Body Fluid Composition

Amrish Jain, MD

Division of Nephrology and Hypertension, The Carman and Ann Adams Department of Pediatrics, Wayne State University School of Medicine, Children's Hospital of Michigan, Detroit, MI.

Educational Gap

Body fluid composition is maintained in a normal physiologic range by regulatory mechanisms that control sodium and water metabolism. A detailed knowledge of the homeostatic mechanisms will help in understanding the pathogenesis and management of disorders of sodium and water balance.

Objectives

After completing this article, readers should be able to:

1. Understand the distribution of fluid and solute in different body compartments.
2. Demonstrate the homeostatic mechanisms involved in maintaining sodium and water metabolism.
3. Calculate osmolality and recognize the clinical importance of maintaining osmotic equilibrium.
4. Recognize common disorders of hypernatremia or hyperosmolality and evaluate and understand the role of calculating free water deficit in the treatment of these disorders.
5. Recognize common disorders of hyponatremia or hypo-osmolality, appreciate the role of urine sodium and urine osmolality in evaluation, and understand the importance of slow correction of these disorders.

AUTHOR DISCLOSURE Dr Jain has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ADH	antidiuretic hormone
AVP	arginine vasopressin
BUN	blood urea nitrogen
DI	diabetes insipidus
ECF	extracellular fluid
FWD	free water deficit
GFR	glomerular filtration rate
ICF	intracellular fluid
SIADH	syndrome of inappropriate antidiuretic hormone
Sosm	serum osmolality
TBW	total body water

CASE SCENARIO

A 6-month-old infant presents to the emergency department with vomiting for 3 days. He is lethargic and has a weak cry. His vital signs reveal an elevated heart rate (140 beats per minute), and physical examination findings are remarkable for dry mucous membranes. His capillary refill is more than 2 seconds. His initial laboratory values are as follows: serum sodium, 122 mEq/L (122 mmol/L); blood urea nitrogen (BUN), 28 mg/dL (10 mmol/L); serum creatinine, 0.4 mg/dL (35 μmol/L); serum glucose, 90 mg/dL (5.0 mmol/L); and serum osmolality (Sosm), 260 mOsm/kg (260 mmol/kg). Urinalysis reveals a specific gravity of 1.030, pH 6.5, and negative results for blood, protein, leukocyte esterase, or nitrite. Additional urine studies reveal a urine osmolality of 900 mOsm/kg (900 mmol/kg) and a urine sodium level of 6 mEq/L (6 mmol/L). A detailed

history also revealed that the patient was exclusively breastfed until age 5 months. At this time, he was switched to a powdered formula that is prepared using tap water. During the acute episode, parents were giving him small amounts of formula along with water at home. What is the most likely cause of hyponatremia in this child?

INTRODUCTION

An understanding of body fluid composition and body water compartments is essential for all clinicians. Our body is predominantly made of water, and as a result, the fluid disorders are commonly encountered in clinical practice. The intake and output of water and solute is finely regulated inside our bodies. A number of mechanisms play a role in maintaining a steady state of water and solute between the body compartments. This homeostasis is achieved by close interplay and feedback loops that involve the central nervous system, endocrine system, gastrointestinal tract, and kidneys.

The current review helps pediatricians understand the physiology of sodium and water metabolism and thus provides insight into the pathogenesis of common disorders of body fluid composition. Knowledge of the homeostatic mechanisms that regulate normal volume and composition will also help in the treatment of children with disorders of body fluids.

TOTAL BODY WATER

Water is the largest single constituent of the body. Total body water (TBW) is represented as a percentage of body weight and varies with age. In early gestation, nearly 90% of fetal body weight consists of water. Premature infants have a TBW content of 75% to 80% of their body weight, depending on their gestational age. The TBW decreases rapidly to 70% in term newborns and to 60% by age 1 year. After puberty and in adulthood, TBW is 60% in males and 55% in females. (1)(2)(3) The difference in TBW between the genders is a result of body fat distribution because adipose tissue is mostly free of water. Females have a higher body fat content and lower skeletal muscle; thus, they have less TBW.

TBW is distributed into 2 body compartments: intracellular fluid (ICF) and extracellular fluid (ECF). Two-thirds of TBW is present in the ICF and one-third in the ECF. The ECF is further divided between the interstitial fluid or extravascular compartment (three-fourths) and blood volume or intravascular compartment (one-fourth). Figure 1 shows the percentage distribution of body water in the various compartments in a 30-kg child. Notably, blood volume is the smallest component (5% of total body weight) of TBW.

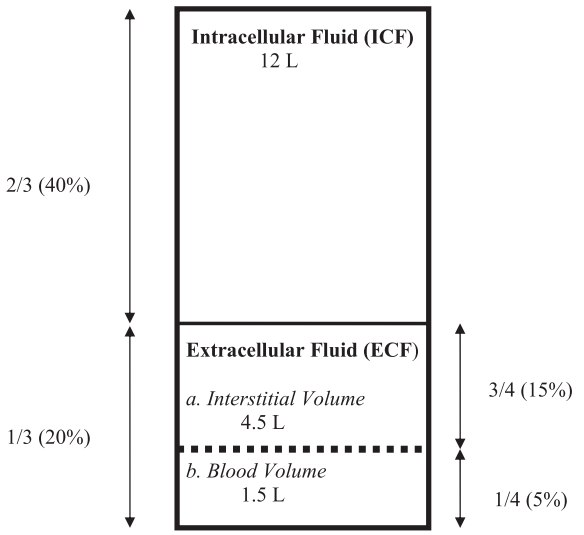

Figure 1. The distribution of total body water in different body compartments in a 30-kg child.

