

## HYPONATREMIA NEJM 2000

- Classified into hypotonic (dilutional) hyponatremia or nonhypotonic hyponatremias (i.e. hyperglycemia)
- Clinical manifestations are related to CNS dysfunction
  - Brain adapts by allowing solutes to leave brain tissues within hours to days → inducing water loss
    - Rapid adaptation: cellular loss of electrolytes → partial resolution of brain volume within a few hours
    - Slow adaptation: loss of organic osmolytes → normalization of brain volume within several days
    - Brain adaptation is also the source of the risk of osmotic demyelination
    - Shrinkage of the brain triggers demyelination of pontine and extrapontine neurons causing neuro dysfunction
- Presence of signs and management largely dependent on the pace of correction
- Osmotic demyelination can develop one to several days after aggressive treatment of hyponatremia

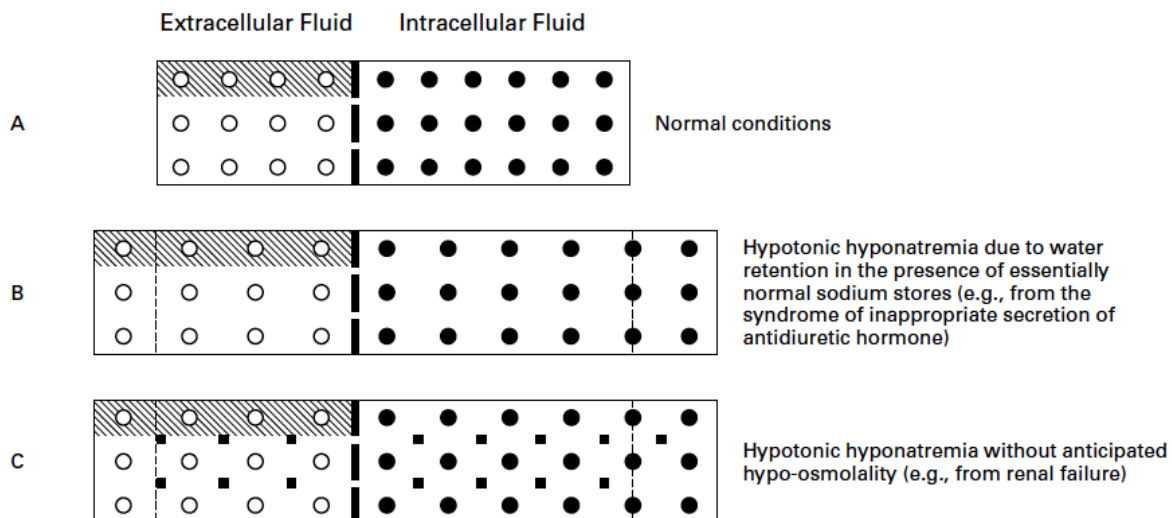
### CLASSIFICATION OF HYPONATREMIA

#### Hypotonic (dilutional) hyponatremia

- Most common form of disorder in humans
- Caused by water retention
- Represents an excess of water in relation to existing Na<sup>+</sup> stores (which can be decreased, normal, or increased)
- Water intake exceeds the capacity of the kidneys to excrete water causing hypo-osmolality and hypotonicity
  - Fig 1B, 1E, 1F, 1G
- Can be associated with normal or high serum osmolality if sufficient amounts of solutes that can permeate cell membranes (urea and ethanol) have been retained
  - Fig 1C

#### Nonhypotonic hyponatremias

- Include: (1) Hypertonic or translocational hyponatremia, (2) Isotonic hyponatremia, (3) Pseudohyponatremia
- **Translocational hyponatremia** represents shift of water from cells to extracellular fluid caused by solutes confined to extracellular compartment (as occurs in hyperglycemia or retention of mannitol) → this causes serum osmolality and tonicity to increase → resulting in dehydration of cells
  - Fig 1D



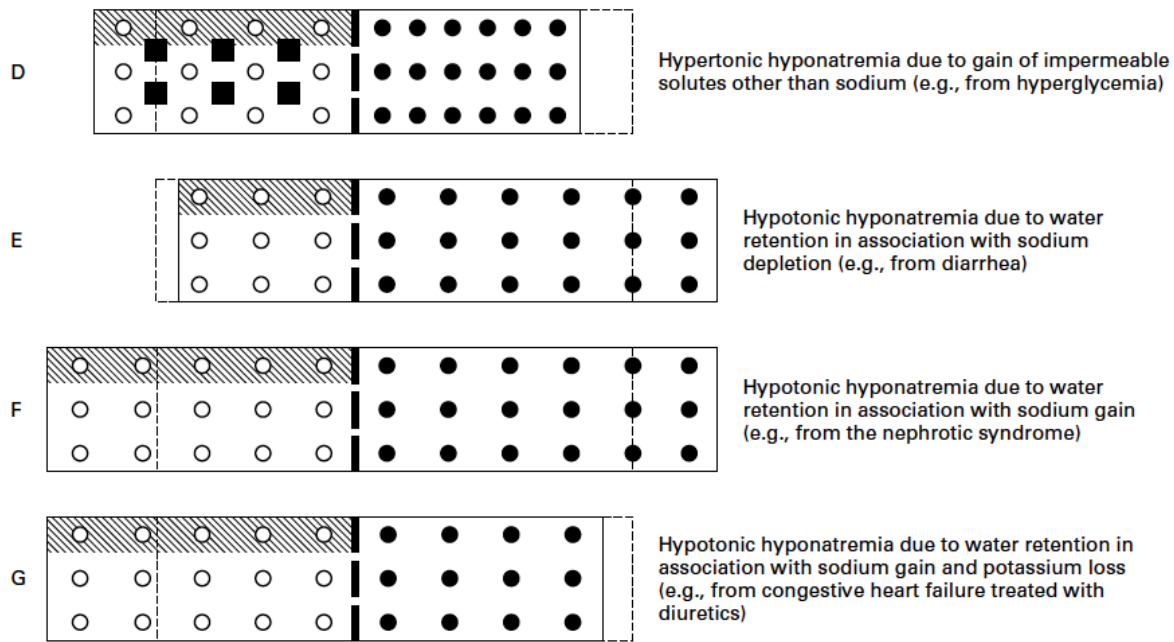


Figure 1. Extracellular-Fluid and Intracellular-Fluid Compartments under Normal Conditions and during States of Hyponatremia.

## CAUSES OF HYPONATREMIA

- Retention of water
  - Most commonly caused by the presence of conditions that impair renal excretion of water
  - Sometimes caused by excessive water intake with normal excretory capacity (overwhelms excretory capacity)
- Conditions of impaired renal excretion of water are categorized according to the characteristics of the extracellular fluid volume (see table 1)
  - These conditions characterized by high plasma concentrations of arginine vasopressin despite the presence of hypotonicity (except in the case of renal failure)
- Hyperglycemia is the most common cause of translocational hyponatremia
  - An increase of 100 mg per deciliter (5.6 mmol per liter) in the serum glucose concentration decreases serum sodium by approximately 1.7 mmol per liter
- Most common causes of **severe hyponatremia in adults**: therapy with thiazides, the postoperative state and other causes of the syndrome of inappropriate secretion of antidiuretic hormone, psychogenic polydipsia and transurethral prostatectomy (that can result in massive absorption of irrigant solutions that do not contain sodium)
- Most common cause of **severe hyponatremia in children**: gastrointestinal fluid loss, ingestion of dilute formula, accidental ingestion of excessive water, and receipt of multiple tap-water enemas

**TABLE 1. CAUSES OF HYPOTONIC HYPONATREMIA.**

<b>IMPAIRED CAPACITY OF RENAL WATER EXCRETION</b>	
<b>Decreased volume of extracellular fluid</b>	<b>Essentially normal volume of extracellular fluid</b>
Renal sodium loss	Thiazide diuretics*
Diuretic agents	Hypothyroidism
Osmotic diuresis (glucose, urea, mannitol)	Adrenal insufficiency
Adrenal insufficiency	Syndrome of inappropriate secretion of antidiuretic hormone
Salt-wasting nephropathy	Cancer
Bicarbonaturia (renal tubular acidosis, disequilibrium stage of vomiting)	Pulmonary tumors
Ketonuria	Mediastinal tumors
Extrarenal sodium loss	Extrathoracic tumors
Diarrhea	Central nervous system disorders
Vomiting	Acute psychosis
Blood loss	Mass lesions
Excessive sweating (e.g., in marathon runners)	Inflammatory and demyelinating diseases
Fluid sequestration in "third space"	Stroke
Bowel obstruction	Hemorrhage
Peritonitis	Trauma
Pancreatitis	Drugs
Muscle trauma	Desmopressin
Burns	Oxytocin
<b>Increased volume of extracellular fluid</b>	Prostaglandin-synthesis inhibitors
Congestive heart failure	Nicotine
Cirrhosis	Phenothiazines
Nephrotic syndrome	Tricyclics
Renal failure (acute or chronic)	Serotonin-reuptake inhibitors
Pregnancy	Opiate derivatives
	Chlorpropamide
	Clofibrate
	Carbamazepine
	Cyclophosphamide
	Vincristine
	Pulmonary conditions
	Infections
	Acute respiratory failure
	Positive-pressure ventilation
	Miscellaneous
	Postoperative state
	Pain
	Severe nausea
	Infection with the human immunodeficiency virus
	Decreased intake of solutes
	Beer potomania
	Tea-and-toast diet

**EXCESSIVE WATER INTAKE**

- Primary polydipsia†
- Dilute infant formula
- Sodium-free irrigant solutions (used in hysteroscopy, laparoscopy, or transurethral resection of the prostate)‡
- Accidental intake of large amounts of water (e.g., during swimming lessons)
- Multiple tap-water enemas

\*Sodium depletion, potassium depletion, stimulation of thirst, and impaired urinary dilution are implicated.

†Often a mild reduction in the capacity for water excretion is also present.

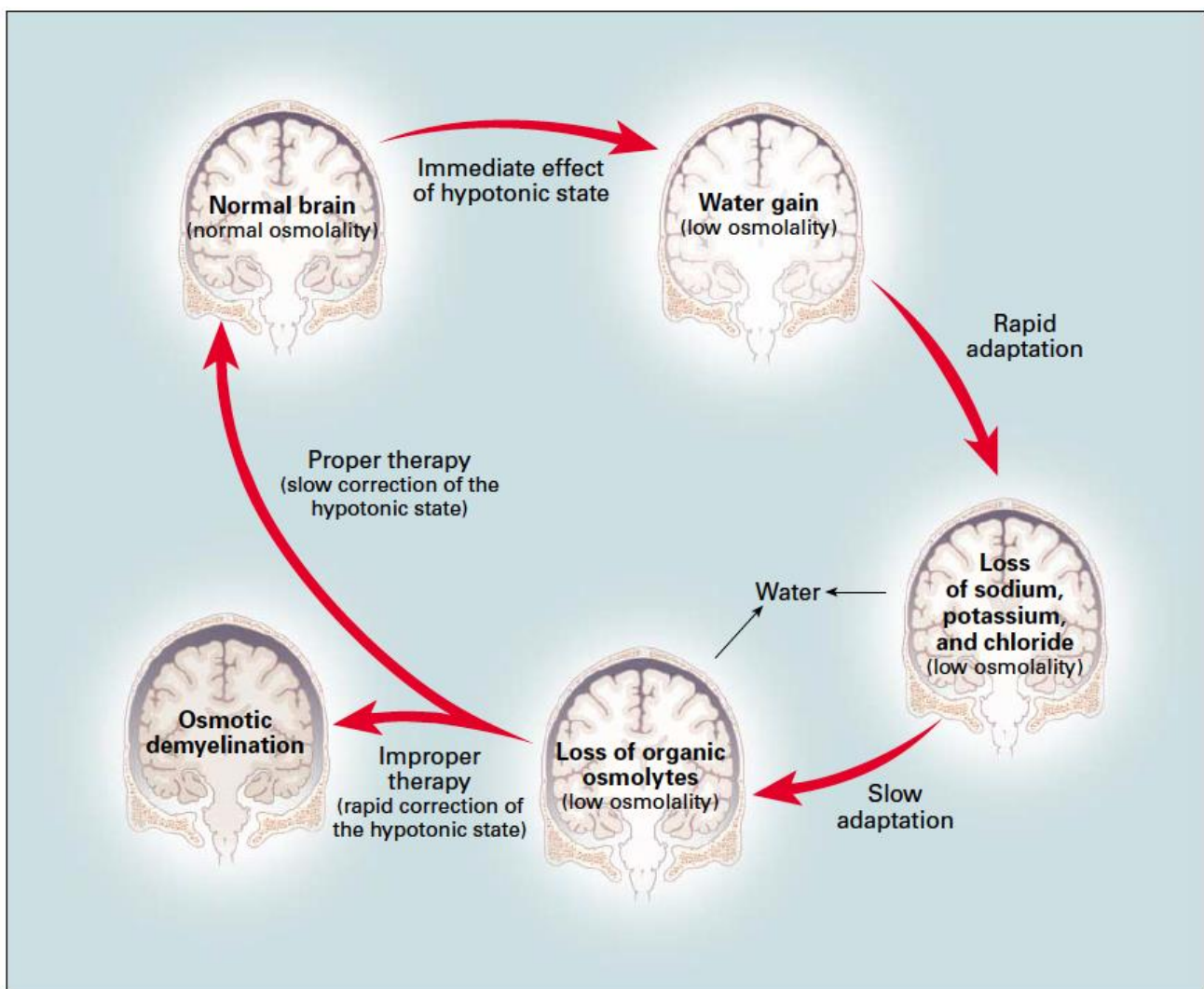
‡Hyponatremia is not always hypotonic.

## CLINICAL MANIFESTATIONS

- Manifestations of hypotonic hyponatremia related to CNS dysfunction
- Headache, nausea, vomiting, muscle cramps, lethargy, restlessness, disorientation, and depressed reflexes
- Severe signs include seizures, coma, permanent brain damage, respiratory arrest, brain-stem herniation, and death.
- In humans patients with  $\text{Na}^+ > 125$  are typically asymptomatic

### Effects of hyponatremia on the brain and adaptive responses (Figure 2)

- Hypotonic hyponatremia causes entry of water into the brain, resulting in cerebral edema
- Surrounding cranium limits expansion of the brain causing intracranial hypertension
- Brain adapts by allowing solutes to leave brain tissues within hours to days → inducing water loss
  - Rapid adaptation: cellular loss of electrolytes → partial resolution of brain volume within a few hours
  - Slow adaptation: loss of organic osmolytes → normalization of brain volume within several days
  - Shrinkage of the brain triggers demyelination of pontine and extrapontine neurons causing neuro dysfunction
- Osmotic demyelination can develop one to several days after aggressive treatment of hyponatremia



**Figure 2.** Effects of Hyponatremia on the Brain and Adaptive Responses.

Within minutes after the development of hypotonicity, water gain causes swelling of the brain and a decrease in osmolality of the brain. Partial restoration of brain volume occurs within a few hours as a result of cellular loss of electrolytes (rapid adaptation). The normalization of brain volume is completed within several days through loss of organic osmolytes from brain cells (slow adaptation). Low osmolality in the brain persists despite the normalization of brain volume. Proper correction of hypotonicity reestablishes normal osmolality without risking damage to the brain. Overly aggressive correction of hyponatremia can lead to irreversible brain damage.

## MANAGEMENT OF HYPONATREMIA

- Presence of signs and management depend on PACE of correction
- Patients with persistent asymptomatic hyponatremia require slow-paced management
- Patients with symptomatic hyponatremia must receive rapid but controlled correction

### 1. Management of symptomatic hypotonic hyponatremia

#### (a) **Symptomatic hyponatremia with concentrated urine + clinical euolemia or hypervolemia**

- Require infusion of hypertonic saline (TABLE 2)
- Hypertonic saline combined with furosemide to limit treatment induced expansion of the extracellular-fluid volume
- Furosemide-induced diuresis is equivalent to a one-half isotonic saline solution

#### (b) **Symptomatic hyponatremia with concentrated urine + hypovolemia**

- Can be treated successfully with isotonic saline

#### (c) **Symptomatic hyponatremia with dilute urine**

- Mild signs: require water restriction and close observation
- Severe signs (seizures): infuse hypertonic saline

- There is no consensus about the optimal treatment of symptomatic hyponatremia
- Most reported cases of osmotic demyelination occurred after rates of correction >12 mmol per liter per day
- Authors recommend a targeted rate of correction that does not exceed 8 mmol per liter on any day of treatment unless signs do not resolve

#### • **Rate of correction**

- Apply formula 1 in Table 2
- Divide the change in serum sodium targeted for a given treatment period by the output of this formula to determine volume of infusate required and hence the rate of infusion

FORMULA*	CLINICAL USE
1. Change in serum Na <sup>+</sup> = $\frac{\text{infusate Na}^+ - \text{serum Na}^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate on serum Na <sup>+</sup>
2. Change in serum Na <sup>+</sup> = $\frac{(\text{infusate Na}^+ + \text{infusate K}^+) - \text{serum Na}^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate containing Na <sup>+</sup> and K <sup>+</sup> on serum Na <sup>+</sup>

### 2. Asymptomatic hypotonic hyponatremia

- Adjust meds contributing
- Water restriction (to <800 ml per day) is the mainstay of longterm management

### 3. Nonhypotonic hyponatremia

- Corrective measures directed at the underlying disorder rather than at the hyponatremia itself
- i.e. Insulin for uncontrolled diabetes

**TABLE 2. FORMULAS FOR USE IN MANAGING HYPONATREMIA AND CHARACTERISTICS OF INFUSATES.**

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INFUSATE	INFUSATE Na <sup>+</sup> mmol per liter	EXTRACELLULAR-FLUID DISTRIBUTION %
5% Sodium chloride in water	855	100†
3% Sodium chloride in water	513	100†
0.9% Sodium chloride in water	154	100
Ringer's lactate solution	130	97
0.45% Sodium chloride in water	77	73
0.2% Sodium chloride in 5% dextrose in water	34	55
5% Dextrose in water	0	40

\*The numerator in formula 1 is a simplification of the expression (infusate Na<sup>+</sup> – serum Na<sup>+</sup>) × 1 liter, with the value yielded by the equation in millimoles per liter.<sup>38</sup> The estimated total body water (in liters) is calculated as a fraction of body weight. The fraction is 0.6 in children; 0.6 and 0.5 in nonelderly men and women, respectively; and 0.5 and 0.45 in elderly men and women, respectively.<sup>39</sup> Normally, extracellular and intracellular fluids account for 40 and 60 percent of total body water, respectively.<sup>39</sup>

†In addition to its complete distribution in the extracellular compartment, this infusate induces osmotic removal of water from the intracellular compartment.

**Question:**

Explain the effect of hyponatremia (<125mmol/L) on the brain and how adaptive responses can lead to neurologic dysfunction.

What is meant by dilutional hyponatremia and how is it different from translational hyponatremia?

**Answers:**

**1. Effects of hyponatremia on the brain and adaptive responses (Figure 2)**

Causes entry of water into the brain, resulting in cerebral edema

Surrounding cranium limits expansion of the brain causing intracranial hypertension

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Caused by water retention

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Water intake exceeds the capacity of the kidneys to excrete water causing hypo-osmolality and hypotonicity

**Nonhypotonic hyponatremias**

Include: (1) **Hypertonic or translocational hyponatremia**, (2) Isotonic hyponatremia, (3) Pseudohyponatremia

Translocational hyponatremia represents shift of water from cells to extracellular fluid caused by solutes confined