 Introduction

- Approximately 60% of body weight is salt water. The blood sodium concentration ([Na⁺]) is approximated by the ratio of total body sodium to total body water, i.e.
  - Blood (plasma or serum) [Na⁺] ~ Total body sodium/Total body water
- Most disorders of sodium concentration are primarily due to alterations in water balance.

 Definitions

- Hyponatremia is defined as a plasma (or serum) sodium concentration ([Na⁺]) of < 135 mEq/L. Hypernatremia is defined as a plasma sodium concentration ([Na⁺]) of > 145 mEq/L.

 Physiologic Regulation of Plasma Sodium Concentration [Na⁺]

- In steady state, water intake = water output
- Water excess without a change in total body sodium content leads to hyponatremia
- Water deficit without a change in total body sodium content leads to hypernatremia
- ↑ water intake → ↓ plasma [Na⁺] → ↓ antidiuretic hormone (ADH) release and thirst → ↑ renal water excretion and ↓ water intake → normalization of plasma [Na⁺].
- ↓ water intake → ↑ plasma [Na⁺] → ↑ ADH and thirst → ↓ renal water excretion and ↑ water intake → normalization of plasma [Na⁺]

 Regulation of ADH

- ADH is arginine vasopressin (AVP), an octapeptide synthesized by the supraoptic and paraventricular nuclei in the hypothalamus and stored and secreted by the posterior pituitary.
- ADH acts on the distal tubule collecting duct to increase water reabsorption and thus decrease renal water excretion. In the presence of substantial amounts of ADH the urine will be concentrated (urine osmolality > plasma osmolality).
- ADH secretion is physiologically regulated by osmotic and non-osmotic factors. A small (1-2%) increase in effective osmolality ([Na⁺] + [glucose]) will increase ADH release (Figure 1). A large (approx. 10%) decrease in blood volume or blood pressure will also increase ADH release and can override the effect of osmolality (Figure 2). ADH release can also be affected by other non-osmotic stimuli (e.g., drugs, pain, stress).
- Assuming normal renal response to its effects, when ADH is completely suppressed, urine osmolality is very low (< 150 to ~ 50 mmol/kg); when maximally active, urine osmolality is high (> 700 to ~ 1200 mmol/kg) (Figure 3)
Osmotic regulation of ADH release and thirst

Relation between plasma antidiuretic hormone (ADH) concentration and plasma osmolality in normal humans in whom the plasma osmolality was changed by varying the state of hydration. The osmotic threshold for thirst is a few mosmol/kg higher than that for ADH.


Figure 1
**Figure 2.** Osmotic vs. non-osmotic regulation of ADH. The percent change of either osmolality or volume is shown on the x-axis and plasma AVP (ADH) levels on the y-axis. It should be noted that plasma AVP is more sensitive to changes in osmolality, but plasma AVP can rise to very high levels in response to large changes in volume.
HYponatREMIA

❖ Etiology of Hyponatremia

- Pseudohyponatremia (plasma [Na⁺] is low due to an increase in the protein and/or lipid content of plasma; plasma water [Na⁺] is normal; plasma osmolality is thus normal).
  - Hypertonic hyponatremia (plasma osmolality is high)
    - Hypertonic hyponatremia (plasma osmolality is high)
      - Hyperglycemia. Elevated glucose in plasma osmotically draws water from cells, lowering the plasma [Na⁺]. Corrected [Na⁺] = measured [Na⁺] + [1.6 x (glucose /100) – 1)] (where glucose concentration is expressed in mg/dL). Note: the correction factor is larger (up to 4) when there is extreme hyperglycemia.
      - Exogenous solutes (i.e., hypertonic mannitol used to treat cerebral edema)
  - Isotonic hyponatremia
    - Addition of an isosmotic but non-sodium-containing fluid to the extracellular space, such as glycine or sorbitol used as endoscopic irrigant solutions.
  - Hypotonic hyponatremia (plasma osmolality is low), which can be further subdivided into euvoletic, hypoelastic, and hypervolemic types based on clinical and laboratory assessment of plasma/extracellular volume. Most hyponatremia falls into this category.