The ICF to ECF ratio is also age dependent. The fetus has a higher proportion of ECF compared with ICF. After birth, an increase in urine output causes a progressive contraction of the interstitial component of the ECF. The ECF and ICF are equivalent by age 1 month and thereafter; there is an increase in the ICF as a result of continued cell growth. Adult values of the ICF and ECF proportions are reached by ages 1 to 3 years. The ICF to ECF ratio is also dependent on gender. At puberty, males have a higher ICF compared with females because of an increased muscle mass.

The other ECF in the body includes lymph, cerebrospinal fluid, aqueous and vitreous humor, synovial fluid, and serous fluid. These fluids typically make a small contribution in the physiologic state but can increase in pathologic states, for example, with ascites. Nephrotic syndrome, liver failure, heart failure, protein-losing enteropathy, and sepsis can all cause an abnormal increase in the interstitial component of ECF, leading to edema or third spacing. The blood volume component of the ECF is decreased with conditions such as dehydration, hypoalbuminemia, and anemia.

SOLUTE COMPOSITION OF BODY WATER

The ICF and ECF vary in solute composition. Solutes are classified into electrolytes (inorganic salts, acids, and bases and some proteins) or nonelectrolytes (glucose, lipids, creatinine, and urea). Sodium is the major cation, and chloride is the major anion in the ECF. Compared with the ECF, potassium is the major cation, and phosphate is the major anion in the ICF. Organic anions and proteins are predominantly present in the

ICF. However, both sodium and chloride levels are low in the ICF. The normal electrolyte composition of fluid compartments is given in Table 1. (1)(2)

The difference in solute composition is in part attributed to the sodium and potassium adenosine triphosphatase pump. The pump actively uses cellular energy to maintain sodium in the ECF and potassium in the ICF. The difference in composition of anions is attributed to the relative impermeability of the cell membrane, which separates the ICF and ECF. The large anionlike proteins cannot cross the cell membrane and as a result are located intracellularly.

Although the ECF and ICF vary in electrolyte composition, the measured serum electrolytes do not always reflect the total body content. Two examples of this caveat are patients treated for diabetic ketoacidosis and children with malnourishment. The measured serum electrolyte concentration is not a reflection of the electrolyte total body content because (1) the ICF is a larger compartment compared with the ECF and (2) a concentration gradient of the electrolytes occurs between the 2 compartments. For example, the intracellular potassium concentration (140 mEq/L [140 mmol/L]) is at least 30 times higher than the serum potassium concentration (4 mEq/L [4 mmol/L]). Despite losses from the ICF, serum potassium may be maintained in the normal range by the shifting of potassium from the ICF to the ECF. Diabetic ketoacidosis, a state of relative insulin deficiency, leads to a transcellular shift of potassium from the ICF to the ECF. The total body potassium is decreased; however, serum potassium levels may be normal or even elevated. Once treatment is started with insulin replacement, potassium rapidly moves back into the cells, and if not aggressively replaced, low serum potassium levels occur. Similarly, total body potassium and phosphorus are depleted with malnutrition. Once nutrition rehabilitation is started, refeeding syndrome leads to hypokalemia and hypophosphatemia because of shifting of potassium and phosphorus to the ICF compartment.

The normal electrolyte composition of the ECF and the ICF is maintained by balanced intake and output. In healthy children, urine is the primary source of electrolyte loss, a small amount occurs through the skin, stool losses are minimal, and essentially no electrolytes are lost through the respiratory system. Sodium losses in urine amount to 2 to 3 mEq/kg per day, and potassium losses amount to 1 to 2 mEq/kg per day. Urinary anion losses are in the form of chloride and organic anions. Skin losses of sodium and potassium are 0.5 mEq/kg per day. To maintain homeostasis, the physiologic requirements are 3 mEq/kg per day for sodium, 2 mEq/kg per day for potassium, and 5 mEq/kg per day for chloride. (4) Maintenance requirements of these electrolytes increase with diarrheal losses, excessive sweating, burns, or increased urinary losses.

WATER AND SOLUTE MOVEMENT: OSMOTIC EQUILIBRIUM

A state of equilibrium exists between the intravascular and interstitial fluids. Three major forces are responsible for movement of fluids between the intravascular and interstitial compartments across the capillary membrane. First, hydrostatic pressure provided by the pumping action of the heart causes the fluids to move from arterial end to venous end. Second, oncotic pressure provided by high protein content (albumin) in the intravascular compartment causes fluid to move into the vascular space. Third, the capillary permeability itself determines the movement of fluids across the capillary membrane. These 3 forces are involved in maintaining the

TABLE 1. **Normal Electrolyte Composition of Extracellular Fluid and Intracellular Fluid (1)(2)**

	EXTRACELLULAR FLUID		
ELECTROLYTE, MEQ/L	PLASMA	INTERSTITIAL	INTRACELLULAR FLUID
Sodium	140	143	13
Potassium	4	4	140
Calcium	5		
Magnesium	4		7
Chloride	104	114	3
Bicarbonate	24	29	10
Proteins	14		40
Phosphate	2		107

Starling equilibrium as shown in Fig 2. A balancing act between the hydrostatic and oncotic pressure maintains the intravascular volume, which is important for perfusion of all tissues and organs.

