mild-mod hypona
  - ??In aSx severe hypoNa (not as good data)
  - ??in future replace fluid restriction as first line??
  - Frequent monitoring

- Many limitations
  - Cost
  - Side effects (liver dz, polyuria, polydipsia, thirst)
  - Concerns with rapid correction
  - Improve Na but don’t change CV outcomes (in CHF)
  - ?duration of therapy (in US approved for up to 30 days)
Objectives

• Approach to diagnosis of hypoNa
  – Acute vs chronic
  – Etiology of hyponatremia

• Treating hypoNa safely
  – Acute vs chronic
  – Symptomatic vs asymptomatic
  – Addressing rapid correction (prevention and reversal)
    • In pts at highest risk for rapid correction
    • In pts at highest risk for osmotic demyelination (ODS)
  – ???Vaptans

• Cases
Summary

• Approach
  – Acute: bring Na up quickly especially if Na < 130 and/or sx of cerebral edema (3% saline 100ml boluses q 10 min prn)
  – If chronic symptomatic treat emergently 3% saline
  – If chronic asymptomatic, NO RUSH: think of etiology, risk of ODS and rapid correction and aim for 24 hour goal of 4-6 mEq/L/d
    • Consider slowing down rate of correction or reversal of correction if it develops using safe strategies based on your clinical judgement, case by case (little evidence to guide)
  – Monitor serum Na, K, urine output and osmolality
  – Too soon to know full utility and indications of vaptans
• BE SAFE
• Questions
• debsrosen@gmail.com
HCTZ and hypoNa

• Patients who are at risk for hypoNa on HCTZ
  – Low Na diet for HTN or tea and toast diet \(\rightarrow\) decreases the amount of obligate urine output as there are less osmoles being excreted
  – capacity to excrete free water decreases with age
  – May become slightly volume depleted with the HCTZ \(\rightarrow\) ADH
  – a high fluid intake

• Prevention of HCTZ induced hypoNa
  – Check Na before and 2 weeks after starting Tx
  – Counsel about excessive fluid intake
  – Check BW in pts on HCTZ who become acutely ill
Reset Osmostat

- In chronic SIADH and chronic volume depletion leading to persistent hypoNa
  - Chronic malnutrition, spinal cord injuries, chronic drug use (tegretol)
- Downward resetting of the osmostat for ADH release and thirst
- Usually mild hypoNa (125-135) stable over many days despite variations in salt and H2O intake
- Can be confirmed by H2O load test
  - 15-20ml/kg of oral water load.
  - In pts with no ADH on board (includes the reset osmostat) excrete more than 80% of H2O load in first 4 hours
  - SIADH impaired H2O excretion (the test could be dangerous)
Beer Potomania

• Prevention of ODS
  – Limit IV if not necessary
  – Abx in D5W
  – Limit refeeding in first couple of days of admission
  – If brisk diuresis with the introduction of an osmole load and can’t keep up with IV D5W or free water intake then give DDAVP
Exercise associated hyponatremia

- Endurance exercise especially marathons
- 13% incidence, 0.6% Na <120 in one study of Boston marathon
- Associated with
  - weight gain during running
  - > 4 hours to complete the run
  - BMI extremes
  - On univariate > 3 L of fluids during the run
- During exercise
  - Increased ADH, drinking hypotonic fluids, diluting capability of kidney is decreased
- Tx: especially if sx, hypertonic saline 100ml over 20-30 min and repeat if needed. Give O2 if hypoxia as hypoxia has potentiating effects in the development of cerebral edema
Urine Na and Urine osmolality

- **SIADH**
  - High urine osm >100 mosm/L
  - Urine Na > 40 mEq/L, unless volume depleted or very low salt diet
- **Glucocorticoid deficiency and hypothyroidism**
  - High urine osm, Urine Na >40 mEq/L
- **Volume depletion (true and effective)**
  - High urine osm > 300mosm/L
  - Urine Na <20 mEq/L unless on diuretics, low mineralcorticoid state, or cerebral/renal salt wasting
- **Low solute state**
  - Low urine osmolality (<200mosm/L)
  - Urine Na depends on diet
- **Water intoxication**
  - Low urine osmolality 50 mosm/L
  - Low Urine Na