❖ Pathogenesis of Hypotonic Hyponatremia

- Plasma sodium concentration [Na⁺] reflects the relationship between total body cations (sodium plus potassium) and total body water (TBW), i.e. [Na⁺] = α(Na⁺₀ + K⁺₀)/TBW + β, where Na⁺₀ = isotopically measured exchangeable sodium, K⁺₀ = isotopically measured exchangeable potassium.
- Thus plasma [Na⁺] only gives an indication of the relative amount of total body cations and TBW, and not the absolute amount of either.
- In the absence of severe potassium depletion, plasma [Na⁺] can be approximated by the ratio of TBNa⁺/TBW.
- Hyponatremia = excess of total body water (TBW) relative to TBNa⁺. Some examples:
  - ↑TBW with normal TBNa⁺. This typically occurs when there is an inappropriate increase in ADH secretion, i.e. SIADH (syndrome of inappropriate antidiuretic hormone). For example, if a tumor is secreting ADH, ADH secretion is not being regulated by the plasma sodium concentration, and if water is ingested it will be retained, causing persistent hyponatremia.
  - ↓ TBW with ↓↓ TBNa⁺. This usually occurs when there are sodium and water losses, with replacement of water but not sodium. For example, some patients taking diuretics (which cause renal loss of sodium and water) will ingest large amount of water possibly due to stimulation of thirst by volume depletion; volume depletion, if severe, can also (appropriately) cause ADH release, which contributes to hyponatremia.
  - ↑↑ TBW with normal or ↑ TBNa⁺. This may occur in edematous disorders, i.e. congestive heart failure (CHF), liver cirrhosis, nephrotic syndrome, and renal failure. For example, in severe CHF, there is a decrease in “effective blood volume” or
“effective circulatory volume” due to impaired cardiac output; since there is decreased renal perfusion, the kidney perceives volume depletion and retains sodium and water. ADH release is increased due to the decrease in effective blood volume and blood pressure, which contributes to hyponatremia.

- It should be obvious that the plasma sodium concentration per se gives no information about the TBNa*. Estimation of TBNa* requires physical examination. Signs of low TBNa* are flat neck veins, decreased skin turgor, dry mucous membranes, absence of edema, and orthostatic changes in pulse and blood pressure. The principal sign of high TBNa* is edema.

- Normal kidneys can excrete a large amount of water, because of the great ability of the kidneys to form dilute urine. In the absence of ADH, urine osmolality can be as low as 50 mmol/L. The daily solute load is generally 600-1200 mmol/day. Even if urine osmole excretion is 600 mmol/day, then 12 L of dilute urine can be excreted (Figure 3). Since sustained fluid intake in excess of 12 L per day is decidedly uncommon, hyponatremia due to fluid ingestion alone is very rare. Therefore, hyponatremia usually indicates impaired renal water excretion due to:
  - Decreased solute excretion. If osmole (solute) excretion is lower than normal, hyponatremia may ensue as a result of smaller fluid intakes. This has been described in beer drinkers, who ingest much fluid but very little (i.e. 100-200 mmol/day) solute (“beer drinker’s potomania”) (Figure 4).
  - Impaired urinary dilution, due to:
    - Excess ADH production (either appropriate, i.e., in response to a physiologic stimulus, or inappropriate).
    - Intrarenal factors (independent of ADH) (Figure 5). Normal renal ability to excrete water depends on 3 factors: (1) Filtration of solute by the glomeruli (2) Delivery of solute to distal (diluting) nephron sites (3) Water-impermeability of diluting nephron sites, which occurs providing ADH is absent. Thus, intrarenal factors that impair water excretion include: (1) renal failure (which decreases GFR and thus filtration of solute), (2) decreased delivery of solute to distal (diluting) segments of the nephron due to solute avidity at proximal nephron sites {for example, with CHF}, (3) diuretics (which impair generation of a dilute urine by preventing solute reabsorption in water-impermeable nephron segments) (Figure 6).