Increased hydrostatic pressure or capillary permeability will lead to fluid leaving the intravascular space. On the other hand, a decrease in oncotic pressure (low albumin) will also cause fluid to leave the intravascular compartment and enter the interstitial compartment. A common clinical condition is nephrotic syndrome, where edema is a result of hypoalbuminemia. These patients have reduced intravascular volume but increased interstitial fluid. On the contrary, patients with congestive heart failure have decreased pumping action of the heart, leading to increased intravascular volume. This in turn leads to edema from increased venous hydrostatic pressure and movement of fluid from the intravascular compartment to the interstitial compartment.

OSMOLALITY

Osmolality is defined as the concentration of all the solutes in a given weight of water. Sosm is equal to the sum of the osmolality of individual solutes in the intravascular space. Sodium is the predominant osmole in blood along with glucose and urea. Serum sodium concentration is measured by the ion selective electrode method. Sosm can be measured directly via determination of freezing point depression (measured osmolality). Sosm can also be estimated using values of sodium, glucose, and urea (calculated osmolality). The formula for calculated osmolality is as follows:

$$\text{Sosm} = 2 \times \text{Sodium (mmol/L)} + \frac{\text{Glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}$$

The normal serum concentrations are 135 to 145 mEq/L (135–145 mmol/L) for sodium, 60 to 100 mg/dL (3.3–5.6 mmol/L) for glucose, and 10 to 20 mg/dL (3.6–7.1 mmol/L) for BUN. On the basis of these reference values, normal Sosm is 275 to 290 mOsm/Kg (275–290 mmol/kg). As evident from the formula, osmolar contribution from glucose and BUN are often minimal, and doubling the sodium value provides the approximate osmolality.

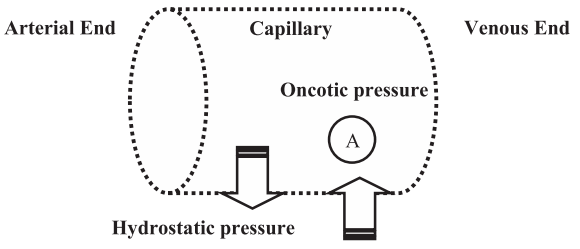

Figure 2. The Starling equilibrium. Hydrostatic pressure, oncotic pressure provided by albumin (A), and capillary permeability are responsible for movement of fluid between the intravascular and interstitial compartments.

In clinical settings, tonicity (also referred as effective osmolality) is a more relevant term compared with osmolality. Tonicity takes into account the relative solute permeability of the membrane separating the ICF and the ECF. The membrane is basically impermeable to sodium and mannitol, and sodium and mannitol are mostly confined to the ECF compartment (sodium and mannitol minimally flow across the membrane). These solutes are effective in creating an osmotic pressure gradient across the membrane, leading to movement of water from the ICF to the ECF. Solutes that are easily permeable to cell membranes (urea, methanol, and ethanol) are ineffective in causing water shifts, thereby unable to create an osmotic pressure gradient. Some solutes, such as glucose, behave differently in physiologic vs pathologic conditions. At normal glucose concentrations, it is an ineffective solute because it is taken up inside the cell via active transport mechanisms. However, in conditions with impaired glucose uptake (such as diabetes mellitus), it becomes an effective solute. If these effective solutes are rapidly cleared, it will also lead to a shift of fluids but in the opposite direction. Thus, rapid correction of hypernatremia or severe hyperglycemia leads to a shift of fluids from the ECF to the ICF and causes cerebral edema.

Measured Sosm is a helpful test to order along with serum sodium in the following situations: (1) differentiating true hyponatremia from pseudohyponatremia, (2) assessing patients with hyperglycemia (increased measured Sosm but low serum sodium level), and (3) diagnosing suspected poisoning. In most circumstances, a difference of 10 mOsm/Kg (10 mmol/kg) between measured and calculated osmolality is normal (osmolar gap). This osmolar gap may be increased, for example, in poisoning with methanol, ethanol, or ethylene glycol. These alcohol molecules are small and can result in a large change in osmolality. Ingestion of antifreeze (ethylene glycol) or windshield fluid (methanol) should be considered in patients with an increased osmolar gap. A large osmolar gap suggests that substances other than urea or glucose are contributing to Sosm.

WATER METABOLISM

Water metabolism is a delicate balance between intake and output of water. Intake consists of 2 components: (1) unregulated intake, which includes water present in ingested foods and consumption of beverages, and (2) regulated intake, which occurs in response to thirst. Similarly, water

output can be (1) unregulated as a result of insensible water losses (sweating, respiration, or gastrointestinal losses) and (2) regulated as a result of action of arginine vasopressin (AVP) or antidiuretic hormone (ADH) on the kidneys.

Thirst is the body's defense mechanism against a decrease in the ECF or the ICF, resulting in increased water intake. Intravascular volume depletion (diarrhea or vomiting) leads to a decrease in the ECF, leading to stimulation of thirst. This mechanism is mediated by activation of baroreceptors and release of angiotensin II. The other mechanism that causes thirst is an increase in tonicity (effective osmolality) of ECF, leading to a decrease in ICF. This mechanism is mediated by osmoreceptors located in the anterior hypothalamus. Overall, osmotic changes are a more effective stimulus of thirst compared with volume changes. Thirst is an important pathologic response to hyperosmolality or hypovolemia. However, during normal physiologic conditions, water balance is regulated by water excretion and not by thirst.

