Water and Sodium Balance and Their Associated Disorders

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Sodium is one of the most important active osmotic solutes in the human body, which is maintained in constant amounts in extracellular and intracellular fluid compartments. Understanding the normal physiological basis of water and sodium balance, and the associated clinical implications of any change in this balance, are of clinical significance, as even small changes can result in emergency conditions. This will be discussed in detail in this article.

Fluid Compartments of the Body

There is normally a continuous exchange of body fluids and solutes with the external environment and different body compartments of the body. The properties of **extracellular fluid (ECF) and intracellular fluid (ICF)** are summarized in the following table:

Total body fluid (42 Liters) is distributed into two compartments	
Extracellular fluid (ECF)	**Intracellular fluid (ICF)**

<table>
<tr><td colspan="2">ECF accounts for 20% (14 L) of total body weight. ECF is divided into:</td><td>ECF accounts for 40% (28 L) of total body weight, distributed in about 75 trillion cells.</td></tr>
<tr><td>Interstitial fluid</td><td>Plasma</td><td rowspan="3">Each cell has its own mixture of different constituents, but the concentrations of these substances are similar in all different cells.</td></tr>
<tr><td>Accounts for 3/4 of ECF</td><td>Accounts for 1/4 of ECF</td></tr>
<tr><td colspan="2">There is a continuous exchange of solutes in ECF between plasma and interstitial fluid through the pores of the capillary membranes. Both plasma and interstitial fluid have the same composition except the protein, which is higher in plasma because the pores are impermeable to protein.</td></tr>
</table>

Difference between the Composition of ECF and ICF

Extracellular fluid (ECF)

There is a highly permeable membrane between the plasma and interstitial fluid, allowing the continuous exchange of solutes between the two compartments. The membrane has a low permeability to proteins, allowing only a small amount of proteins to be leaked from the plasma to the interstitial fluid. This makes the concentration of **proteins in plasma higher than interstitial fluid.**

Donnan effect

The large **anionic proteins** in plasma make a **net negative charge**, therefore attracting the **positively charged ions** (**cations**), such as potassium and sodium ions; thus, holding an extra amount of cations in the plasma along with protein.

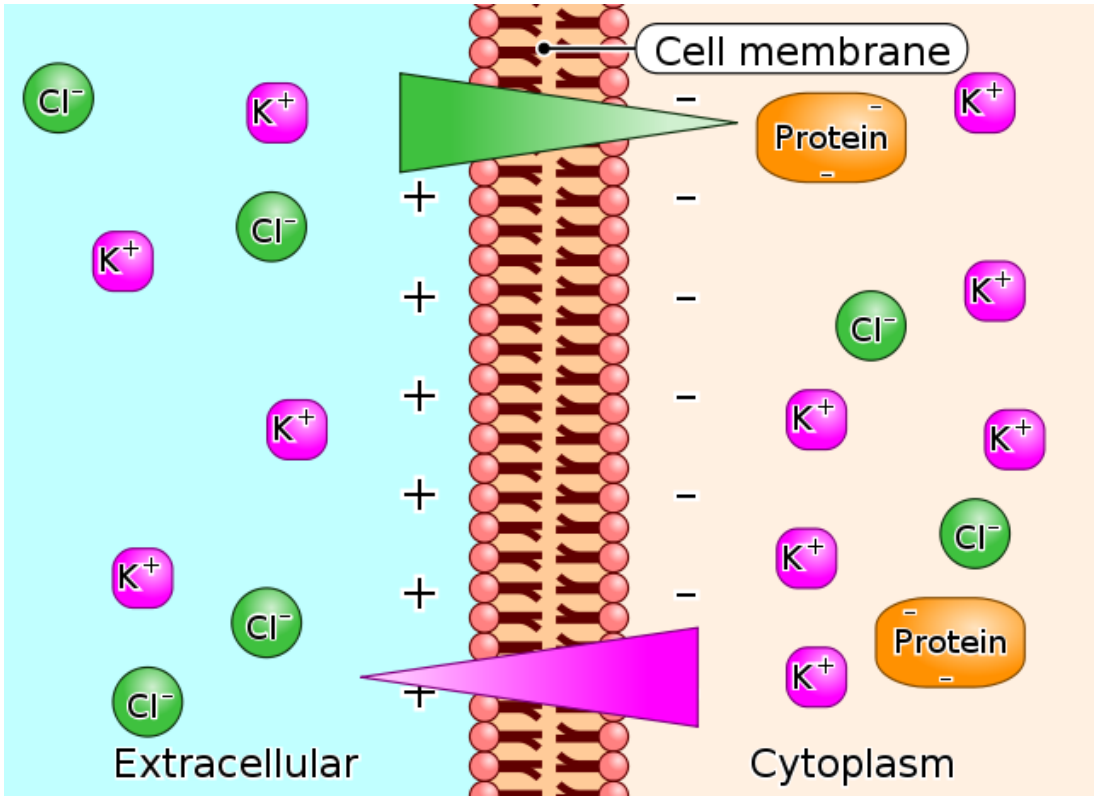

Image: “Gibbs-Donnan-Effect” by Biezl. License: Public Domain

The negative charges of protein in plasma repel the **negatively charged ions (anions)**, such as chloride ions; thus, there is a slightly higher concentration of anions in interstitial fluid than the plasma. Because of the Donnan effect, the concentration of cations is about 2% greater in the plasma than interstitial fluid.