The Importance of Volume Status in Hyponatremia

- Clinically, hyposmolar hyponatremia is divided into hypovolemic, euvoletic, and hypervolemic hyponatremia depending on the clinical evaluation.

- Total body water is divided into intracellular fluid (ICF) and extracellular fluid (ECF).
- Sodium is present in high concentrations in the ECF but only in low concentrations in the ICF.
- Clinically, it is usually ECF volume that is detected, and thus the term “volume” generally refers to the clinical assessment of ECF volume, which is dependent on total body sodium content.
- Hypovolemia: low total body sodium (ECF volume), as reflected by clinical findings such as flat neck veins, decreased skin turgor, and, if the extent of volume depletion is greater than 15%, orthostatic changes in heart rate and blood pressure (increase in heart rate and decrease in blood pressure with standing).
**Figure 3.** Effect of ADH on urine osmolality and volume. When ADH is absent, urine can become maximally dilute (urine osmolality 50 mmol/L) resulting in copious amount of urine formation. As ADH progressively increases, the urine becomes progressively concentrated and urine volume falls. Calculations assume that there is excretion of 600 mmol of solute per day.

<table>
<thead>
<tr>
<th>ADH</th>
<th>Urine osmolality (mmol/kg)</th>
<th>Urine volume (L/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>++</td>
<td>400</td>
<td>1.5</td>
</tr>
<tr>
<td>++++</td>
<td>1200</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Figure 4.** Effect of low-solute intake and excretion on ability to excrete urine as seen in “beer drinker’s syndrome”. Calculation assumes that there is excretion of 200 mmol of solute per day.

<table>
<thead>
<tr>
<th>ADH</th>
<th>Urine osmolality (mmol/kg)</th>
<th>Urine volume (L/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>4</td>
</tr>
</tbody>
</table>
Figure 5. Renal water excretion depends on (1) glomerular filtration (2) delivery of solute to the diluting nephron sites in the distal tubule (3) reabsorption of salt but not water in the distal tubule, resulting in the formation of dilute urine.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Decreased filtration of solute</th>
<th>Increased solute reabsorption in proximal nephron</th>
<th>Decreased solute reabsorption in distal nephron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Decreased GFR</td>
<td>Reduced renal blood flow resulting in stimulation of proximal solute reabsorption</td>
<td>Inhibitors of solute reabsorption in distal nephron</td>
</tr>
<tr>
<td>Example</td>
<td>Renal failure</td>
<td>Congestive heart failure</td>
<td>Thiazide diuretics</td>
</tr>
</tbody>
</table>

Figure 6. Mechanism of impaired renal water excretion in several common clinical settings.
- Hypervolemia: high total body sodium (ECF volume), as reflected by the presence of edema
- Euvolemia: on clinical assessment, ECF volume appears to be normal, i.e., there are no findings of either hypovolemia or hypervolemia.

- Volume depletion vs. dehydration: These two terms are often used synonymously in clinical practice, but this is not correct. Volume depletion (hypovolemia) means ECF volume depletion due to depletion of both salt and water. Dehydration means depletion of water. Volume depletion can be associated with hyponatremia, normonatremia, or hypernatremia, whereas dehydration results in hypernatremia.

A 70-kg man has a TBW of $0.6 \times 70 \text{ kg} = 42 \text{ L}$, of which about $2/3$ is in the ICF and $1/3$ in the ECF (the ECF is about $1/5$ plasma and $4/5$ interstitial fluid)

<table>
<thead>
<tr>
<th>ICF</th>
<th>ECF</th>
</tr>
</thead>
<tbody>
<tr>
<td>28L</td>
<td>14L</td>
</tr>
</tbody>
</table>

Loss of 3L of ECF results in a 21% decrease in ECF volume, resulting in symptoms and signs of hypovolemia. However, loss of 3L of TBW results in a 2L decrease in ICF and only a 1L (7%) decrease in ECF, and there are no symptoms or signs of hypovolemia.