AVP, also known as ADH, is primarily responsible for regulation of urine flow and water excretion in the body. Because of its antidiuretic function, the hormone responsible for regulation of urine flow and water excretion was called ADH. However, once ADH was found to be a 9–amino acid peptide; ADH was renamed AVP. The peptide is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and is transported to the posterior pituitary for storage. Once an appropriate stimulus is received, AVP is released into the circulation. Antidiuresis ensues when AVP interacts with AVP V2 receptors in the kidney, resulting in insertion of aquaporin 2 channels on the luminal surface of collecting tubule principal cells. As a result, water permeability is increased in the collecting tubules leading to increased water reabsorption, increased urine osmolality, and decrease urine flow.

The release of AVP is determined primarily by osmotic regulation and volume regulation. A change in 1% of plasma osmolality can cause a significant increase in AVP levels and a proportional increase in urine osmolality. This response is rapid, and AVP has a short half-life (10–20 minutes); osmotic regulation can control renal water excretion on a minute-to-minute basis. Hypovolemia also acts as a stimulus for secretion of AVP. In response to hypovolemia, AVP release is increased, which in turn leads to increased urinary concentration and renal water absorption. However, osmolality is a more sensitive stimulus to regulate water balance, and only moderate to severe hypovolemia causes a direct effect on AVP secretion.

On a daily basis, unregulated fluid intake is excreted via AVP-regulated urine flow. The predominant stimulus for AVP is osmolality. An increase in osmolality causes increases in AVP and stimulates thirst. When these mechanisms are inadequate to maintain homeostasis (severe reduction in blood pressure or volume), thirst-induced intake is the prominent defense mechanism to dehydration. In a state of altered mental status, thirst as a defense mechanism to prevent dehydration is ineffective.

SODIUM METABOLISM

Sodium is important to maintain the ECF volume, which in turn is essential for maintaining blood pressure and delivery of essential nutrients to cells. As with water metabolism, maintenance of sodium homeostasis requires a balance between intake and output of sodium. Similar to water metabolism, mechanisms regulate the excretion of sodium to maintain sodium balance. Changes in ECF volume provide feedback to maintain total sodium content by increasing or decreasing sodium excretion in urine.

Sodium intake is generally not affected by ECF volume. For example, patients with severe blood loss or hypotension become thirsty but do not crave salt. On the same note, athletes lose sodium and chloride because of sweating and have to be instructed to take electrolyte-rich solutions because they do not develop a salt appetite. Most patients with adrenal insufficiency or salt-losing nephropathy have a desire for increased salt intake. Patients with congestive heart failure have a normal salt appetite despite excess sodium and ECF and are advised to restrict sodium in the diet. Thus, sodium intake has a lesser role in physiologic maintenance of sodium metabolism.

Sodium excretion is regulated by complex mechanisms and is essential for maintenance of the ECF volume as shown in Fig 3. A low ECF volume is detected by cardiopulmonary baroreceptors. These afferent receptors are located in the atria, ventricles, and pulmonary interstitial tissue. A high ECF volume or pressure is detected by aortic and carotid baroreceptors. A low ECF volume is also detected by intrarenal receptors in the juxtaglomerular apparatus and renal interstitium. These receptors respond by increasing the renin secretion and in turn lead to activation of the renin-angiotensin-aldosterone system. The central nervous system has additional receptors that detect changes in the ECF volume and also is responsible for integration of afferent signals, ultimately sending signals to kidneys to affect renal sodium excretion.

Glomerular filtration rate (GFR) is a major factor controlling sodium excretion. Kidneys filter a large amount of sodium in a day, and so one expects that small increases in GFR can cause a significant increase in filtered sodium. However, sodium reabsorption in the proximal tubules increases as filtered sodium increases (tubuloglomerular feedback), thereby

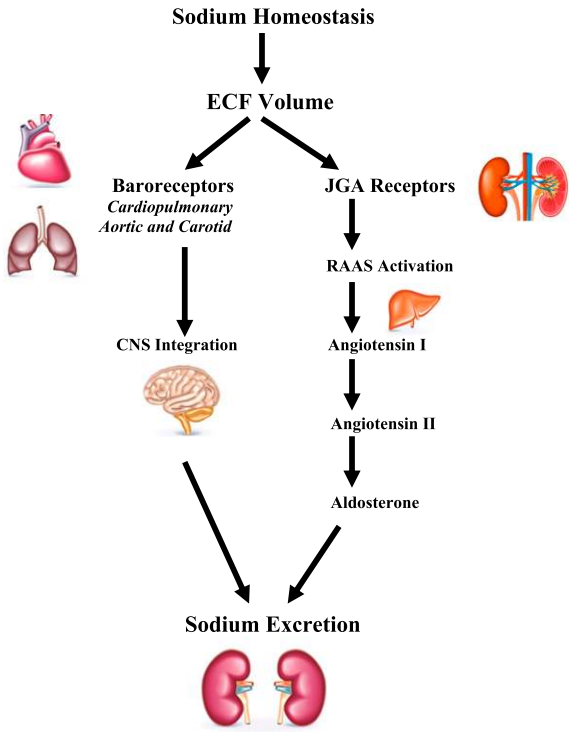

Figure 3. Flow diagram depicting regulation of sodium in response to changes in the extracellular fluid (ECF) volume.
CNS=central nervous system; JGA=juxtaglomerular apparatus; RAAS=renin-angiotensin-aldosterone system.

dampening sodium excretion. Another classic mechanism to regulate sodium excretion is through aldosterone. As discussed above, low ECF volume stimulates the release of renin, which transforms angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II and acts as a potent vasoconstrictor and also causes increased sodium reabsorption in the proximal renal tubules. Angiotensin II also leads to increased aldosterone production, which causes sodium reabsorption in the collecting tubules and leads to salt and water retention and restoration of the ECF volume. Besides GFR and aldosterone action regulating sodium excretion, there are other factors that play a minor role. These factors include redistribution of intrarenal blood flow, renal prostaglandins, and natriuretic hormones, such as atrial natriuretic peptide. A comparison of major factors responsible for regulation of salt and water homeostasis is given in Table 2.