Extracellular fluid contains a high concentration of:

- Sodium ions
- Chloride ions
- Bicarbonate ions

Extracellular fluid contains a low concentration of:

- Potassium
- Calcium
- Magnesium
- Phosphate
- Organic acid ions

The compositions of extracellular fluid are regulated chiefly by **the kidneys** (discussed in a later section). The ECF balance between plasma and interstitial fluid is determined chiefly by the **balance of hydrostatic and colloid osmotic forces across the capillary membranes.**

Intracellular fluid (ICF)

There is a highly permeable cell membrane which separates the ECF from the ICF, allowing the water to diffuse easily from interstitial fluid into the cells. In contrast to ECF, intracellular fluid contains a high concentration of:

- Potassium ions

- Phosphate ions
- Magnesium ions (moderate amount)
- Sulfate ions (moderate amount)

Intracellular fluid contains a low concentration of:

- Sodium ions
- Chloride ions
- Calcium ions

Also, the ICF contains a large amount of protein, which is four times the amount of plasma protein.

Distribution of fluid between ICF and ECF is determined mainly by the **osmotic effect of sodium and chloride,** which are the most osmotically active solutes acting across the cell membrane. The **concentration of sodium in ECF is the most important determinant of ECF volume** because changes in concentration of chloride are, to a greater extent, secondary to changes in the concentration of sodium.

The water moves rapidly across the cell membrane by this osmotic effect to **keep the ECF isotonic with the ICF**.

Osmosis

Osmosis is the net diffusion of water across a selectively permeable membrane from a region of **low solute concentration** (high water concentration) to one with a **high solute concentration** (low water concentration).

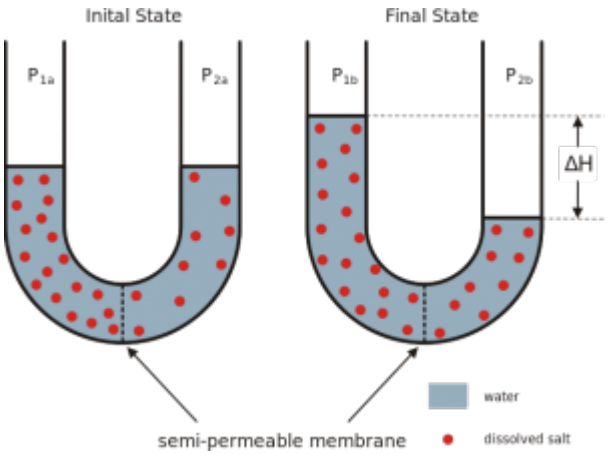

Image: "An example of osmosis: dissolved salt forcing water to pass through a semi-permeable membrane" by Hans Hillewaert.
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Osmolality and Osmolarity

The total number of particles in a solution is measured in **Osmoles.**

One osmole (osm) = 1 mole (mol) of solute particles

For example, a solution containing 1 mole of glucose in each liter has a concentration of 1 osm/L.

Osmolality is the osmolar concentration of a solution when it is expressed as

osmoles/kg of water. **Osmolarity** is the osmolar concentration of a solution when it is expressed as **osmoles/L of water.** About 80% of total osmolarity of the interstitial fluid and plasma is due to sodium and chloride ions, while half of the total osmolarity of the intracellular fluid is due to potassium ions and the remainder is due to other intracellular substances.

Plasma Osmolality

POsm = 2 (serum Na^+) + (serum glucose/18) + (serum blood urea nitrogen (BUN)/(2.8)
= 280 – 295 mOsm/kg

There is an osmotic equilibrium between intracellular and extracellular fluids, and even small changes in the concentration of these impermeant solutes in extracellular fluids can make a large **osmotic pressure** across the cell membrane, with the subsequent rapid movement of water across the cell membrane.

- **If the plasma osmolality is high (hypertonic state),** water will diffuse out of the cells to the ECF, and will result in cell shrinkage.
- **If the plasma osmolality is low (hypotonic state),** water will diffuse into the cells, and will result in cell swelling.
- **If the osmolality is equal between ICF & ECF (isotonic state),** water will not diffuse across the cell membrane and the cells will not shrink nor swell.

Macromolecules (mainly proteins) determine the so-called **oncotic pressure.** Intravasal situated Albumin keeps water in plasma. In the case of a loss of Albumin (cirrhosis, nephrotic syndrome), the oncotic pressure of the plasma decreases and water moves into the interstitium. Edemas will be the outcome.

The **hydrostatic pressure** is mainly determined by the blood pressure. Decreased venous return (e.g. right heart failure) increases the hydrostatic pressure and water gets pressed out of the vessels into the interstitium which, as well, then leads to edemas.

Clinical Significance of Plasma Osmolality

Decreased plasma sodium concentration

Decreased plasma sodium concentration (Hyponatremia < 135 mEq/L) occurs from either:

1. Loss of NaCl from ECF or
2. Additional excess water to the ECF

Loss of NaCl from ECF results in **hypo-osmotic (hyponatremic/hypotonic) dehydration,** in which the water moves from the region of low solute concentration (plasma) to the region of high solute concentration (intracellular), leading to:

1. Decrease in ECF, with signs and symptoms of volume depletion:

- Orthostatic hypotension (defined as a decrease in systolic blood pressure of 20 mm Hg or a decrease in diastolic blood pressure of 10 mm Hg within three minutes of standing when compared with blood pressure from the sitting or supine position)*,* **is the earliest sign of volume depletion**
- Reflex tachycardia with weak pulse

- Delayed capillary refilling
- Dry mucus membranes (as dry tongue)
- Cold extremities
- Oliguria

2. Expansion of ICF, which results in cell swelling and edema. The most dangerous is brain edema, which may lead to lethargy and coma. Furthermore:

- Rapid correction of hypernatremia can create a new gradient that causes water movement from the extracellular space into the cells of the brain; this can produce cerebral edema.
- Avoid more **than a 12-mEq/L** decrease in the serum Na every 24 hours.

Increased plasma sodium concentration

Increased plasma sodium concentration (Hypernatremia > 145 mEq/L) occurs from either:

1. Loss of water from the ECF or
2. Additional excess sodium to the ECF

Loss of water from ECF results in **Hyper-osmotic (hypernatremic/hypertonic) dehydration**, in which the water moves from the region of low solute concentration (intracellular) to the region of high solute concentration (plasma) resulting in:

1. Increase in ECF, making the clinical signs of dehydration (e.g. signs of shock) less severe.

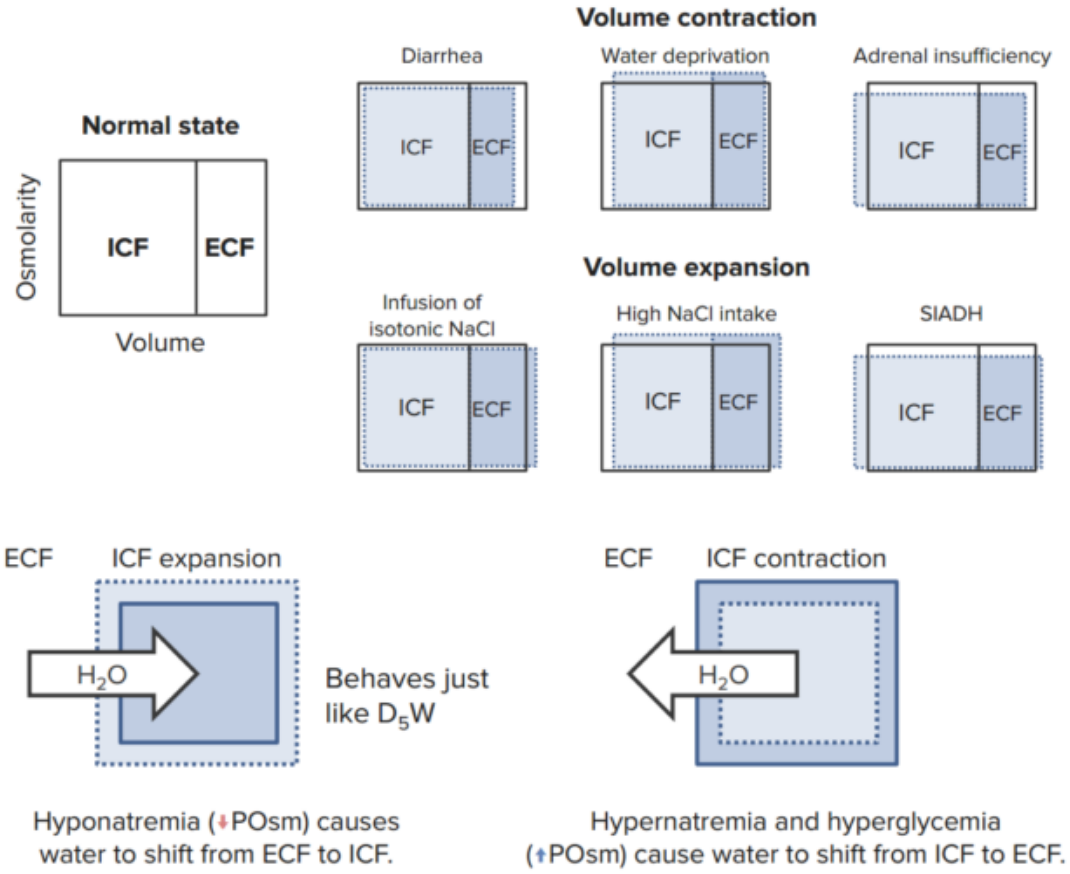
2. Decrease in ICF, which leads to cell shrinkage:

- Making the mucus membranes severely dry (woody tongue).
- Shrinkage of brain cells may result in seizures and coma.
- Rapid correction of hyponatremia can produce **central pontine myelinolysis**.
- Avoid more **than a 12-mEq/L/24** increase in the serum Na every day, especially if the hyponatremia developed gradually.

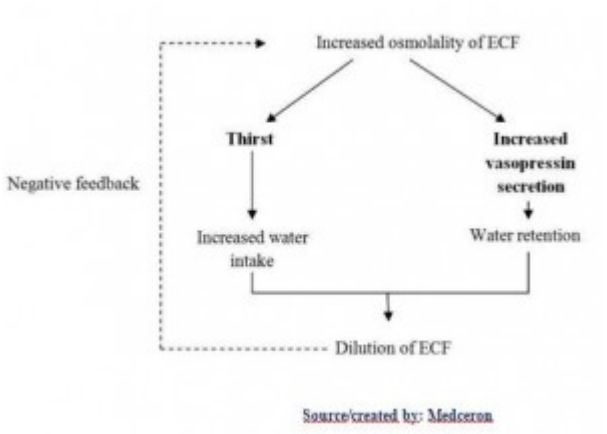
When proportionally the same amount of water and sodium are lost from the body, the sodium concentration in the ECF will not change, resulting in iso-osmotic (normonatremic/isotonic) dehydration. Therefore, the mechanisms that control **Na^+ balance** are the major mechanisms that **control ECF volume.**

Summary

Decreased extracellular fluid volume	Normal extracellular fluid volume	Increased extracellular fluid volume
Volume depletion (hemorrhage, etc.)	Sepsis	CHF
		Cirrhosis
		Nephrotic syndrome



Regulation of Extracellular Fluid Composition & Volume



The two main mechanisms in the regulation of the ECF osmolality, and sodium concentration are:

1. Antidiuretic hormone (vasopressin) secretion
2. Thirst mechanism

Anti-diuretic hormone (vasopressin) secretion

Antidiuretic hormone (ADH), also called vasopressin, is a very important mechanism that regulates the plasma osmolality and sodium concentration by altering the water excretion by the kidneys.

It is synthesized in the hypothalamus and stored in the posterior pituitary. They are released into the bloodstream in response to various stimuli. **Its secretion is regulated** by osmoreceptors which are located in the anterior hypothalamus.

The stimuli of the ADH secretion are:

1. Osmotic stimulus

When the osmolality (plasma Na concentration) rises above the normal 285 mOsm/kg, as in the case of water deficit, this causes **shrinkage of osmoreceptors** in which signals are transmitted to the posterior pituitary and stimulates release of ADH into the bloodstream to reach the kidney, and vice versa.

2. Volume stimulus

When the volume of ECF is decreased, this stimulates **stretch receptors** in the low- and high-pressure portions of the vascular system, in which impulses pass to the posterior pituitary and stimulates the release of ADH. **Low-pressure receptors** are present in the great veins, right and left atria, and pulmonary vessels. **High-pressure receptors** present in the carotid sinuses and aortic arch.

3. Blood Pressure/volume stimulus

The decrease of arterial pressure and/or blood volume, as in the case of the hypovolemia, stimulates the release of ADH, as well as activation of **the Renin-Angiotensin system, which** stimulates aldosterone secretion and promotes sodium and water retention (discussed later in details).

ADH reaches the kidney and increases the permeability of the late distal tubules and collecting ducts, so the water diffuses into the hypertonic interstitium of the renal pyramids. This results in the reabsorption of water into the bloodstream, while the sodium and other solutes are continuously excreted in the urine. This causes dilution of solutes in ECF and correction of the high osmolality, and forming concentrated urine.

The opposite of these sequences occurs when there is **low osmolality of ECF.** (Less ADH is secreted which leads to a decrease of water permeability of late distal tubules and collecting ducts, resulting in an increase of water excretion (this results in an increase of the ECF osmolality), and formation of a diluted urine.)

Thirst mechanism

Increased ECF osmolality causes a shrinkage of the **thirst center** (located anterolaterally in the preoptic nucleus), resulting in stimulating thirst sensation (thus increases fluid intake and dilutes high ECF osmolality to the normal, and vice versa).

Both osmoreceptor-ADH secretion and thirst mechanisms work simultaneously to keep the ECF osmolality and volume within normal levels. Here you have a summary of different factors that affect the regulatory mechanisms of ECF composition and volume:

Increase ADH & Thirst	Decrease ADH & Thirst

↑ Plasma osmolality ↓ Blood volume ↓ Blood pressure	↓ Plasma osmolality ↑ Blood volume ↑ Blood pressure

Role of Renin-Angiotensin-Aldosterone System

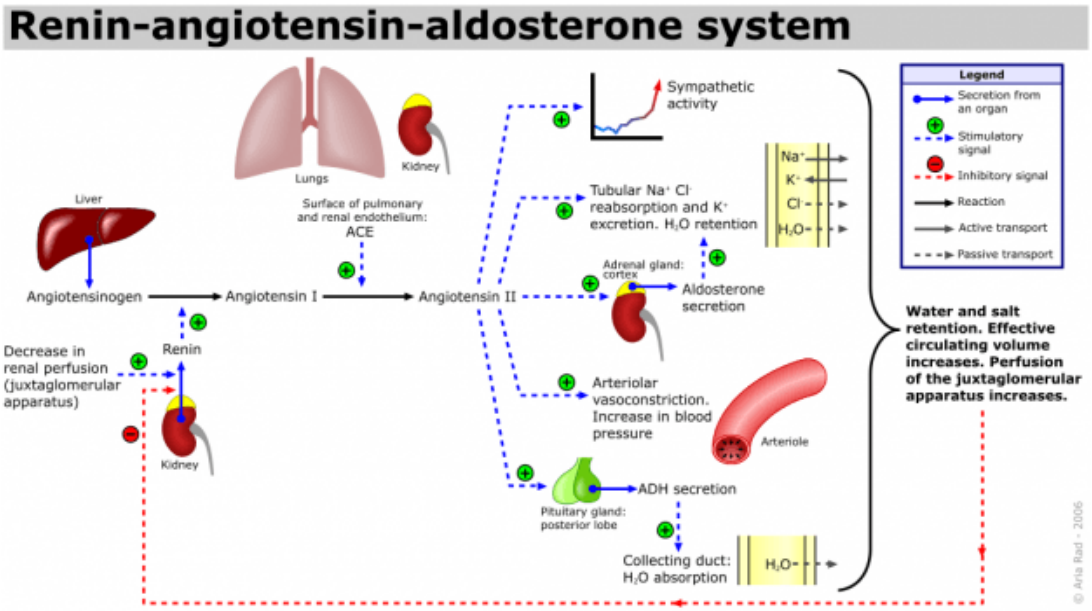


Image: "The renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS). Start reading this schematic from the left, where it says "Decrease in renal perfusion (juxtaglomerular apparatus)". Alternatively, the RAAS can also be activated by a low NaCl concentration in the macula densa or by sympathetic activation." by A. Rad. License: CC BY-SA 3.0. The blue and red dashed arrows indicate stimulatory or inhibitory signals, which is also indicated by the +/-. In the tubule and collecting duct graphics, the grey dashed arrows indicate passive transport processes, contrary to the active transport processes which are indicated by the solid grey arrows. The other solid arrows either indicate a secretion from an organ (blue, with a starting spot) or a reaction (black). These 2 processes can be stimulated or inhibited by other factors.

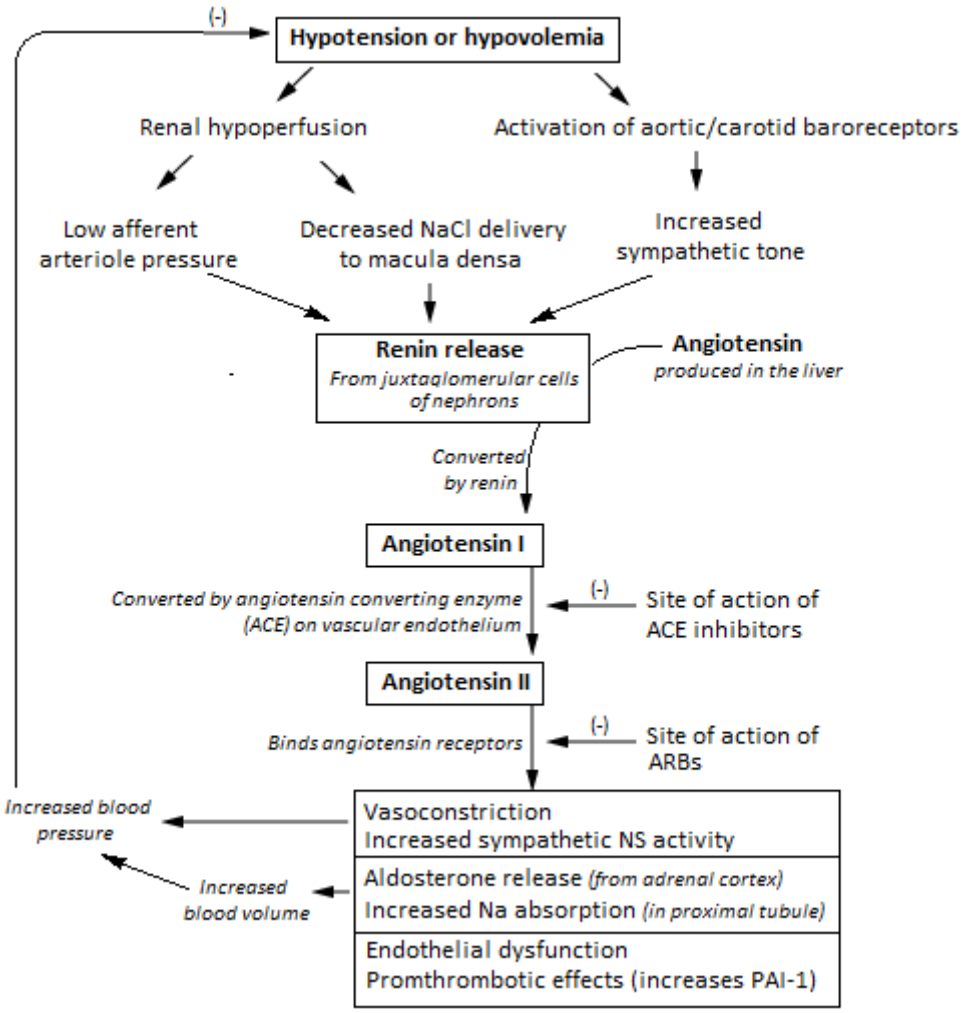
Angiotensin II and aldosterone regulate the concentration of sodium in **extreme conditions** by altering the reabsorption of sodium by the renal tubules. This results in altering the water reabsorption, along with the sodium. Thus, activation of this system leads to **an increase of both the sodium quantity and ECF volume** (hence also a little change in the sodium concentration because the water is absorbed along with sodium, a process called as sodium and water retention.

When the blood pressure/volumes falls, the juxtaglomerular apparatus of the kidneys start to release **renin**, which passes out of the kidney and enters into the circulation. The renin then acts enzymatically on the **angiotensinogen** to release **angiotensin I.**

Within a few seconds to minutes after the formation of angiotensin I, it is converted to **angiotensin II** by the effect of **angiotensin-converting enzyme (ACE)** that is present in the endothelium of the lung vessels.

Angiotensin II has two principal effects that can elevate arterial pressure:

1. Firstly, it causes vasoconstriction of the arterioles in many areas in the body (resulting in an increase in the total peripheral resistance, thereby raising the arterial pressure).
2. Secondly, it decreases the excretion of both salt and water by the kidneys through stimulating the adrenal glands to secrete **aldosterone**. Aldosterone increases the absorption of sodium and water by the renal tubular cells (causing **Na and water retention** and simultaneously increases excretion of potassium and H ions).



Disorders Causing Hypernatremia

(Serum Na < 146 mEq/L): always a hyperosmolar state

1. Net water loss

Hypotonic fluid

Renal losses:

- Loop diuretics
- Osmotic dieresis
- Postobstructive dieresis
- Intrinsic renal disease

Non-renal losses:

- Vomiting
- NG suctioning
- Enterocutaneous fistula
- Burns
- Excessive sweating

Diabetes Insipidus

- **Central DI** (low ADH secretion, causes: idiopathic 50%/head trauma/destructive diseases)
- **Nephrogenic DI** (unresponsiveness of renal tubules to ADH, acquired: chronic lithium use (most)/hypercalcemia/UTI (pyelonephritis), can be congenital)

Diagnosis:

- Urine: ↓ Specific Gravity, ↓ Osmolality
- Plasma osmolality: **280 to 310 mOsm/kg**
- Water deprivation test (withhold fluids and measure urine osmolality every hour; When urine osmolality is stable (< 30 mOsm/kg hourly increase for 3 hours), inject 2 g desmopressin S.C. and measure urine osmolality 1 hour later)

	↑ Urine osmolality	↑ Response to ADH
Normal	+	–
C-DI	–	+
N-DI	–	–

2. Hypertonic Sodium Gain

Primary hyperaldosteronism

Increase aldosterone secretion from the adrenal gland.

Causes:

- Functioning adenoma: **“Conn Syndrome”**
- Bilaternal Adrenal Hyperplasia

Clinical picture:

- ↑ Na & Water → **Hypertension**
- ↑ K & H ions → **Hypokalemia & M. Alkalosis**
- Polydipsia, nocturnal polyuria (due to hypokalemia)
- Absence of peripheral edema

Diagnosis:

- Screening: Plasma: ↑ aldosterone/↓ Renin/**A:R ratio>30**
- Confirmation: with either **1) Saline infusion test** (Infusion of saline will decrease aldosterone levels in normal patients) or **2) Oral Sodium Loading**

Cushing syndrome

Cushing syndrome means an abnormal increase in cortisol level.

Causes:

- A) Iatrogenic: exogenous steroids (most common)
- B) Non-iatrogenic:
    - ACTH independent → from adrenal gland (primary)
    - ACTH dependent→ secondary: ↑ ACTH From pituitary (“Cushing’s disease”) and ectopic ACTH production (as in small cell carcinoma (SSC) of lung)

Clinical picture

- Changes in appearance: central obesity, hirsutism, moon facies, “buffalo hump,” purple striae on abdomen, acne
- Hypogonadism, masculinization in females, proximal muscle wasting and weakness, psychiatric disturbances

Diagnosis:

- Screening:
  - **1) low-dose dexamethasone suppression test: i**f the serum cortisol is < 5 → No Cushing; if the serum cortisol is > 5 → Cushing syndrome
  - **2) 24-hour urinary free cortisol level**
- ACTH level:
  - If low→ 1ry Cushing (adenoma or hyperplasia)
  - If high→ 2ry (pituitary or ectopic production)
  - To differentiate between pituitary & ectopic ACTH: **High dose dexa suppression test** (in Pituitary → decrease in cortisol > 50% | in ectopic → No suppression occur)

Treatment of Hypernatremia

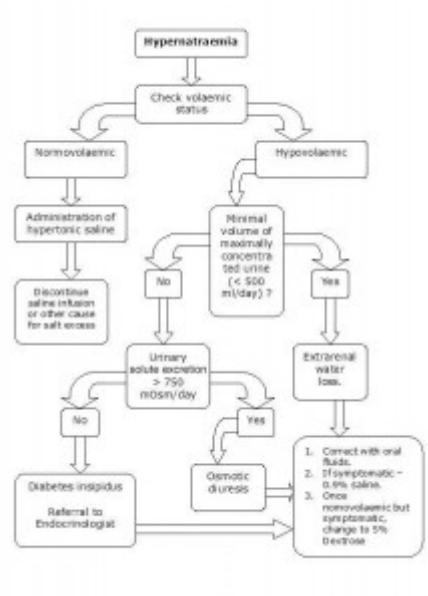


Image: “Management of Hypernatremia” by HarishV. License: CC BY-SA 3.0

If there is a circulatory compromise, this should be **treated with isotonic saline** to correct the water deficit.

In patients without circulatory compromise, they should be treated with **hypotonic solutions**.

If hypernatremia developed in hours, rapid correction at a rate of 1 mEq/L/h can be done with no risk of brain edema. However, if the time of development of hypernatremia is unknown, the rate of correction should be 0.5 mEq/L/h and the correction should not exceed 10–12 mEq/L in 24 hours to avoid **brain edema.**

Disorders causing Hyponatremia

(Serum Na < 136 mEq/L): it can be hyper-,hypo-, isotonic

Isotonic hyponatremia

Hyperlipidemia, **hyperproteinemia** and **hyperglycemia** can cause a laboratory artifact as a result of a decreased water component of the plasma, so it is needed to rule out the spurious hyponatremia at first.

Hypertonic hyponatremia

It occurs in hyperosmolar states, in which a large amount of impermeable solutes can't cross cell membranes, such as **mannitol** and **glucose** (hyperglycemia). In prolonged uncorrected hyperglycemia, the hyperosmolality can withdraw water into ECF, diluting the Na and results in hyponatremia. Hypernatremia can also occur if osmotic diuresis developed.

Hypotonic hyponatremia

It is classified according to the **volume status of the body** into:

1. Euvolemic hyponatremia
2. Hypovolemic hyponatremia
3. Hypervolemic hyponatremia

Euvolemic hyponatremia

- **If urine osmolality < 100 mOsm/kg:** indicates **"Psychogenic Polydepsia"**
- **If urine osmolality > 100 mOsm/kg:** indicates that urine is inappropriately concentrated, occurs in the following:

Syndrome of inappropriate secretion of ADH (SIADH)	**Causes:** • Subarachnoid hemorrhage • Sarcoidosis • Paraneoplastic syndromes as in SCC • Drugs: SSRis, tricyclic antidepressants **Diagnosis:** • Diagnostic test: ↑ Urine osmolality > 100, ↑ urine Na > 40, ↓ Plasma osmolality < 280 • The most accurate test is a **high ADH level.**

<table>
<tr><td rowspan="5">Adrenal Insufficiency</td><td colspan="2">• It results in decrease secretion of aldosterone → thus inability of the kidneys to absorb sodium.
• Clinical features: Weakness, fatigability, anorexia, vomiting, weight loss, hypotension, hyperpigmentation.
• Types:</td></tr>
<tr><td>Primary</td><td>Secondary</td></tr>
<tr><td>Most common cause: Autoimmune destruction of adrenal glands (Addison’s disease)</td><td>Due to decreased ACTH production by the pituitary due to long term steroid use or brain tumor</td></tr>
<tr><td colspan="2">Both of these conditions are associated with hyponatremia, to differentiate:</td></tr>
<tr><td>There is no aldosterone production, due to cortical destruction of adrenal gland, leading to hyperkalemia.</td><td>There is no destruction of cortical adrenal gland and, since the aldosterone secretion is maintained because it’s ACTH-independent, there’s a normal potassium level.</td></tr>
<tr><td colspan="2">• Diagnosis: Synthetic ACTH stimulation test: Cosyntropin → causes plasma cortisol level to < 20 ug/dl</td></tr>
</table>

Hypovolemic Hyponatremia

- Urine Na < 20 mEq/L
  - Vomiting
  - Diarrhea
  - Nasogastric tube
  - Sequestration of fluid in: burns, ileus, traumatized muscle, pancreatitis
- Urine Na > 20 mEq/L:

Overuse of Diuretics		**Mineralocorticoid deficiency**
Loop	**Thiazides**	Aldosterone deficiency results in the inability to reabsorb water & Na in exchange with K & H ions leading to: • **Hyponatremia & hypovolemia** • **Hyperkalemic metabolic acidosis**
Other side effects: • **↓ Ca2+** • ↓K+ • Sulfa allergy • **Ototoxicity**	Other side effects: • **↑ Ca2+** • ↓ K+ • **↓ Na+** • **↑ glucose** • **↑ Uric acid** • **Pancreatitis**	

Hypervolemic Hyponatremia

Urine Na < 20 mEq/L	**Urine Na > 20 mEq/L**
• Congestive heart failure • Cirrhosis • Nephrotic syndrome	• Acute or chronic renal failure • Adrenal insufficiency

Treatment of Hyponatremia

Urgent treatment

It’s indicated in:

- Severe hyponatremia (Sodium < 120 mEq/L and symptoms: mental status changes, seizure, or coma)
- Abrupt hyponatremia developed
- Should be treated with infusion of 3% hypertonic saline solution, and should be

corrected at rate of 1 mEq/L/h for the first 3–4 hours or until symptoms resolve, with a rate of correction less than 10–12 mEq/L in 24 hours to avoid Osmotic demyelination in case of rapid correction

Emergency dialysis is indicated in patients with:

- Renal failure
- Volume overload
- Severe hyponatremia

Non-urgent treatment

Those who don't need urgent treatment can be treated with **fluid restriction with an isotonic saline replacement** to avoid circulatory compromise**,** together with continuous observation of the patient. Do not forget to treat the underlying cause, e.g. hormonal replacement in adrenal insufficiency.

Review Questions

The answers are below the references.

1. A 78-year-old male is admitted to the hospital. He is presented with severe hyponatremia (sodium < 120 mEq/L). Other symptoms observed in the patient are nausea, malaise, lethargy, headache, seizures and coma. The most appropriate treatment for the patient is…

A. …infusion of 3% hypertonic saline solution.
B. …infusion of 6% hypertonic saline solution.
C. …infusion of 3% mannitol solution.
D. …infusion of 3% glucose solution.
E. …infusion of 3% hypotonic solutions.

2. What is the correct definition of osmosis?

A. Osmosis is the net diffusion of water across a selectively permeable membrane from a region of low solute concentration to one with a high solute concentration.
B. Osmosis is the net diffusion of water across a selectively permeable membrane from a region of high solute concentration to one with a low solute concentration.
C. Osmosis is the osmolar concentration of a solution when it is expressed as osmoles/Kg of water.
D. Osmosis is the osmolar concentration of a solution when it is expressed as osmoles/L of water.
E. Osmosis is the property of a system in which variables are regulated so that internal conditions remain stable and relatively constant.

3. The osmotic pressure and compositions of extracellular fluid are regulated chiefly by which of the following organ of the body?

A. Liver
B. Heart
C. Lungs
D. Villi of the intestine
E. Kidney

References

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Current Diagnosis & Treatment Emergency Medicine, 6th edition. Lange McGraw Hill. Fluid, Electrolyte, & Acid–Base Emergencies, Disorders of serum sodium concentration.

Step-up to USMLE step 2 CK / Brian Jenkins, Michael McInnis, Chris Lewis. — 4th edition.

General principles of disorders of water balance (hyponatremia and hypernatremia) and sodium balance (hypovolemia and edema) via uptodate.com

Correct answers: 1A, 2A, 3E

Notes