- Water depletion alone will only lead to clinically-evident hypovolemia if it is very severe. This is not common.

- Etiology of Hypotonic Hyponatremia

- Hypovolemic hyponatremia implies a decrease in TBNa⁺, which can be due to either renal or extrarenal sodium losses.
  - Renal Na⁺ losses – diuretics, primary adrenal insufficiency (Addison's disease), isolated mineralocorticoid deficiency, salt-wasting nephropathies
  - Extrarenal Na⁺ losses – diarrhea, vomiting, excessive sweating
Mechanisms of Human Disease Disorders of Plasma Sodium Concentration
Thursday, October 25, 2018 – 9:30am David J. Leehey, M.D.

- Euvolemic hyponatremia implies normal of near normal TBNa⁺. Examples:
  - SIADH (syndrome of inappropriate antidiuretic hormone secretion) – most commonly due to (1) tumor (2) pulmonary disease (3) central nervous system disease. In some cases, the set-point for ADH secretion is altered (“reset osmostat”). Medications associated with SIADH or SIADH-like syndrome include chlorpropamide, carbamazepine cyclophosphamide, vinca alkaloids, amitriptyline, haloperidol, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase (MAO) inhibitors.
  - NSIAD (nephrogenic syndrome if inappropriate antidiuresis). This rate disorder looks similar to SIADH except ADH levels are unmeasurable. In this condition ADH receptors are mutated and constitutively activated.
  - Severe hypothyroidism (decreased cardiac output and GFR)
  - Psychogenic polydipsia (increased water intake)
  - “Beer drinker’s potomania” (decreased solute intake)
  - Exercise hyponatremia (increased water intake plus ADH release)
  - Post-operative hyponatremia (increase hypotonic fluid administration plus ADH release)

- Hypervolemic hyponatremia indicates increased TBNa⁺. Examples:
  - Congestive heart failure (CHF)
  - Liver cirrhosis
  - Nephrotic syndrome
  - Renal failure

Laboratory Evaluation of Hyponatremia

- Plasma osmolality (low in hypotonic hyponatremia; see above)
- Urine osmolality (urine should be maximally dilute, i.e., Uosm ~ 50 mmol/L in the presence of hypoosmolality; however, generally urine is inappropriately concentrated, except in psychogenic polydipsia, reset osmostat, and “beer drinker’s syndrome”)
- Low UNa⁺ (< 10 mEq/L) or FENa⁺ (fractional excretion of sodium) (< 1%) suggests extrarenal loss of Na⁺ or an edematous disorder (in which kidneys are avidly reabsorbing sodium, and thus causing edema, usually due to a decrease in effective circulatory volume); “normal” UNa⁺ (> 40 mEq/L) or FENa⁺ > 1suggests renal loss of Na⁺ or excess ADH in the absence of renal sodium avidity, as in SIADH.
- Serum urea nitrogen levels are typically increased in hypovolemic or hypervolemic hyponatremia (due to increased proximal tubule urea reabsorption) and low or normal in euvolemic hyponatremia.
- Serum uric acid levels are typically reduced in SIADH and cerebral salt wasting but elevated in most patients with hypovolemic or hypervolemic hyponatremia (due to increased proximal tubule urate reabsorption).
- Thyroid-stimulating hormone (TSH) and serum cortisol levels may indicate hypothyroidism or hypoadrenalism, respectively
- Head computed tomography (CT) scanning and chest radiography can be helpful if SIADH or a cerebral disorder is suspected.