HYPEROSMOLALITY AND HYPERNATREMIA

The concepts of TBW, osmolality, and sodium and water regulation are helpful in understanding disorders related to sodium and water. Hyperosmolality is an indicator of relative deficiency of water to solute in the ECF. To balance the osmoles, water moves from the ICF to the ECF.

The pathogenesis of common hyperosmolar disorders is given in Table 3. Hyperosmolar disorders result from decreased water intake or increased water excretion and only rarely are caused by excessive salt intake. In clinical practice, inadequate water intake is usually not due to suppression of thirst but a result of generalized depression in sensorium or the inability to gain access to water (infants, children with developmental delay, and quadriplegic patients). Increased free water excretion results from insufficient action of the AVP (diabetes insipidus [DI]), although the thirst mechanism may be intact. In patients with osmoreceptor dysregulation (hypodipsia), an uncommon condition, both thirst mechanism and AVP secretion can be affected. Hyperosmolarity also results from increased renal losses of free water (acute tubular necrosis and diuretic use) or extrarenal losses of free water (burns, phototherapy, diarrhea, and vomiting). All these disorders lead to increased serum sodium, but the total body sodium level is normal or low and the TBW is decreased. Excessive salt administration is rarely responsible for hypernatremia or hyperosmolality.

A detailed evaluation of a patient with hyperosmolality includes a careful history, clinical assessment of the ECF volume, and laboratory evaluation, including assessment of serum electrolytes, BUN, creatinine, serum glucose, measured and calculated osmolality, urine osmolality, and urine electrolytes. Hypernatremia is always associated with hyperosmolality because sodium is the key component in Sosm. However, hyperosmolality can exist without hypernatremia when other solute levels are elevated. In severe hyperglycemia, Sosm is high with a relative hyponatremia.

Urine concentrating ability (urine osmolality or urine specific gravity) helps distinguish disorders of renal concentrating defect vs disorders that result from water losses from extrarenal sources. Hyperosmolality is a stimulus for AVP secretion and leads to increased urine concentrating ability. In most cases, an appropriately increased urine osmolality in a hyperosmolar state rules out a primary renal cause. In these patients, extrarenal causes of fluid loss (skin, gastrointestinal, and pulmonary) are likely causes of hyperosmolality or hypernatremia. Less common, thirst itself is dysregulated, as in older patients or patients with hypodipsia. In contrast, an inappropriately low urine osmolality in a hyperosmolar patient signifies a renal concentration defect. Common causes include the polyuric phase of acute tubular necrosis and the diuresis that results after relieving urinary obstruction (posterior urethral valves or ureterostomies). Diuresis that results from osmosis (hyperglycemia or mannitol administration) would also lead to excretion of large amounts of dilute urine. In addition, DI is a cause of hyperosmolality and dilute urine and is due to inadequate AVP

TABLE 2. Comparison of Major Factors Responsible for Water and Sodium Balance

	WATER HOMEOSTASIS (OSMOREGULATION)	SODIUM HOMEOSTASIS (VOLUME REGULATION)
Regulator	Plasma osmolality	ECF volume
Affector	Osmoreceptor (hypothalamic)	Baroreceptors (cardiopulmonary and carotid) JGA
Effector	AVP Thirst	RAAS (aldosterone and angiotensin II) SNS AVP GFR Others (ANP, prostaglandins)
Net Result	Water excretion or intake	Sodium excretion

ANP=atrial-natriuretic peptide; AVP=arginine vasopressin; ECF=extracellular fluid; GFR=glomerular filtration rate; JGA=juxtaglomerular apparatus; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system.

secretion (central DI) or inadequate renal response to AVP (nephrogenic DI). Although patients with DI may initially present with normal Sosm and serum sodium, because they have an intact thirst mechanism, their Sosm increases with water deprivation.

The ECF volume evaluation is helpful to guide fluid replacement. Hyperosmolality causes fluid shifts from the ICF to the ECF, and as a result, the ECF volume is relatively preserved. Thus, patients with hypernatremic dehydration may appear less ill compared with patients with hyponatremic dehydration because of the relative sparing of the ECF. Most patients with hyperosmolality have some degree of ECF volume compromise except for patients with mild forms of DI who are able to maintain TBW by responding to thirst stimulation.

TABLE 3. Etiopathogenesis of Common Disorders Leading to Hyperosmolality or Hypernatremia

WATER DEPLETION (↓ TBW > ↓ SOLUTE)	SOLUTE EXCESS (↑ SOLUTE > ↑ TBW)
Renal free water losses	***Salt supplementation***
- ATN (diuretic phase)	- Sodium chloride
- Postobstructive diuresis	- Sodium bicarbonate
- Osmotic diuresis (hyperglycemia)	- Hyperalimentation
- Diuretics (loop, thiazide)	
- Decreased AVP secretion (central DI)	
- Decreased AVP action (nephrogenic DI)	
Nonrenal free water losses	***Other***
- Gastrointestinal (vomiting, diarrhea)	-Sea water drowning
- Pulmonary (hyperventilation, tachypnea)	
- Skin (burns, sweating, phototherapy)	
Low water intake - Decreased availability (infants, cognitive impairment, quadriplegic) - Hypodipsia (osmoreceptor dysfunction)	

ATN=acute tubular necrosis; AVP=arginine vasopressin; DI=diabetes insipidus; TBW=total body water.

Clinicians can determine fluid therapy based on a free water deficit (FWD) estimation. FWD can be calculated using the following formula:

$$\text{FWD} = 0.6 \times \text{Weight (kg)} \times \left(\left\{ \frac{\text{Serum Sodium (mEq/L)}}{140} \right\} - 1 \right)$$

This formula assumes TBW is approximately 60% of body weight and normal serum sodium is 140 mEq/L (140 mmol/L). However, this formula does not take into account ongoing water losses that need to be additionally replaced. The estimated FWD is replaced in 48 to 72 hours to avoid a rapid decrease in Sosm. Prolonged hyperosmolality leads to accumulation of osmotically active substances within the cells of the brain that help counter the extraosmolality of plasma. These osmotic substances (taurine, glutamine, glycine, sorbitol, and inositol) are termed idiogenic osmoles and protect the brain from fluid shifts. If hyperosmolality is corrected rapidly, idiogenic osmoles continue to occupy intracellular brain compartments and create a fluid shift from the ECF (lower osmolality after correction) to the ICF, producing cerebral edema. Hence, FWD should be corrected slowly in cases of hypernatremic dehydration to prevent seizures and cerebral edema. Slow correction also holds true in cases of diabetic ketoacidosis, when hyperglycemia is corrected by slowly infusing insulin and dextrose to prevent cerebral edema. Patients with renal failure undergoing initial hemodialysis can also have an acute decrease in Sosm due to a rapid decrease in BUN. These patients may need mannitol (hyperosmolar agent) during hemodialysis to prevent cerebral edema.

HYPO-OSMOLALITY AND HYPONATREMIA

Hypo-osmolality is an indicator of relative excess of water to solute in the ECF. To balance the osmoles, water moves from the ECF to the ICF. Thus, there is excess of TBW relative to total body solute. Hypo-osmolar disorders (hyponatremia) result from dilution of solute by increased body water (dilutional hyponatremia) or depletion of body solute more than body water (total body deficit of sodium). Most hypo-osmolar disorders may occur as a result of a combination of solute depletion and water retention. (5) Common conditions of renal solute depletion are salt-losing nephropathy, diuretic use, and mineralocorticoid deficiency. Patients with nonrenal solute losses (diarrhea, vomiting, and burns) present with hyponatremia when replacement occurs with excess free water. Dilutional hyponatremia occurs as a result of decreased free water excretion (nephrotic syndrome, congestive heart failure, and cirrhosis) or increased free water intake (primary polydipsia). The pathogenesis of common hypo-osmolar disorders is given in Table 4. It is noteworthy that most disorders of solute depletion are associated with secondary water retention by the kidneys in response to intravascular depletion. On the other hand, disorders of water retention (solute dilution) can cause hypo-osmolality with or without solute losses. Often, water retention leads to intravascular hypervolemia and secondary solute losses, exacerbating hypo-osmolality.

As in patients with hyperosmolality, hypo-osmolar patients also require a detailed evaluation to confirm the cause.

TABLE 4. **Etiopathogenesis of Common Disorders Leading to Hypo-osmolarity or Hyponatremia**

SOLUTE DEPLETION (↓ SOLUTE + WATER RETENTION)	SOLUTE DILUTION (↑ TBW ± SOLUTE DEPLETION)
Renal solute losses	***↓ Renal free water excretion***
- Salt-losing nephropathy	A. ↑ Proximal tubular reabsorption
- Diuretics	- Nephrotic syndrome
- Solute diuresis (mannitol, hyperglycemia)	- Congestive heart failure
- Mineralocorticoid deficiency	- Cirrhosis - Hypothyroidism
	B. ↑ Water permeability of collecting tubule - SIADH - Glucocorticoid deficiency
Nonrenal solute losses (+ water replacement)	***Normal renal water excretion***
- Gastrointestinal (vomiting, diarrhea)	-Primary polydipsia
- Blood loss	
- Skin (burns, sweating)	

SIADH=syndrome of inappropriate anti-diuretic hormone; TBW=total body water.

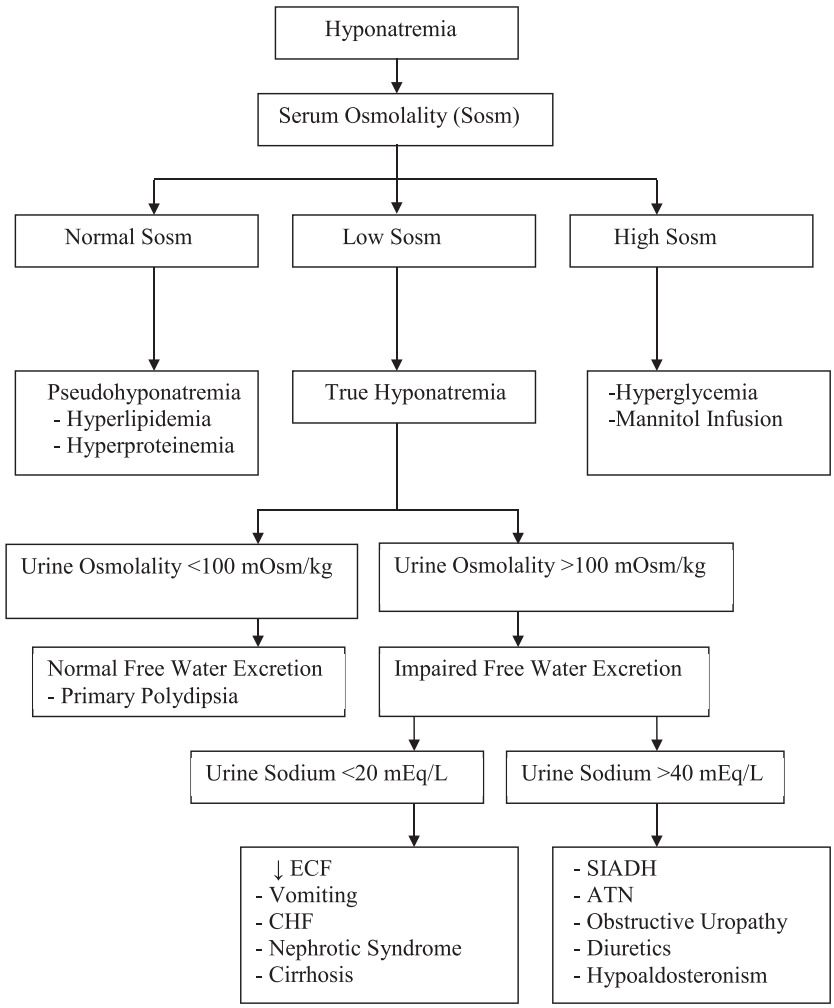

Figure 4. A systematic approach to a patient with hyponatremia using urine sodium and urine osmolality. (6)
ATN=acute tubular necrosis; CHF=congestive heart failure; ECF=extracellular fluid; SIADH=syndrome of inappropriate antidiuretic hormone.

Evaluation includes a careful history, clinical assessment of the ECF volume, and laboratory evaluation, including assessment of serum electrolytes, BUN, creatinine, serum glucose, measured and calculated osmolality, urine osmolality, and urine electrolytes. Hyponatremia is invariably associated with hypo-osmolality (hypotonic hyponatremia), but in rare circumstances Sosm may be high (hypertonic hyponatremia) or normal (isotonic hyponatremia). Pseudohyponatremia (normal measured Sosm and low serum sodium) is caused by increased levels of lipids or proteins. Hypertriglyceridemia and hyperproteinemia increase the nonaqueous component of plasma and as a result decrease the concentration of sodium per liter of plasma but do not affect the concentration of sodium per liter of plasma water. In hyperglycemia (increased measured Sosm), there is a relative decrease of serum sodium. Serum sodium can be corrected in such cases by adding 1.6 mEq/L (1.6 mmol/L) for each 100-mg/dL (5.6-mmol/L) elevation in serum glucose above 100 mg/dL (5.6 mmol/L).

The urine sodium level is low with extrarenal losses (diarrhea, vomiting, and burns) and helps to differentiate from renal losses of sodium. Low urine sodium levels can also be seen when there is increased proximal tubular reabsorption of sodium (congestive heart failure, nephrotic syndrome, and cirrhosis). High urine sodium levels are seen with diuretics such as thiazides, which are more commonly associated with hyponatremia compared with loop diuretics, such as furosemide. Other salt-losing states, such as obstructive uropathy and Bartter syndrome, are also associated with high urine sodium. High urine sodium also indicates dilutional hyponatremia as in patients with syndrome of inappropriate antidiuretic hormone (SIADH). The ECF volume expansion (not depletion) results in increased urinary sodium in patients with SIADH. Next, urine osmolality helps to narrow the differential diagnosis further. An inappropriate concentration of urine (high osmolality) along with high urine sodium in a euvolemic patient suggests SIADH.

A simplified approach to etiology of hyponatremia using urine sodium and urine osmolality is shown in Fig 4. (6)

Hyponatremia or hypo-osmolality can present with neurologic symptoms as a result of the osmotic shift of water into the brain. Patients may have confusion, headache, or seizures as a result of cerebral edema. How rapidly hyponatremia develops determines the likelihood of neurologic symptoms. The brain counteracts osmotic shifts by losing intracellular solutes (potassium and organic osmoles). If hyponatremia develops acutely, brain adaptation may be incomplete, and severe neurologic symptoms may ensue. On the same note, rapid correction of hyponatremia causes an osmotic shift of water from brain cells to the ECF and leads to central pontine myelinolysis. The target increase in sodium is not more than 0.5 mEq/L (0.5 mmol/L) per hour or 10 to 15 mEq/L (10–15 mmol/L) in 24 hours. Thus, patients developing severe hyponatremia (sodium, <120 mEq/L [<120 mmol/L]) acutely (within 48 hours) are at increased risk of neurologic complications and should be treated promptly. On the contrary, patients with chronic hyponatremia, developing over more than 48 hours, should undergo a slow correction to decrease the risk of demyelination.

CASE SCENARIO CONTINUED

The 6-month-old child with a history of vomiting described in the vignette at the beginning of article has hyponatremia (sodium, 122 mEq/L [122 mmol/L]). A low Sosm (260 mOsm/kg [260 mmol/kg]) confirms true hyponatremia. The patient's high urine osmolality (900 mOsm/kg [900 mmol/kg]) and high urine specific gravity (1.030) suggest impaired free water excretion in response to dehydration. The patient's low urine sodium level (<20 mEq/L [<20 mmol/L]) rules out renal losses of sodium. In conclusion, the hyponatremic dehydration in the patient described in the vignette is due to a combination of extrarenal losses of sodium (vomiting) and increased TBW due to the parents' attempt to rehydrate the child with free water and a diluted formula.

Summary

On the basis of evidence available from initial studies on body fluids and consensus:

- Total body water (60% of body weight in male adolescents) is divided into extracellular fluid (ECF) and intracellular fluid (ICF). Blood volume (5% of body weight) is responsible for ensuring circulatory flow to organs.
- Sodium is primarily present in the ECF and potassium in the ICF, but serum concentrations of sodium or potassium do not reflect their respective total body content.
- Two major mechanisms regulate water metabolism: thirst and arginine vasopressin (also known as antidiuretic hormone). Sodium content, regulated by complex mechanisms (juxtaglomerular apparatus, renin-angiotensin-aldosterone system, glomerular filtration rate, and others), is responsible for maintaining the ECF volume.
- Serum osmolality is calculated using sodium, glucose, and blood urea nitrogen measurements.
- Hypernatremia or hyperosmolality is an indicator of relative deficiency of water to solute in the ECF. This free water deficit is corrected slowly to prevent seizure and cerebral edema.
- Hyponatremia or hypo-osmolality is an indicator of relative excess of water to solute in the ECF (dilutional or total body deficit of solute). Rapid correction causes osmotic shift of water from brain cells to the ECF and leads to central pontine myelinolysis.

To view Reference list for this article, visit https://pedsinreview.aappublications.org and click on the "Body Fluid Composition" link.

PIR Quiz

1. You are seeing one of your adolescent patients on the ward. She is a 16-year-old girl with severe anorexia nervosa and weighs just 34 kg. Which of the following electrolyte disturbances would be most likely in anorexic patients who are severely malnourished but beginning to eat?
    A. Malnourishment is associated with shifting of potassium and phosphorous to the extracellular fluid (ECF).
    B. Malnourishment is associated with shifting of potassium to the intracellular fluid (ICF) and phosphorus to the ECF.
    C. Refeeding syndrome is associated with hyperkalemia and hyperphosphatemia.
    D. Refeeding syndrome is associated with hyperkalemia and hypophosphatemia.
    E. Refeeding syndrome is associated with hypokalemia and hypophosphatemia.
2. You are preparing a lecture for third-year medical students on fluid and electrolytes in pediatric patients. You are attempting to delineate the fluid shifts and the resulting clinical presentation in nephrotic syndrome and congestive heart failure. Which of the following best describes the Starling equilibrium?
    A. Hydrostatic pressure is created by the juxtaglomerular apparatus in the kidney.
    B. Increased oncotic pressure results in fluid leaving the intravascular space.
    C. Patients with congestive heart failure have cardiac dysfunction that leads to increased intravascular volume, increased hydrostatic pressure, and resulting increased interstitial volume.
    D. Patients with nephrotic syndrome typically have increased oncotic pressure resulting from hypoalbuminemia.
    E. The balance between oncotic and hydrostatic pressure maintains the interstitial volume.
3. A 15-year-old athlete completes a half marathon in 90°F (32.2°C) weather. He is brought to the medical tent, where measurement of his serum sodium reveals a level of 156 mEq/L (156 mmol/L). Estimated free water deficit should be replaced:
    A. Depending on his half marathon time.
    B. During 1 to 2 hours.
    C. During 12 hours.
    D. During 48 to 72 hours.
    E. For any duration because duration is not important.
4. Your 10-year-old patient has developed a viral gastroenteritis with vomiting and diarrhea. He is afebrile but very sleepy. His serum sodium level is 126 mEq/L (126 mmol/L). In the emergency department, the resident suggests that her urine sodium be measured. With extrarenal losses of fluids and electrolytes, the urine sodium level is usually:
    A. Elevated.
    B. Low.
    C. Measurement is not helpful.
    D. Normal.
    E. Unmeasurable.
5. You are making night rounds in the pediatric intensive care unit with a group of medical students. You are discussing a 12-year-old boy who was admitted with a serum sodium level of 119 mEq/L (119 mmol/L) and serum osmolality of 242 mOsm/kg (242 mmol/kg). You are discussing serum osmolality and osmotic shifts in the intracellular and extracellular spaces. Which of the following is most accurate?
    A. Brisk correction of severe hyponatremia results in osmotic shift of water from brain cells to the ECF leading to cerebral edema.
    B. Children who develop severe hyponatremia during greater than 48 hours should receive replacement fluid briskly to prevent neurologic symptoms.
    C. Children who develop severe hyponatremia within 48 hours should receive replacement fluid slowly.

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2015 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

This journal-based CME activity is available through Dec. 31, 2017, however, credit will be recorded in the year in which the learner completes the quiz.

D. The brain corrects for major osmotic shifts by producing intracellular solutes, such as sodium.
E. The rate at which hyponatremia develops determines the probability of symptoms, such as headache and seizures.

Body Fluid Composition

Amrish Jain

Pediatrics in Review 2015;36;141
DOI: 10.1542/pir.36-4-141

Body Fluid Composition

Amrish Jain

Pediatrics in Review 2015;36;141
DOI: 10.1542/pir.36-4-141