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

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

Total body fluid (42 L) is distributed into 2 compartments	
Extracellular fluid (ECF)	**Intracellular fluid (ICF)**
ECF accounts for **20% (14 L)** of total body weight. ECF is divided into:	ICF accounts for **40% (28 L)** of total body weight, distributed in about 75 trillion cells.

Interstitial fluid	Plasma	
Accounts for **three-quarters** of ECF	Accounts for **one-quarter** of ECF	Each cell has its own mixture of different constituents, but the concentrations of these substances are similar in all different cells.
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.		

Difference Between the Composition of Extracellular Fluid and Intracellular Fluid

Extracellular fluid

There is a highly permeable membrane between the plasma and interstitial fluid, allowing the continuous exchange of solutes between the 2 compartments. The membrane has a low permeability to proteins, allowing only a small amount of proteins to leak from the plasma into the interstitial fluid. This makes the concentration of **proteins in plasma higher than that in interstitial fluid.**

Donnan effect

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

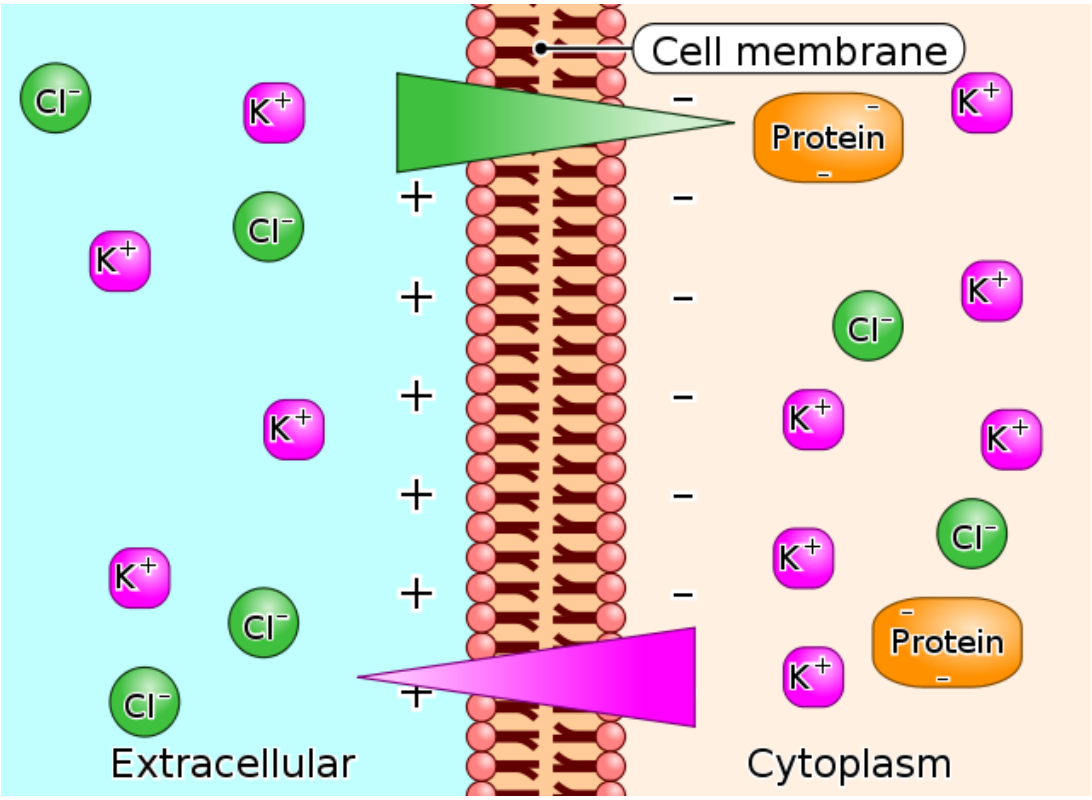


Image: “Gibbs-Donnan-Effect” by Biezl. License: Public Domain

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 in the plasma. Because of the Donnan effect, the concentration of cations is about 2% greater in plasma than in 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

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

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

ICF contains a low concentration of:

- Sodium ions
- Chloride ions
- Calcium ions

Moreover, ICF contains a large amount of protein, which is 4 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 the concentration of chloride are, to a greater extent, secondary to changes in the concentration of sodium.

Water moves rapidly across the cell membrane by this osmotic effect to **keep ECF isotonic with 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).

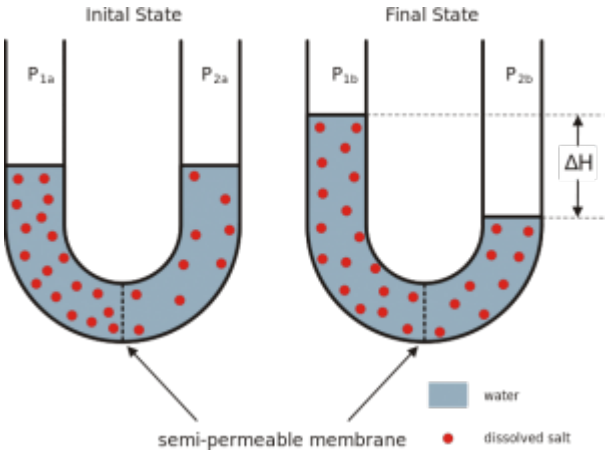


Image: “An example of osmosis: dissolved salt forcing water to pass through a semi-permeable membrane” by Hans Hillewaert. License: CC BY-SA 3.0

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 **osm/kg of water**. **Osmolarity** is the osmolar concentration of a solution when it is expressed as **osm/L of water.** About 80% of the total osmolarity of interstitial fluid and plasma is due to sodium and chloride ions, while half of the total osmolarity of ICF 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 ICF and ECF, and even small changes in the concentration of these impermeant solutes in ECF can lead to a large **osmotic pressure** across the cell membrane, with the subsequent rapid movement of water across the cell membrane.

- **If plasma osmolality is high (hypertonic state),** water will diffuse out of the cells to ECF and will result in cell shrinkage.
- **If plasma osmolality is low (hypotonic state),** water will diffuse into the cells and will result in cell swelling.
- **If osmolality is equal between ICF and ECF (isotonic state),** water will not diffuse across the cell membrane and the cells will not shrink or swell.

Macromolecules (mainly proteins) determine the so-called **oncotic pressure.** Intravascular 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; edema then results.

Hydrostatic pressure is mainly determined by blood pressure. Decreased venous return (e.g. right heart failure) increases hydrostatic pressure and water moves out of the vessels into the interstitium also leading to edema.

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 ECF

Loss of NaCl from ECF results in **hypo-osmotic (hyponatremic/hypotonic) dehydration,** in which the water moves from a region of low solute concentration (plasma) to that 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 3 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 mucous membranes (e.g., 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 12 mEq/L** decrease in serum sodium every 24 hours.

Increased plasma sodium concentration

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

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

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

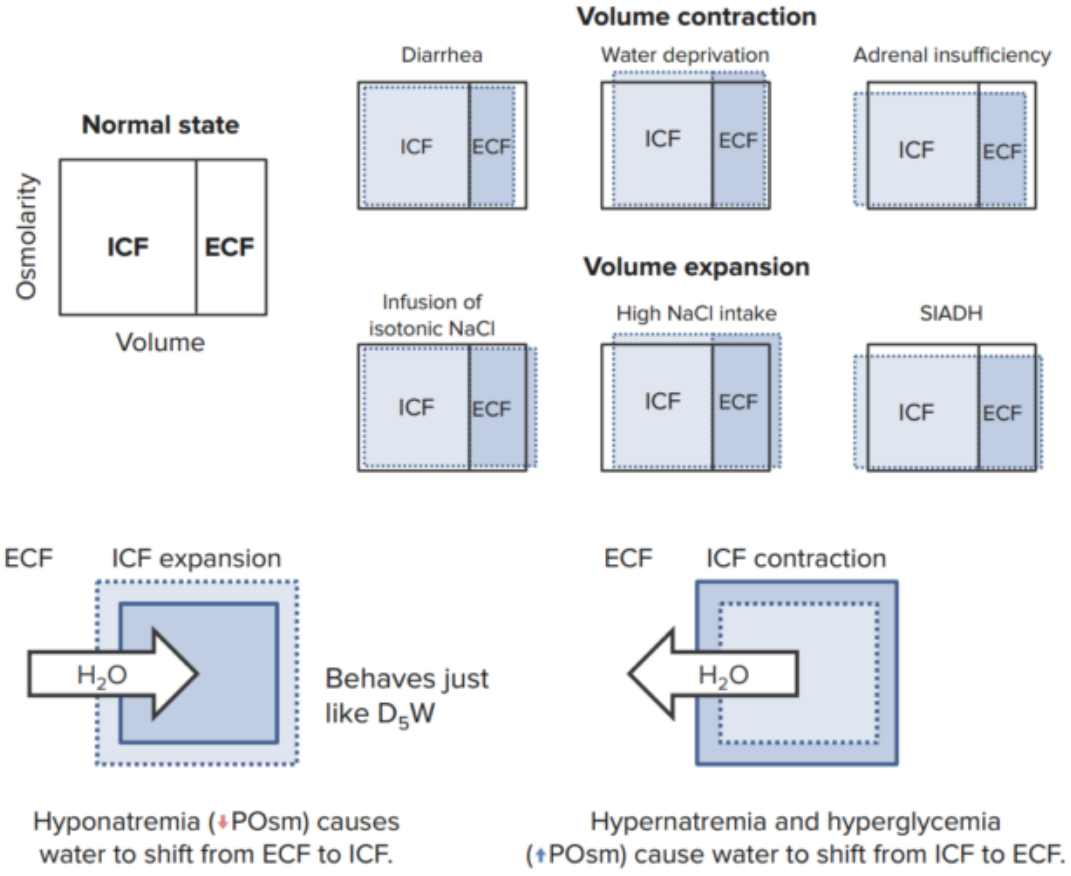
1. **Increase in ECF**, with the clinical signs of dehydration (e.g., signs of shock) being less severe.
2. **Decrease in ICF**, which leads to cell shrinkage:
    - Markedly dry mucous membranes (woody tongue)

- Shrinkage of brain cells may result in seizures and coma
- Rapid correction of hyponatremia can produce **central pontine myelinolysis**
- Avoid more **than 12 mEq/L/24 h** increase in serum sodium, especially if the hyponatremia developed gradually

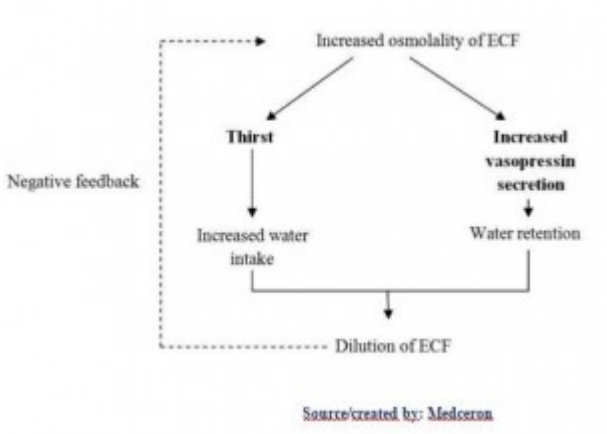
When proportionally the same amount of water and sodium are lost from the body, the sodium concentration in ECF will not change, resulting in iso-osmotic (normonatremic/isotonic) dehydration. Therefore, the mechanisms that control **sodium balance** are the major mechanisms that **control ECF volume.**

Summary

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



Regulation of Extracellular Fluid Composition & Volume



The 2 main mechanisms in the regulation of ECF osmolality, and sodium concentration are:

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

Antidiuretic hormone (vasopressin) secretion

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

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

The stimuli of ADH secretion are:

1. **Osmotic stimulus**

When the osmolality (plasma sodium concentration) rises above the upper normal limit (285 mOsm/kg) as in the case of water deficit, the **shrinkage of osmoreceptors** occurs. These osmoreceptors transmit signals to the posterior pituitary which stimulates the release of ADH into the bloodstream to reach the kidney, and vice versa.

2. **Volume stimulus**

Decrease in ECF volume stimulates **stretch receptors** in the low- and high-pressure portions of the vascular system, in which impulses pass to the posterior pituitary, stimulating the release of ADH. **Low-pressure receptors** are present in the great veins, right and left atria, and pulmonary vessels. **High-pressure receptors** are 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 hypovolemia, stimulates the release of ADH, as well as the activation of **the renin-angiotensin system, which** stimulates aldosterone secretion and promotes sodium and water retention (discussed later).

ADH reaches the kidney and increases the permeability of the late distal tubules and collecting ducts, so that water diffuses into the hypertonic interstitium of the renal pyramids. This results in the reabsorption of water into the bloodstream, while sodium

and other solutes are continuously excreted in the urine. This causes dilution of solutes in ECF and correction of the high osmolality, 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 in the water permeability of the late distal tubules and collecting ducts, resulting in increased water excretion (this results in an increase in ECF osmolality) and formation of diluted urine.

Thirst mechanism

Increased ECF osmolality causes a shrinkage of the **thirst center** (located anterolaterally in the preoptic nucleus), resulting in the stimulation of thirst sensation (leading to increased fluid intake and dilution of the high ECF osmolality to normal, and vice versa).

Both osmoreceptor ADH secretion and thirst mechanisms work simultaneously to keep ECF osmolality and volume within normal levels. Below is 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

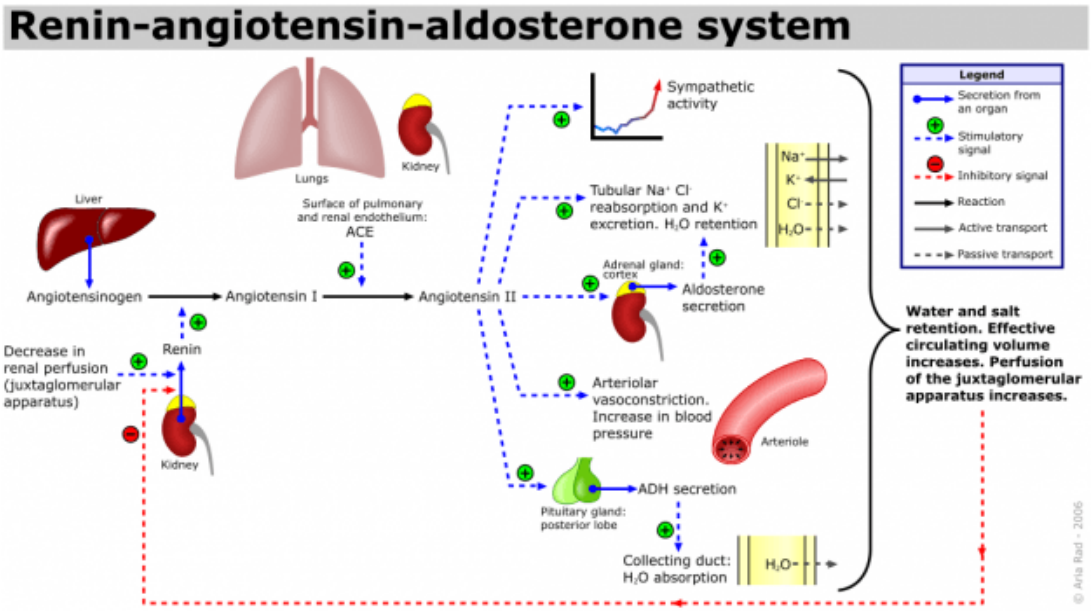


Image: "The renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS). Start reading this schematic from the left, where it says "Decrease in renal perfusion (juxtaglomerular apparatus)". Alternatively, the RAAS can also be activated by a low NaCl concentration in the macula densa 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.

Role of the renin-angiotensin-aldosterone system

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 the alteration of water reabsorption, along with sodium. Thus, activation of this system

leads to **an increase of both sodium quantity and ECF volume** (hence also a little change in the sodium concentration because water is absorbed along with sodium, a process called sodium and water retention.

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

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

Angiotensin II has 2 principal effects that can elevate arterial pressure:

1. Firstly, it causes vasoconstriction of the arterioles in many areas of the body (resulting in an increase in the total peripheral resistance and increased 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 **sodium and water retention** and simultaneously increasing the excretion of potassium and hydrogen ions).

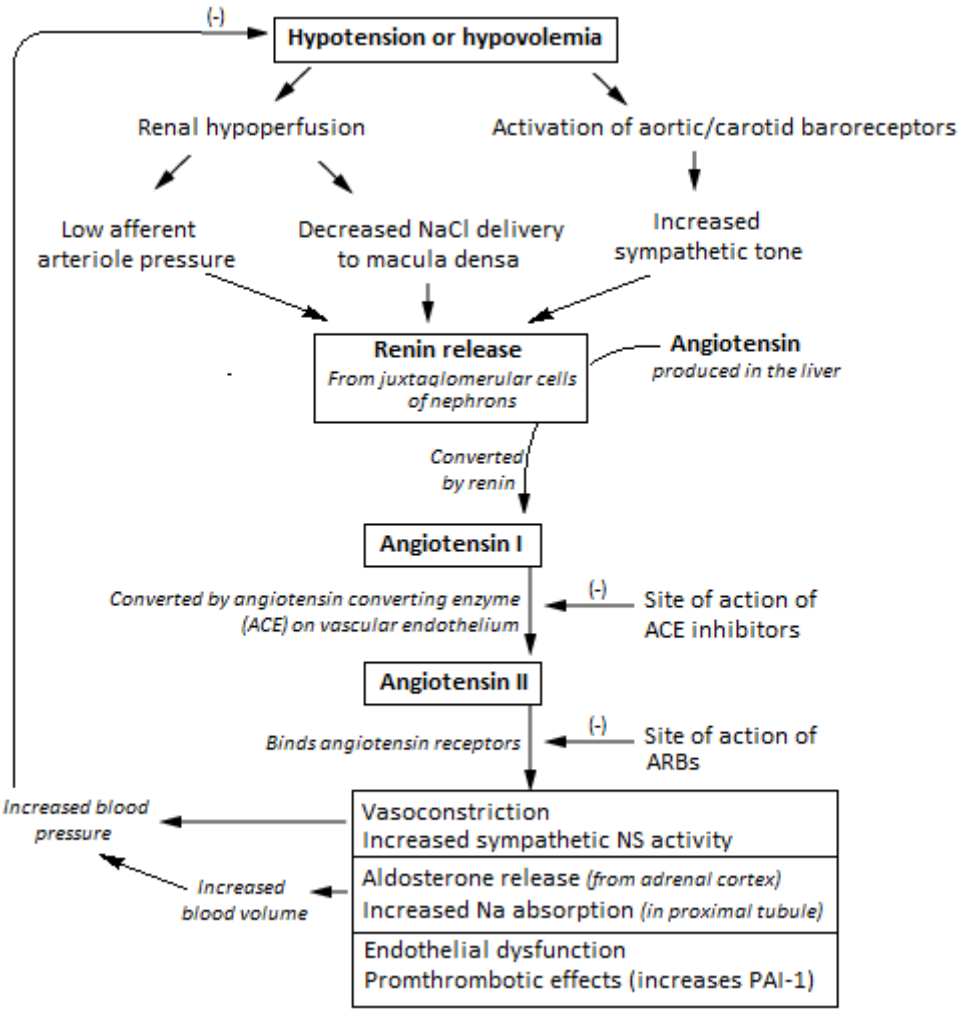


Image: "Flowchart of the renin angiotensin aldosterone system and its clinical effects." by Npatchett.
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Disorders Causing Hypernatremia

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

1. **Net water loss**

Hypotonic fluid

Renal losses:

- Loop diuretics
- Osmotic diuresis
- Post-obstructive diuresis
- Intrinsic renal disease

Non-renal losses:

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

Diabetes Insipidus

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

Diagnosis:

- Urine: ↓ Specific Gravity, ↓ Osmolality
- Plasma osmolality: **280–310 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 subcutaneously and measure urine osmolality 1 hour later).

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

C-DI: central diabetes insipidus

N-DI: nephrogenic diabetes insipidus

2. **Hypertonic Sodium Gain**

Primary hyperaldosteronism

Increase aldosterone secretion from the adrenal gland.

Causes:

- Functioning adenoma: '**Conn Syndrome'**

- Bilateral adrenal hyperplasia

Clinical picture:

- ↑ Na & Water → **Hypertension**
- ↑ K & H ions → **Hypokalemia and Metabolic 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 is an abnormal increase in cortisol levels.

Causes:

- A) Iatrogenic: exogenous steroids (most common)
- B) Non-iatrogenic:
    - ACTH independent → from the adrenal gland (primary)
    - ACTH dependent→ secondary to increased ACTH from the pituitary ("Cushing's disease") and ectopic ACTH production (as in small cell carcinoma of the 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→ Primary Cushing (adenoma or hyperplasia)
    - If high→ Secondary Cushing (pituitary or ectopic production)
    - To differentiate between pituitary & ectopic ACTH: **High-dose dexamethasone suppression test** (in pituitary → decrease in cortisol > 50%, or in ectopic → No suppression occurs)

Treatment of Hypernatremia

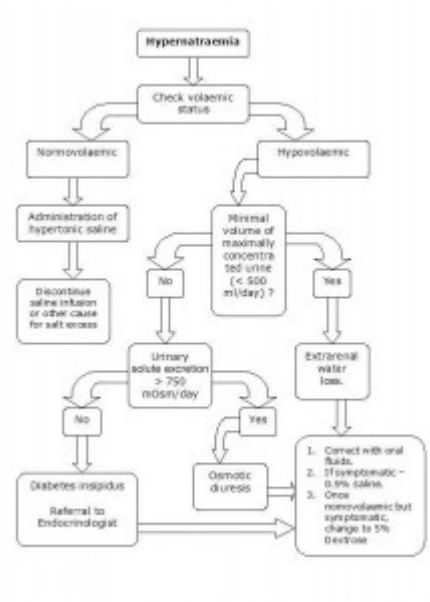

Image: “Management of Hypernatremia” by HarishV. License: CC BY-SA 3.0

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

Patients without circulatory compromise should be treated with **hypotonic solutions**.

If hypernatremia develops within hours, rapid correction at a rate of 1 mEq/L/h can be initiated with any risk of brain edema. However, if the timeframe of the 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

Hyponatremia is a serum sodium level of < 136 mEq/L. It can be hypertonic, hypotonic, or 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 cannot cross cell membranes, such as **mannitol** and **glucose** (hyperglycemia). In prolonged uncorrected hyperglycemia, hyperosmolality can withdraw water into ECF, diluting the sodium and resulting in hyponatremia. Hypernatremia can also occur if osmotic diuresis develops.

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

- **Urine osmolality < 100 mOsm/kg** indicates '**Psychogenic polydipsia'**
- **Urine osmolality > 100 mOsm/kg** indicates that urine is inappropriately concentrated, as noted in the table below:

<table>
<tr><td rowspan="2">Syndrome of inappropriate secretion of ADH (SIADH)</td><td colspan="2">Causes:
• Subarachnoid hemorrhage
• Sarcoidosis
• Paraneoplastic syndromes as in squamous cell carcinoma
• Drugs: SSRIs, tricyclic antidepressants
Diagnosis:
• Diagnostic test: ↑ Urine osmolality > 100, ↑ urine Na > 40, ↓ Plasma osmolality < 280
The most accurate finding is a high ADH level</td></tr>
<tr><td rowspan="5">Adrenal Insufficiency</td><td colspan="2">• Results in decreased secretion of aldosterone → 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 the adrenal gland, leading to hyperkalemia</td><td>There is no destruction of the cortical adrenal gland and, since the aldosterone secretion is maintained because it is ACTH-independent, there is a normal potassium level</td></tr>
<tr><td colspan="2">• Diagnosis: Synthetic ACTH stimulation test: Cosyntropin → causes plasma cortisol level to reach < 20 µg/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 (Table below):

<table>
<tr><th colspan="2">Overuse of Diuretics</th><th>Mineralocorticoid deficiency</th></tr>
<tr><th>Loop</th><th>Thiazides</th><td rowspan="2">Aldosterone deficiency results in the inability to reabsorb water and Na in exchange with K and H ions leading to:
• Hyponatremia and hypovolemia
• Hyperkalemic metabolic acidosis</td></tr>
<tr><td>Other side effects:
• ↓ Ca2+
• ↓K+
• Sulfa allergy
• Ototoxicity</td><td>Other side effects:
• ↑ Ca2+
• ↓ K+
• ↓ Na+
• ↑ Glucose
• ↑ Uric acid
• Pancreatitis</td></tr>
</table>

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

This is indicated in:

- Severe hyponatremia (Na < 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 do not 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.

References

Textbook of medical physiology / Arthur C. Guyton, John E. Hall.—11th edition, Unit V: The body fluids & kidneys, Chapter 25: The body fluid compartments, page: 291-306, and Chapter 28: Regulation of extracellular fluid osmolality and sodium concentration, page: 348 – 364.

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