Important Points to Remember

- Hyponatremia usually indicates impaired urinary dilution, either due to high ADH or ADH-independent intrarenal mechanisms. Rarely, diluting ability is normal, as in psychogenic polydipsia, reset osmostat, and decreased solute excretion (“beer drinkers syndrome”).
• In hypovolemic hyponatremia, osmoreceptors and volume receptors receive opposing stimuli (low osmolality and low volume respectively). This causes the osmoreceptors to lower their set point. Thus, ADH is secreted even in the presence of hypoosmolality.

• In edematous disorders, both sodium and water retention occur. In CHF, the aortic and carotid sinus baroreceptors sense decreased effective blood volume (because of decreased cardiac output) and stimulate ADH release. In cirrhosis, there is decreased effective blood volume and enhanced ADH release due to systemic vasodilation and decreased intrathoracic blood volume. In addition, hypoalbuminemia and third-spacing may decrease plasma volume and stimulate ADH release. Intrarenal mechanisms may also be operative. In renal failure, hyponatremia may occur due to a decrease in free water clearance coupled with increased fluid intake.

❖ Symptoms of Hyponatremia
• With decreased sodium in the extracellular compartment, water moves into the cells and, in severe cases, causes cellular swelling.
• Since the calvarium cannot expand, brain swelling can be very symptomatic. Fatigue, headache, irritability, restlessness, loss of appetite, cramps, weakness, nausea, vomiting, confusion, decreased consciousness, hallucinations, convulsions, and coma may result.

❖ Treatment of Hyponatremia
• Rate of correction is dependent on acuity of problem, i.e., whether hyponatremia is deemed to be acute or chronic.
• Hypovolemic hyponatremia is generally treated with physiologic saline
• Hypervolemic hyponatremia is generally treated with fluid restriction and diuretics.
• Euvolemic hyponatremia (e.g., SIADH):
  o Mild asymptomatic hyponatremia should be considered a diagnostic clue but does not mandate treatment.
  o More severe asymptomatic hyponatremia (i.e., plasma sodium < 125 meq/L) should be treated with water restriction and/or saline infusion depending on the volume status.
  o Vasopressin receptor antagonists (vaptans) are being developed for treatment of euvolemic (and hypervolemic) hyponatremia. Conivaptan is currently available for IV treatment. Concomitant fluid restriction will probably be necessary with prolonged IV or oral therapy with vaptans.
  o Symptomatic hyponatremia (confusion, seizures, coma due to hyponatremia) is considered a medical emergency. The optimal treatment has been the source of much controversy and a host of articles in the medical literature. However, it can be summarized as follows:
    ▪ Initial treatment with hypertonic (3%) saline is appropriate. However, the magnitude of correction should not exceed 10 meq/L from baseline (e.g., from 100 to 110 meq/L). The rate of correction should not exceed 2 meq/L/hr (some recommend slower rates of correction).
    ▪ In the absence of overt volume depletion, a loop diuretic such as furosemide may be administered in order to “fix” urinary sodium concentration, usually at about 75 meq/L. Theoretically, the patient will then lose more water than sodium in the urine and the sodium lost can be replaced by hypertonic saline.
Greater acute increases in plasma sodium concentration must be strictly avoided to avoid the complication of central pontine myelinolysis (CPM), which is frequently fatal. CPM has been associated with rapid correction or overcorrection of hyponatremia, and is due to cerebral dehydration. Remember that even in symptomatic hyponatremia the amount of excess brain water cannot exceed 10% above normal because of the limited ability of the brain to swell in the cranial cavity. Therefore, an approximately 10% increase in plasma sodium and plasma osmolality should restore brain water to the normal range.
HYPERNATREMIA

❖ Etiology of Hypernatremia

- Sodium is the primary determinant of plasma osmolality; hypernatremia is thus always a hypertonic or hyperosmolar condition. Plasma osmolality = 2(Na) mEq/L + BUN (mg/dL)/2.8 + serum glucose (mg/dL)/18.

- Hypernatremia occurs only when hyperosmolality is accompanied by an impaired thirst mechanism or when water ingestion is restricted.

- In response to hypernatremia, water moves out of cells with a resulting decrease in brain volume. The brain responds by intracellular uptake of electrolytes, amino acids, and other organic solutes. Therefore, rapid hydration can cause cerebral edema.

❖ Pathogenesis of Hypernatremia

- Hypernatremia = increased [Na+] = decrease in total body water (TBW) relative to TBNa+. Some examples:
  o ↓ TBW with normal TBNa+. This is typical of two clinical conditions: (1) patients in nursing homes with decreased thirst or inability to drink water; (2) diabetes insipidus (DI), in which ADH release is impaired or absent (central DI) or the kidney does not respond to ADH (nephrogenic DI).
  o ↓↓ TBW with ↓ TBNa+. This can occur when water losses exceed sodium losses either from sweat, GI tract, or kidneys.
  o Normal TBW with ↑ TBNa+. This is usually iatrogenic due to administration of hypertonic fluids or isotonic fluids in the setting of renal water losses (i.e., concentration of sodium in administered fluid is greater than urinary concentration).
  o Again, it should be obvious that the serum sodium concentration per se gives no information about the TBNa+.

- In the presence of ADH, normal kidneys can concentrate urine to a urine osmolality of 1200 mmol/L (in older patients, urine osmolality generally will only increase to the 700-1000 mmol/L range). Thus, if the daily solute load is 600 mmol/day, urine output can be as low as 500 ml/day (with lesser daily solute loads, daily urine output can be theoretically even lower when maximally concentrated). These low urinary volumes will minimize renal water loss if water intake is impaired. However, remember that insensible water loss (primarily via respiration) is about 500-700 mL/day. Therefore, even when there is maximum antidiuresis, total cessation of water intake will lead to hypernatremia over a period of hours to a few days (Desert animals such as the kangaroo rat can concentrate urine to 3000 mmol/L and thus can live without water for much longer than can humans!)

❖ Etiology of hypernatremia

- Hypernatremia is always associated with hyperosmolality. Analogous to hyponatremia, it can be divided into hypovolemic, euvolemic, and hypervolemic hyponatremia depending on the clinical evaluation.

- Hypovolemic hypernatremia implies a decrease in TBNa+ due to either:
Renal Na$^+$ losses – diuretics (with inadequate water intake), osmotic diuresis (due to hyperglycemia, mannitol, urea), post-obstructive diuresis, tubular injury (recovery phase of ATN)

- Extrarenal Na$^+$ losses – sweating, diarrhea, vomiting (with inadequate water intake).

- Euvolemic hypernatremia implies normal of near normal TBNa$^+$.
  - Central diabetes insipidus (trauma, idiopathic, tumor)
  - Nephrogenic diabetes insipidus (congenital, drugs, hypercalcemia, tubular disease)
  - Decreased water intake (“nursing home syndrome”)

- Hypervolemic hypernatremia
  - Iatrogenic administration of hypertonic fluid (hypertonic saline, bicarbonate, etc.)
  - Mineralocorticoid excess states (e.g., hyperaldosteronism) – causes mild hypernatremia
  - Salt poisoning (and seawater ingestion)

Clinical evaluation involves history and physical examination. Urine chemistries (especially osmolality) may also be very helpful. For instance, in central DI, the urine osmolality < plasma osmolality (usually < 100 mmol/kg), whereas with osmotic diuresis, the urine osmolality > plasma osmolality.

**Treatment of Hypernatremia**

- Hypovolemic hypernatremia is generally treated with hypotonic fluids.
- Euvolemic hypernatremia is treated with water administration (+ ADH in central DI)
- Hypervolemic hypernatremia can be problematic. If severe, it may require both water administration plus either diuretics or dialysis to remove the excess sodium.
- Rate of correction should not exceed 0.5 meq/L/hr, as too rapid a reduction in serum sodium and osmolality may result in shift of water into the brain and brain edema. Acute hypernatremia is very rare, so caution in rate of correction is usually in order!
REFERENCES:


BOOKS:
