1 Disorders of Water Homeostasis

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Key Points

1. To understand that disorders of sodium balance are related to conditions that alter extracellular fluid volume.
2. To appreciate the physiologic influences of antidiuretic hormone (ADH) and the stimuli resulting in its release.
3. To gain an understanding of the differences between *sodium status* (which determines the volume of extracellular volume) and *water status* (which determines the serum sodium concentration).
4. To recognize clinical signs and symptoms of the different forms of dehydration.
5. To appreciate that the management of hypernatremic dehydration differs from that of isonatremic/hyponatremic dehydration.

Key Words: Hyponatremia; hypernatremia; antidiuretic (ADH); vasopressin; diabetes insipidus; extracellular volume; intracellular dehydration; SIADH; osmolality

1. INTRODUCTION

The disorders of water balance of the body relate to volume control in body fluid compartments *(1)*. Osmotic shifts of water are directly dependent on the number of osmotic or solute particles (such as sodium and accompanying anions) that reside within the membranes of our body fluid compartments *(2)*. The osmolality of the body fluid compartments (extracellular and intracellular) contributes to the movement of water that occurs in a variety of disease states such as gastroenteritis/dehydration. An acute increase in the extracellular fluid osmolality due to a sodium chloride load results in a shift of water from the intracellular fluid compartment to reduce the osmolality and achieve a new, higher osmolar balance between the two compartments. The reverse would occur if there is an acute loss of osmolality from the extracellular fluid compartment. It is simple to appreciate the delicate interaction between osmolality and water balance. As discussed in Chapter 2, disorders of sodium balance are related to conditions that alter extracellular fluid volume (ECF). The simplest example is the requirement to maintain adequate extracellular volume to sustain perfusion of vital organs and tissues.

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Impairment of tissue perfusion will lead to decreased oxygen delivery and anoxic damage resulting in organ failure (i.e., acute renal failure, hepatic failure, brain anoxia). It is therefore necessary to consider the clinical management of disorders of water (osmolality) and sodium balance (ECF volume) collectively. The identification and management of fluid and electrolyte disorders are essential in order to maintain body fluid balance.

1.1. Physiology of Water Homeostasis

Maintaining water homeostasis is an essential feature of adaptation for all mammals. Environments rarely provide water in the precise amount and at the precise time needed. A complex set of homeostatic mechanisms are at play, which regulate water intake and water excretion. These include the hypothalamus and surrounding brain, which control the sense of thirst and the production and release of arginine vasopressin (AVP), the antidiuretic hormone (ADH). AVP in turn acts on the second important organ in water homeostasis – the kidney – leading to increased reabsorption of water by the collecting duct of the kidney.

Because of the central role AVP plays in water homeostasis understanding the physiologic influences on AVP production and release is important. AVP is produced in the paraventricular and supraoptic nuclei, which project into the posterior hypothalamus. It is from the posterior hypothalamus that AVP is released. The stimuli that lead to AVP release also influence AVP production.

The elegant studies performed by Verney established the role of osmolality in the release of AVP *(3)*. Under normal conditions, it is the osmolality of plasma and extracellular fluid as defined by the extracellular sodium concentration and associated anions along with a small contribution from glucose, which is "sensed" by osmoreceptors in the anteromedial hypothalamus. Small increases in osmolality of 1–2% (increase in 2–5 mOsm/kg H_2O) will result in the release of AVP. Conversely, a similar decrease in osmolality from approximately 290 to 280 mOsm/kg H_2O will result in cessation of AVP release and decreased production *(4)*.

Non-osmotic stimuli will also cause AVP to be released. Gauer and Henry *(5)* demonstrated that a reduction in "effective circulating volume" [blood loss, hemorrhage, ECF volume depletion (dehydration, diuretics, etc.), nephrotic syndrome, cirrhosis, congestive heart failure/low cardiac output] will be "sensed" by the pressure or stretch sensitive receptors in the left atrium or large arteries of the chest then through the vagus and glossopharyngeal nerve will signal production and release of AVP. Other nonosmotic stimuli for AVP secretion include anesthetics and medications, nausea and vomiting, and weightlessness *(6)* (Table 1).

AVP circulates unbound, is rapidly metabolized by the liver or excreted by the kidney. The half-life is probably no more than approximately 20 minutes.

AVP plays a central role in thirst control. Thirst is the drive to consume water to replace urinary and obligate water losses such as sweating and breathing. Thirst is stimulated by an increase in serum osmolality and by extracellular volume depletion. AVP release appears to occur prior to the sensation of thirst, which is about 290 mOsm/L with maximal urinary concentration (~1200 mOsm/L) at about 292–295 mOsm/L.

The kidney plays a crucial role in the conservation of water when osmolality is increased or effective plasma volume is decreased. Similarly the kidney can excrete

Table 1
Non-osmotic Stimuli of Physiologic AVP Secretion

Hemodynamic (see text)	*Non-hemodynamic*	*Medications*
Increased Secretion	*Increased Secretion*	*Increased Secretion*
Acetylcholine	Hypoglycemia	Acetaminophen
Angiotensin II	Increased pCO_2	Beta-2 agonists
Bradykinin	hypercapnia	Chlorpropamide
Gastroenteritis	Low pO_2 – hypoxia	Clofibrate
Histamine	Motion sickness	Cyclophosphamide
Isoproterenol	Nausea/vomiting	Epinephrine
Nitroprusside	Pregnancy	Lithium
	Stress/pain	Morphine (high dose)
		Nicotine
		NSAIDs
		Prostaglandins
		Tricyclic antidepressants
		Vincristine
Decreased Secretion	*Decreased Secretion*	*Decreased Secretion*
Atrial tachycardia	Swallowing	Alpha-adrenergic
Left atrial distention		agonists
Norepinephrine		Carbamazepine
		Clonidine
		Ethanol
		Glucocorticoids
		Morphine (low dose)
		Phenytoin
		Promethazine

NSAID – non-steroidal anti-inflammatory drugs
From Cogan *(42)*; Robertson *(43)*.

water rapidly in response to excess water intake. This effect is accomplished by AVP stimulating (1) interstitium through the active transport of urea from the tubule lumen to the renal epithelial cells of the thick ascending limb of the loop of Henle and the collecting duct resulting in the development of the osmotic gradient needed to reabsorb water, and (2) the transepithelial transport of water through opened water channels in the collecting duct resulting in water reabsorption (Fig. 1).

The transepithelial transport of water across the collecting duct (primary site of action is principle cell) is accomplished by the binding of AVP to its receptor (V2R) on the basolateral (non-luminal) surface of the epithelial cell. The intracellular action is mediated through cyclic AMP and protein kinase A leading to phosphorylation of aquaporin-2 water channels *(7)*.

Aquaporins are channels that transport solute-free water through cells by permitting water to traverse cell membranes. In the kidney, aquaporin-2 is the channel through which water leaves the lumen of the tubule and enters epithelial cells of the collecting

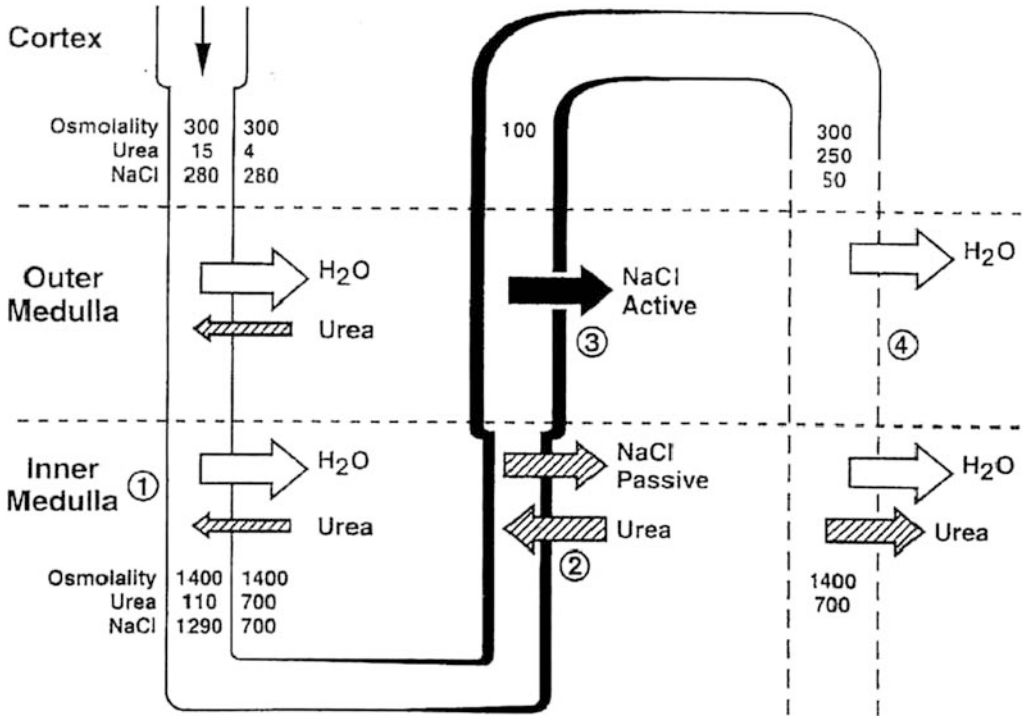

Fig. 1. Countercurrent mechanism for water reabsorption by the nephron. Reproduced with permission from *(38, Fig. 11.10)*.

duct. Water leaves these same cells through aquaporins-3 and 4. When AVP binds to the V2R receptor, aquaporin-2, which resides in intracytoplasmic vesicles, is inserted into the luminal membrane allowing water to move into the cell *(8)*. Aquaporins-3 and 4 appear to reside in the basolateral membranes and facilitate water movement from the intracellular space into the interstitium *(9)*. This movement of water into the interstitium is down a concentration gradient. The higher solute concentration in the interstitium of the kidney is facilitated by the action of AVP on epithelial sodium channels (eNaC) and the urea transporter (UT-A1) *(10, 11)*.

By 2–3 months of age, the normal infant born at term can maximally concentrate urine to 1100–1200 mOsm/kg H_2O similar to an older child or adult. AVP has been measured in amniotic fluid and is present in fetal circulation by mid-gestation. AVP levels rise (in fetal sheep) with stimuli such as increased serum osmolality *(12)*. At birth, vasopressin levels are high but decrease into "normal" ranges within 1–2 days *(13, 14)*. In neonates, AVP responds to the same stimuli as older children and adults. However, the ability to concentrate urine to the maximum achieved by older children or adults does not occur. Term infants concentrate up to 500–600 mOsm/kg H_2O and preterm infants up to 500 mOsm/kg H_2O. These low concentrating levels are probably due to a number of reasons including decreased glomerular filtration rate, decreased renal blood flow, reduced epithelial cell function in the loop of the Henle and collecting

duct, reduced AVP receptor number and affinity and reduced water channel number or presence on the cell surface. Along with decreased renal capacity to reabsorb water, neonates have a reduced capacity to dilute urine so that the range of urine osmolality in the neonate is between 150 and 500 mOsm/kg H_2O as compared to the older child of 50 and 1200 mOsm/kg H_2O. Neonates have increased non-urinary water losses (skin and respiratory) as a function of weight, which are greater compared to older children and adults. The net effect is that neonates are at greater risk of dehydration either due to inadequate water provision or to high osmolar loads provided in enteral or parenteral feeds. Also, neonates are at greater risk of hyponatremia (hypo-osmolality) if water is administrated in large quantities or at too rapid rates.

2. CLINICAL ASSESSMENT OF RENAL WATER EXCRETION

Under normal conditions the "gold" standard for testing whether water homeostasis is being maintained is to measure serum and urine osmolality. Normal serum osmolality is approximately 280–290 mOsm/kg H_2O. As noted above, urine osmolality, except in neonates, can range from 50 to 1200 mOsm/kg H_2O and will depend on the physiologic circumstances. A slight increase in serum osmolytes over a short interval (i.e., NaCl) will result in AVP release (two- to fourfold increase in circulating concentration of AVP) and a marked increase in water reabsorption and urine osmolality. The concomitant measurement of an elevated serum osmolality should be matched by an appropriately elevated urine osmolality (>500 mOsm/kg H_2O >> the serum osmolality). Likewise, a decrease in serum osmolality, usually the result of water consumption or other hypotonic solutions, will reduce AVP production and secretion leading to the excretion of large volumes of water and a lowered urine osmolality. A serum osmolality below 280 mOsm/kg H_2O should be associated with urine osmolality <250 (often below 200 mOsm/kg H_2O). This physiological response depends on an intact hypothalamus–pituitary axis and normal renal function. Any stimulus (medications, anesthetics, nausea/vomiting) which directly stimulates AVP release, could interfere with normal physiologic mechanisms. Renal disease, which impairs water delivery to the kidney or affects loop of Henle or collecting duct function, could impair the response to AVP and lead to pathology.

Often in clinical situations a quick measure of serum osmolality is the equation

$$\text{serum osmolality} = 2[\text{Na}] + \frac{[\text{glucose}]}{18} + \frac{[\text{BUN}]}{2.8}$$

where [Na] is the sodium concentration in mEq/L or mmol/L (doubling the sodium value takes into account the accompanying anions – Cl^-, HCO_3^-); the glucose is measured in mg/dL and the BUN (blood urea nitrogen) in mg/dL. The BUN is often omitted if it is not rapidly changing since its impact on osmolality is muted by its ability to move freely across cell membranes. By eliminating the BUN term from the equation, the formula is a measure of effective serum osmolality or tonicity. Similarly, the specific gravity on a urine dipstick is used as a quick measure of urine osmolality. A specific gravity of 1.010 is routinely considered to correlate with a urine osmolality of

300–400 mOsm/kg H_2O (multiplying the number to the right of the decimal point by $40{,}000 = 0.010 \times 40{,}000 = 400$). The higher the specific gravity, the higher the osmolality. Unfortunately, specific gravity is a crude test that can be affected by solutes such as albumin (patients with proteinuria have high urinary specific gravity) or glucose. In order to aid in the diagnosis of diabetes insipidus, direct measurement of osmolality is required.

2.1. Measurement of the Diluting and Concentrating Ability of the Kidney

The defense of tonicity (effective osmolality) involves the thirst mechanism and the ability of the kidneys to excrete or conserve solute-free water depending upon the presence of ADH. Urine can be divided into two components. One component is the urine volume containing a solute concentration equal to that of plasma. This isotonic component has been termed the osmolar clearance (C_{osm}) and is an index of the kidney's ability to excrete solute particles. The second component is the volume of solute-free water (C_{H_2O}). It is this latter volume that effectively changes the osmotic concentration of the extracellular fluid compartment and is an index of the kidney's ability to maintain the serum in an iso-osmolar state *(15, 16)*.

Free-water clearance, abbreviated C_{H_2O}, is calculated as shown:

$$C_{H_2O} = \dot{V} - C_{\text{osm}},$$

where

$$C_{\text{osm}} = \frac{(U_{\text{osm}}) \times (\dot{V})}{(P_{\text{osm}})}$$

and where $\dot{V}$ is the urine flow rate (mL/min), P_{osm} is the plasma osmolality, and U_{osm} is the urine osmolality.

When the kidney reabsorbs equal proportions of water and solute as they exist in the plasma, the urine has a osmolality equal to plasma, therefore, $C_{\text{osm}} = \dot{V}$. In this situation, the osmolality of the ECF remains unchanged. When ADH is present or elevated, then solute-free water is reabsorbed in a greater proportion than filtered solute thereby resulting in a concentrated (hypertonic) urine ($C_{\text{osm}} > \dot{V}$) or a negative C_{H_2O} value. For example, consider a situation where the urine flow rate is 1 L/day, serum osmolality of 300 mOsm, and urine osmolality of 600 mOsm:

$$\begin{aligned} C_{H_2O} &= 1\text{L/day} - (600\,\text{mOsm} \times 1\text{L/day})/300\,\text{mOsm} \\ &= 1\text{L/day} - 2\text{L/day} \\ &= -1\text{L/day (or 1L of free water was reabsorbed)} \end{aligned}$$

On the other hand, when ADH levels are low, then solute-free water is excreted in a greater proportion than the filtered solute thereby resulting in a dilute (hypotonic) urine

($C_{osm} < \dot{V}$) or a positive C_{H_2O} value. For example, consider a situation where the urine flow rate is 1 L/day, serum osmolality of 300 mOsm, and urine osmolality of 150 mOsm:

$$\begin{aligned} C_{H_2O} &= 1\text{L/day} - (150\,\text{mOsm} \times 1\text{L/d})/300\,\text{mOsm} \\ &= 1\text{L/day} - 0.5\text{L/day} \\ &= 0.5\text{L/day free water excreted} \end{aligned}$$

Changes in the free-water excretion and reabsorption occur independent of changes in the solute excretion (C_{osm}).

2.2. Composition of Body Fluids

As individuals age, the proportion of total body water (TBW) to body weight decreases. Water accounts for 60% of TBW in men and 50% in women while infants have a higher proportion of water, 70–80%, due to the lower proportion of muscle in comparison to adipose *(17)*. The higher proportion of TBW to whole body weight in younger children is mainly due to the larger ECF volume when compared to adults. The disproportionate weight of brain, skin, and the interstitium in younger children contributes to the variability in the ECF volume. Water is distributed between two main compartments, the intracellular fluid compartment (ICF) and extracellular fluid compartment (ECF) (Fig. 2). The intracellular compartment makes up approximately 2/3

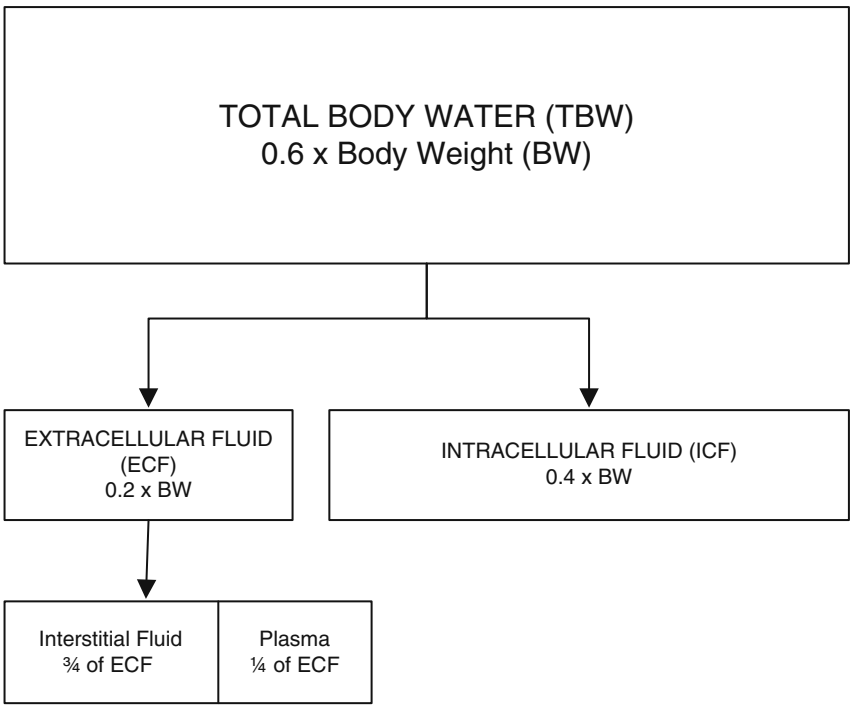

Fig. 2. Body fluid compartments.

of the TBW. The ECF constitutes 1/3 of the TBW composed of plasma and interstitial fluid. Abnormal accumulation of plasma ultrafiltrate, also referred to as "third spaced fluids," can result in edema, ascites, or pleural effusions.

Sodium along with Cl^- and HCO_3^- are the primary determinants of the ECF and provide the osmotic drive to maintain the ECF volume (Fig. 3, Table 2). Water moves freely across cell membranes between the ICF and ECF compartments to maintain osmotic

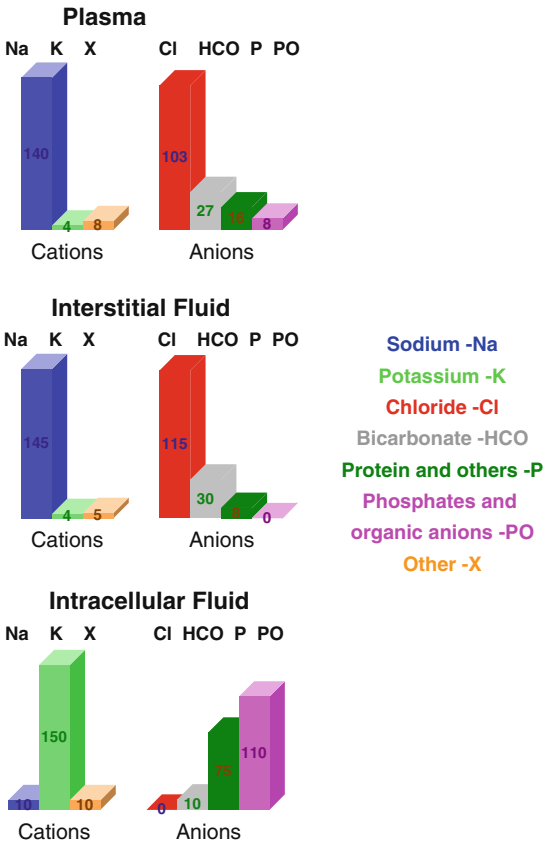

Fig. 3. Comparison between plasma, interstitial, and intracellular fluid (ICF).

Table 2
Approximate Mineral Composition of the ECF and ICF

	***ECF** (mEq/L)*	***ICF** (mEq/L)*
Na^+	135–145	10–20
K^+	3.5–5	120–150
Cl^-	95–105	0–3
HCO_3^-	22–30	10
Phosphate	2	110–120

equilibrium. For example, an increase in the water content of the ECF causes movement of water into the ICF from the ECF resulting in an expansion of both the ICF and ECF and a new osmolar balance (Fig. 4). If extensive, volume overload is clinically recognized as edema, ascites, or pleural effusions. In contrast, loss of sodium from the ECF results in ECF depletion with some relative ICF expansion and presents as signs of dehydration (Fig. 5). The kidneys are responsible for regulating the water balance and eliminate the majority of water from the body.

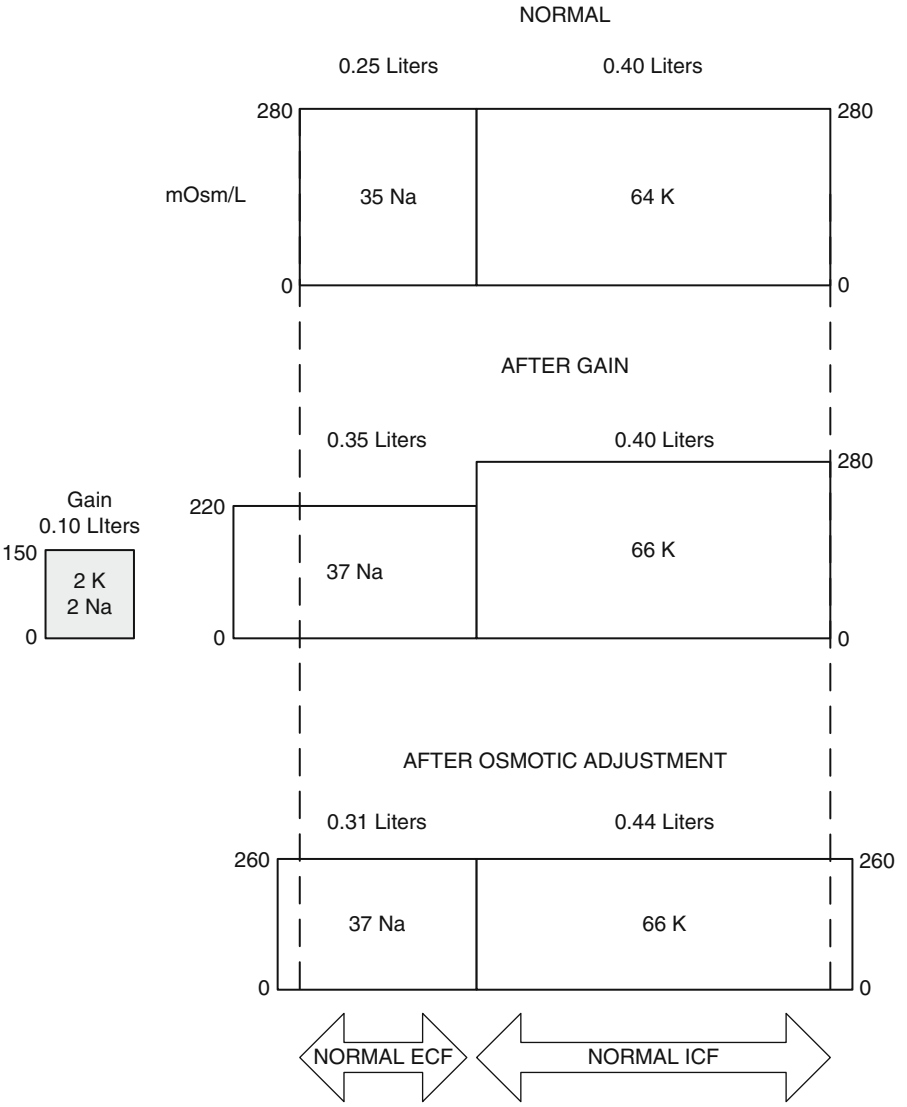

Fig. 4. ECF fluid gain with a redistribution of water resulting in a lower osmolality in a 5-year-old.

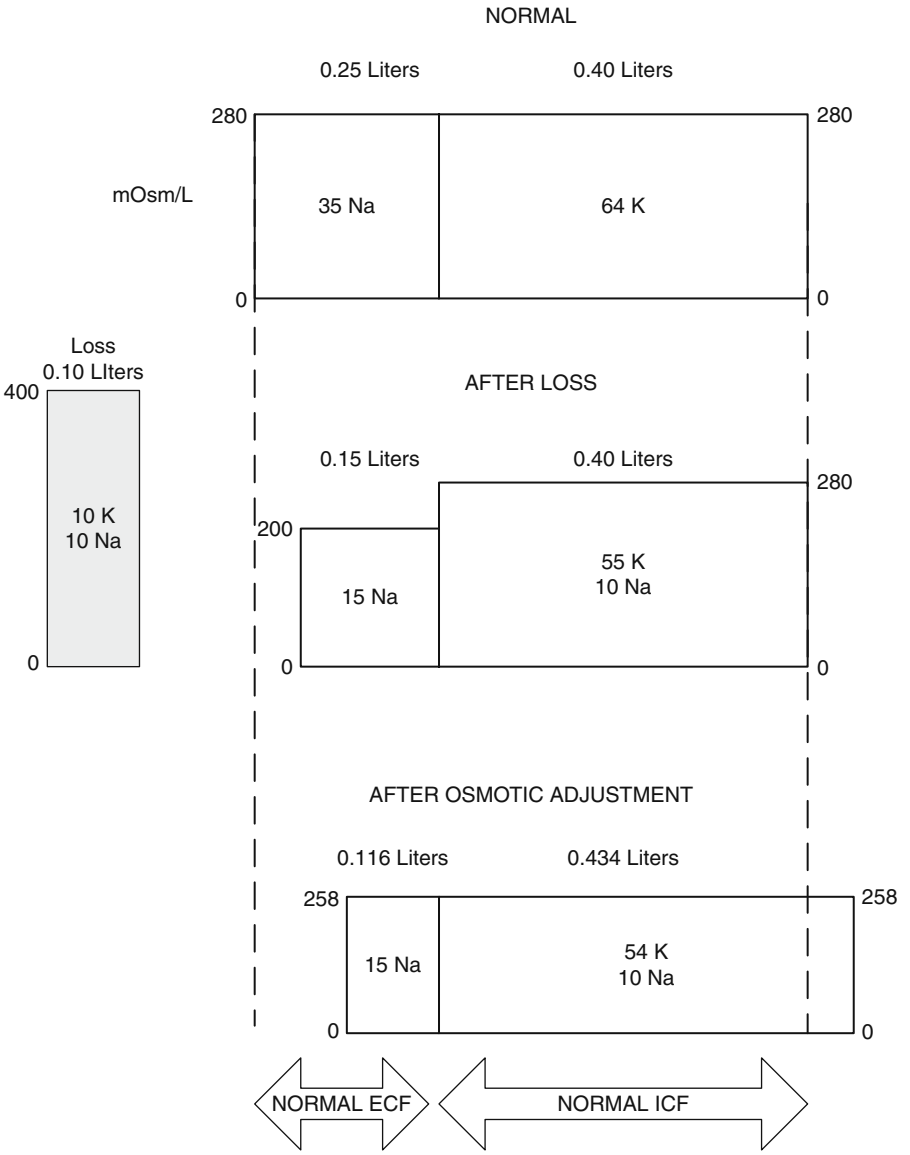

Fig. 5. Loss of hypertonic fluid and sodium from the ECF secondary to dehydration in a teenager. Reproduced with permission from Winters *(39)*.

2.3. Maintenance Requirements

For nearly 50 years, we have estimated the caloric and fluid requirements each day based on the Holliday and Segar method *(18)*. It is based on caloric requirement each day and the amount of fluid needed based on caloric expenditure (Table 3).

Table 3
Caloric, Water, and Basic Electrolyte Requirements Based on Weight

Body weight (kg)	*Calories*	*Water*	*Sodium mEq/100 mL H_2O*	*Chloride mEq/100 mL H_2O*	*Potassium mEq/100 mL H_2O*
3–10 kg	100/kg	100/kg Or 4 mL/kg/h	3	2	2
11–20 kg	50/kg	1000 mL + 50 mL/kg for each kg above 10/ Or 40 mL/h + 2 mL/kg/h	3	2	2
>20 kg	20/kg	1500 mL + 20 mL/kg for each kg above 20 Or 60 mL/h + 1 mL/kg/h	3	2	2

EXAMPLE of a calculation for maintenance fluid requirements for a 15 kg child

BW = 15Kg

Calories: 100 calories/kg for 1st 10 kg + 50 calories/kg for 5 kg (15–10 kg) = 1250 calories/day

Water: 100 mL/kg for 1st 10 kg + 50 mL/kg for 5 kg (15–10 kg) = 1250 mL/day

Sodium: 3 mEq/100 mL water = 3 mEq × 12.5 = 36.5 mEq/day or 30 mEq/L of solution

Potassium: 2 mEq/ 100 mL water = 2 mEq × 12.5 = 25 mEq/day or 20 mEq/L of solution

The child requires intravenous fluids ~ 1250 mL/day

5% Dextrose with 30 mEq/L of NaCl and 20 mEq/L of KCl at 50 mL/h

5% dextrose is provided to deliver 5 g of carbohydrate per 100 mL of solution or 50 g/L or 200 calories/L (50 g × ~4 calories/g of carbohydrate).

NOTE: This solution will only deliver 20% of the daily caloric requirement of 250 calories at the maintenance rate. For a limited period of time (generally under 5–7 days) this amount of carbohydrate will be sufficient to prevent protein breakdown. If it is anticipated that there will be a need for prolonged parenteral therapy, a higher dextrose solution will be required and provided through a central venous access if the dextrose concentration in the final solution will exceed 10–12.5%.

Recently, a modification to maintenance therapy was proposed substituting isotonic saline for the hypotonic solution recommended by Holliday and Segar *(19)*. The case for this modification is based on the observation that some children have been seriously injured [cerebral edema, brain injury and death] by the inappropriate use of maintenance solutions [hypotonic] especially in situations of unappreciated volume contraction or nonosmotic release of antidiuretic hormone. To date, studies regarding the use of isotonic saline as maintenance fluid therapy across the full range of hospitalized pediatric patients are lacking *(20)*.

Intravenous fluids that are safe to administer parenterally based on their osmolality are shown in Table 4. Each solution is selected based on the clinical status of the patient. Solutions without dextrose (0.45% isotonic saline) or without electrolytes 5% dextrose in water are only administered under special clinical situations.

Table 4
Solutions Used for Intravenous Administration

Solution	*Osmolality mOsm/L*	*Sodium mEq/L*	*Potassium Eq/L*	*Chloride mEq/L*	*Dextrose mOsm/L*
0.9% Isotonic saline (normal saline)	308	154		154	
0.45% Isotonic saline* (1/2 Normal)	154	77		77	
5% Dextrose in Water					278
5% Dextrose + 0.33% isotonic saline	378	50		50	278
5% Dextrose + 0.45% isotonic saline	432	77		77	278

*The lowest intravenous solution that can be used safely is 0.45% isotonic saline with an osmolality of 154 mOsm/L or approximately 50% of plasma. Any solution with an osmolality under this value will result in cell breakdown with a large potassium load to the extracellular space resulting in severe hyperkalemia leading to cardiac arrhythmias and possibly death.

3. HYPONATREMIA AND HYPO-OSMOLALITY

A low serum sodium less than 130 mmol/L (hyponatremia) is nearly always associated with water retention by the kidney. Hyponatremia can occur with extracellular volume depletion or even extracellular volume expansion such as in the syndrome of inappropriate antidiuretic hormone (AVP) release or SIADH. The presence of elevated levels of AVP in blood alone does *not* result in hyponatremia. Patients must have an intake of water or receive a hypotonic solution under the influence of high or excessive AVP to become hyponatremic or hypo-osmolar. Rarely, hyponatremia is the result of excessive salt loss. Recently an expert panel provided guidelines for hyponatremia in adults *(21)*. The evaluation and approach to hyponatremia in children is shown in Fig. 6a,b.

3.1. Hyponatremic Dehydration

Hyponatremic dehydration is a common condition usually associated with acute gastroenteritis. The pathophysiology of this condition involves loss of fluid and electrolytes in stool (sodium, bicarbonate, water usually hypo-osmolar to extracellular fluid) and emesis. This extrarenal loss results in extracellular volume depletion leading to the release of aldosterone and the non-osmotic release of AVP. Aldosterone will increase renal sodium reabsorption with a loss of urinary potassium eventually leading to hypokalemia. AVP will increase water reabsorption, and if the extracellular volume depletion is allowed to persist with the patient provided hypo-osmolar fluids either by mouth (clear liquids) or intravenously (5% dextrose + 0.225 (1/4) isotonic saline or 5% dextrose + 0.45 (1/2) isotonic saline), the patient develops a hypo-osmolar or hyponatremic state.

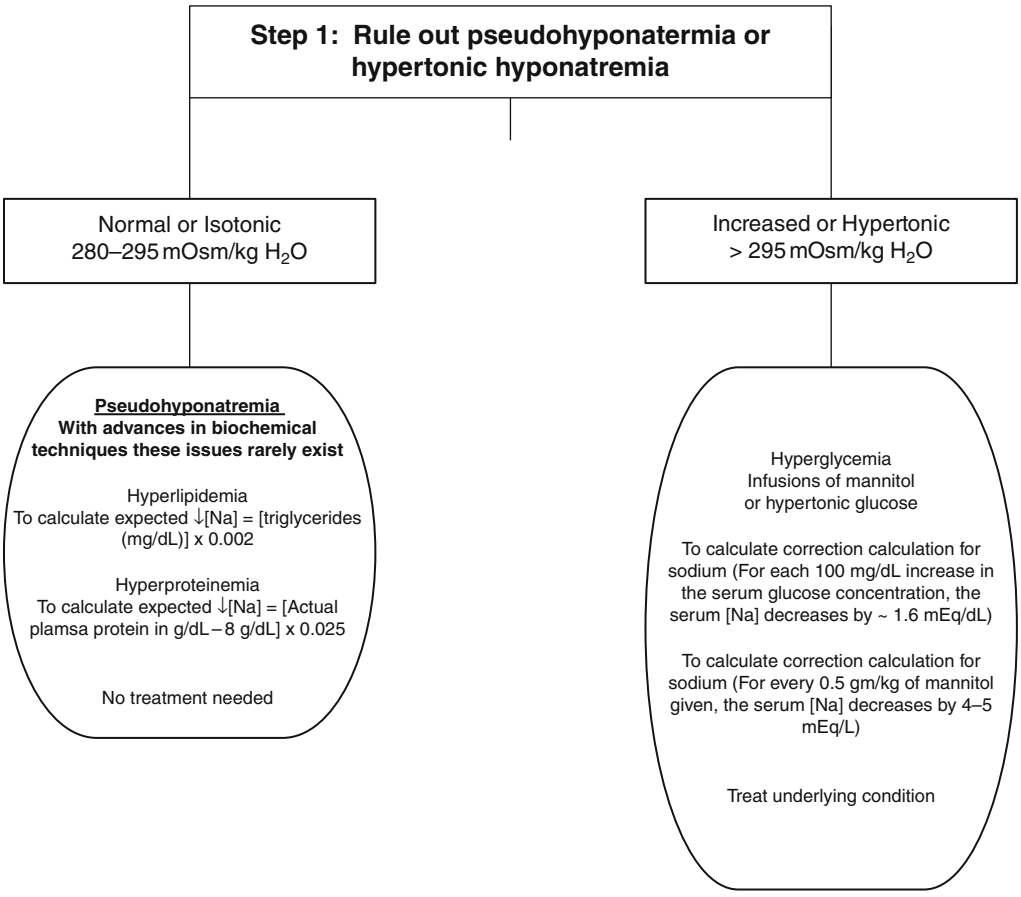

Fig. 6. Suggested evaluation of hyponatremia based on plasma osmolality or tonicity. Modified with permission from Feld *(40)*.

(*Continued*)

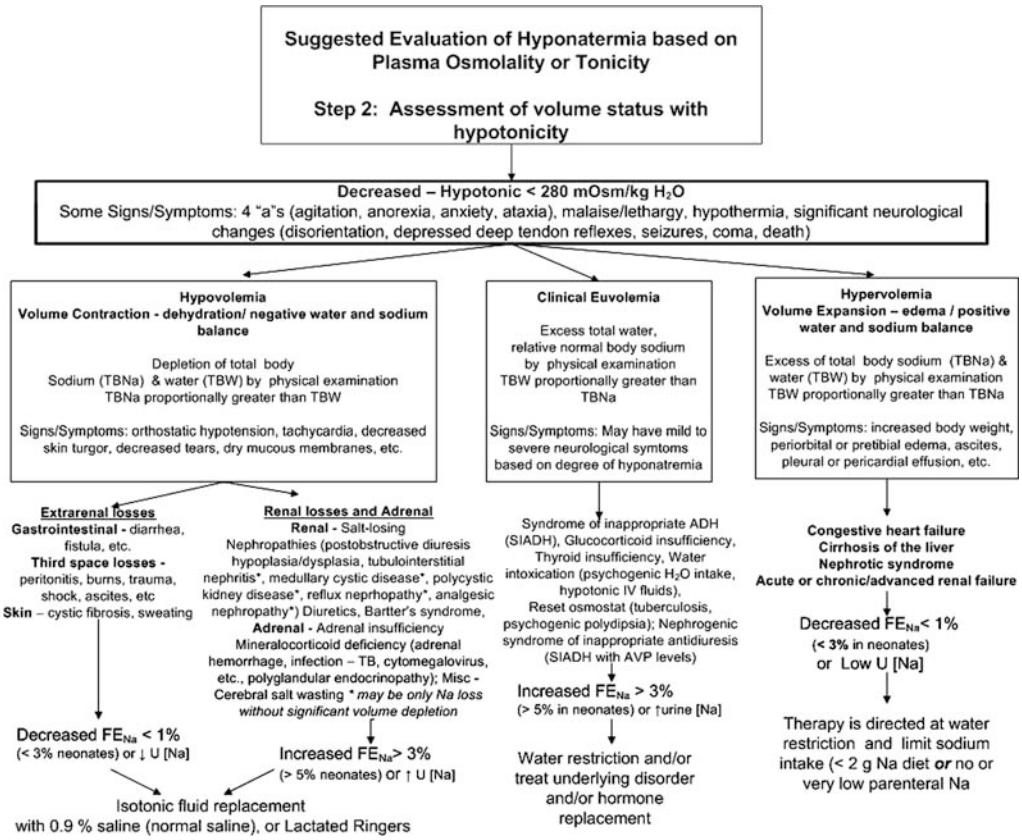

Fig. 6. (Continued)

The signs and symptoms of hyponatremic dehydration are primarily those of dehydration. Table 5 describes the generally accepted clinical signs and symptoms of dehydration as a percent of body weight lost. In general, with hyponatremia (hypo-osmolality) the symptoms/signs are more pronounced than the actual percent of body weight lost. This occurs because the extracellular fluid space is more significantly impacted than in iso-osmolar (normal serum sodium) or hyperosmolar (hypernatremic) dehydration. If the serum sodium falls rapidly (>10 mEq/L per 24 h) or decreases below 125 mEq/L, the patient may experience more significant central nervous system symptoms – more profound lethargy, obtundation, and seizures. Seizures associated with hyponatremia are more refractory to treatment with antiepileptics and requires an increase in serum osmolality or reversal of the hypo-osmolality (hyponatremia).

The approach to hyponatremic dehydration involves treatment of the underlying condition, administration of oral or intravenous therapy to correct the dehydration and direct treatment of the hyponatremia, if necessary (Scenario 1). For mild to moderate dehydration providing oral restoration usually is sufficient unless vomiting is frequent and there is lack of evidence that fluids consumed in a therapeutic fashion (5–15 mL every

Table 5
Severity of Dehydration

Characteristics			
Infants	*Mild – 1–5%*	*Moderate – 6–9%*	*Severe – >10% (=> 15% = shock)*
Older Children	*Mild – 1–3%*	*Moderate – 3–6%*	*Severe – >6% (=> 9% = shock)*
Pulse	Full, normal	Rapid	Rapid, weak
Systolic BP	Normal	Normal, Low	Very Low
Urine output	Decreased	Decreased (<1 mL/kg/h)	Oliguria
Buccal mucosa	Slightly dry	Dry	Parched
Ant fontanel	Normal	Sunken	Markedly sunken
Eyes	Normal	Sunken	Markedly sunken
Skin turgor/capillary refill	Normal	Decreased	Markedly decreased
Skin	Normal	Cool	Cool, mottling, Acrocyanosis
Infants < 12 months of age			

Reproduced with permission from Feld *(41)*.

Table 6
Restoration Oral Solutions

	Restoration (rehydration) oral solutions			
Solution	*Carbohydrate g/L*	*Na mmol/L*	*K mmol/L*	*Osmolality mOsm/kg H_2O*
URS (WHO)	20 (dextrose)	90	25	310
Pedialyte®	25	45	20	250
Rehydralyte	25	75	20	210

5–10 min) would be retained. Tables 6 and 7 describe commonly used oral and intravenous restoration (rehydration) fluids. For moderate dehydration, the World Health Organization recommends oral rehydration solutions. However, many clinicians will initiate intravenous treatment followed by oral therapy. The restorative, intravenous treatment for extracellular volume depletion is isotonic saline (normal saline). For moderate to severe dehydration, an intravenous bolus of 20–40 mL/kg of isotonic saline should be provided over 30–60 min depending on the clinical state (more rapid administration

Table 7
Intravenous Restoration (Rehydration) Solutions

Solution	*Na mmol/L*	*K mmol/L*	*Cl mmol/L*	*Ca mmol/L*	*Lactate mmol/L*
NS (normal saline)	154		154		
LR (Lactated Ringers)	130	4	109	3	28

in patients with hypotension, decreased turgor or tachycardia). The vast majority of patients will improve and the institution of oral fluids can be started. With improvement in extracellular volume depletion in patients with gastroenteritis, gut perfusion improves and oral rehydration is better tolerated *(22)*. This approach will not only restore extracellular volume but allow the serum sodium concentration to approach normal values.

Case Scenario 1. Hyponatremia with Sodium and Water Deficits = Hypovolemia

A 4-month-old infant presents to her pediatrician with a 4–5 day history of low-grade fever (38–38.5°C), numerous watery diarrhea, and decreased activity. Since the child refused to take her usual breast milk volume or solid foods, the mother and grandmother substituted non-carbonated soda (coca-cola, ginger ale, apple juice, or orange juice will have ~550–700 mOsm/kg H_2O with less than 5 mEq/L of sodium) and "sweet" (sugar-added) iced tea. Over the last 12 h there were a few episodes of emesis and there were less wet diapers.

On examination the child was lethargic, dry mucous membranes, no tears, sunken eyeballs, and reduced skin turgor. Vitals signs were the following: blood pressure 74/43 mmHg, temperature of 38°C, respiratory rate of 36/min, and pulse of 175 beats/min. The weight was 6 kg. Weight at the time of her immunization 7 days ago was 6.6 kg. There were no other significant findings.

With the magnitude of dehydration and lethargy, the decision by the clinician was to initiate parenteral fluid replacement rather than oral rehydration therapy. The child was admitted to the hospital with diagnosis of dehydration. On admission the laboratory studies were as follows:

Sodium 124 mEq/L, chloride 94 mEq/L (normal 98–118 mEq/L), potassium 4 mEq/L (normal 4.1–5.3 mEq/L), bicarbonate (or total CO_s) 12 mEq/L (normal 20–28 mEq/L or mmol/L), serum creatinine 0.8 mg/dL (normal ~0.3–0.5 mg/dL), blood urea nitrogen 40 mg/dL, blood glucose 70 mg/dL; complete blood count was normal except for a hematocrit of 38% (normal ~36%);

Urinalysis/chemistries: specific gravity of 1.030, trace protein, no blood or glucose, small ketones; urine creatinine 40 mg/dL and sodium 15 mEq/L.

Fractional excretion of sodium (FE_{Na})

([urine sodium × serum creatinine]/[serum sodium × urine creatinine] × 100%) =
([15 mEq/L × 0.8 mg/dL]/[129 mEq/L × 40 mg/dL]) = 0.23%
Normal values for $FE_{Na} = \sim 1 - 2\%$; decreased renal perfusion
(dehydration, decreased intravascular volume) < 1%

3.2. Assessment

The clinical and laboratory information suggest *hyponatremic dehydration* secondary to extrarenal losses from diarrhea with administration by the family of hypotonic or dilute fluids. The child has lost proportionally more sodium than water or a relatively hypertonic fluid loss. The result is a lower extracellular fluid osmolality compared to the intracellular fluid osmolality. The magnitude of the dehydration is about *10% or moderate to severe*. The pre-illness weight was 6.6 kg with a current weight of 6 kg or a 0.6 kg loss over the last week. Estimated guidelines for vital signs at this age: the normal respiratory rate for children is approximately 36; normal pulse is about 130 (standard deviation is ~45) beats/min; normal blood pressure is approximately 89/54 mmHg. As noted above, the decision by the clinician was to initiate parenteral fluid replacement rather than oral rehydration therapy. The relative contraindications for oral rehydration therapy would include a young infant less than 3–4 months of age, the presence of impending shock or markedly impaired perfusion (increased capillary refill time/decreased skin turgor), inability to consume oral fluids due to intractable vomiting, marked irritability or lethargy/unresponsiveness or the judgment of the clinician.

3.3. Therapeutic Plan

1. Volume deficit, electrolyte calculations: traditionally, treatment has been divided into three phases: an emergent or acute phase – isotonic saline fluid infusion over about 1 h; replacement phase – over 24 h unless there are on-going losses that are not replaced adequately in the first day of treatment; and the maintenance phase – day 2 continuing to home management.

Emergent or acute phase – Over about 1 h (this may need to be prolonged in cases of more significant volume depletion). In order to re-establish circulatory volume to prevent prolonged loss of perfusion to the key organs such as kidney, brain, gastrointestinal tract, the fluid choices would be isotonic (0.9%) saline (normal saline) or another isotonic/hypertonic solution such as 5% albumin, Ringer's lactate, or a plasma preparation. With the availability of isotonic saline, this is the usual fluid choice.

Weight (kg) × fluid bolus of 20 mL/kg over 30–60 min.
(If the patient was in shock the fluid delivery would be a more rapid infusion to prevent organ failure.)
6 kg × 20 mL = 120 mL over 30–60 min. This only replaces 20% of the losses [total losses 600 mL].

Acute – Repletion/Replacement/Restoration Phase – Over 24 h; in this period the daily fluid/electrolyte maintenance requirements and deficit calculation are derived from standard estimates.

1. *Maintenance fluid/electrolyte calculations for 24 h*:
   Calculations based on daily caloric requirements.

Body weight (BW) in kg	*Caloric needs calories/kg BW*	*Water needs mL/100 calories used per day – each mL equals about 1 calorie∗*	*Electrolyte needs mEq/100 calories used per day (alternate method is mEq/kg per day)*	*Calories derived from glucose/dextrose*
3–10	100	100	Sodium = 2.5–3 mEq (or 3 mEq/kg)	5 g/100 calories used
11–20	1000 + 50 calories/kg for each kg above 10	1000 + 50 mL/kg for each kg above 10	Potassium = 2–2.5 mEq (or ∼ 2 mEq/kg)	
>20	1500 + 20 calories/kg for each kg above 20	1500 + 20 mL/kg for each kg above 20		

∗Kidney losses are about 45–75 mL/100 calories expended; sweat losses usually 0; stool losses are about 5–10 mL/100 calories expended, and insensible losses (skin ∼30 mL + respiratory ∼15 mL) are about 45 mL/100 calories expended – 100 mL of total daily water losses = 100 calories expended per day or *1 mL = 1 calorie.*

For this 6.6 kg infant
Maintenance requirements for 24 h

Water	100 mL/kg × 6.6 kg = 660 mL
Sodium	3 mEq/100 mL × 660 mL = 20 mEq
Potassium	2 mEq/100 mL × 660 mL = 13 mEq

2. *Deficit Replacement of water and electrolytes:* In most circumstances the acid–base disorder is a simple metabolic acidosis that does not require bicarbonate replacement unless there is severe tissue/impaired circulatory compromise such as shock (generally 15% dehydration). In general, there is only partial replacement of potassium deficits that are fully corrected over 2–4 days following resumption of oral intake.

There are two approaches to calculate deficits in hyponatremic dehydration.
Approach 1: Use of the table below for 10% dehydration

Type of dehydration∗ based on serum [Na] in mEq/L	*Water (mL/kg)*	*Sodium (mEq/kg)*	*Potassium (mEq/kg)*
Isonatremic [Na] 130–150	100	10	8
Hyponatremic [Na] < 130	100	10–12	8
Hypernatremic [Na] > 150	100		2–2

∗Isonatremic dehydration is the most common accounting for 70–80% of infants and children; hypernatremic dehydration accounts for about 15%, and hyponatremic dehydration for about 5–10% of cases. Adapted from Winter RW: Principles of Pediatric Fluid Therapy, 2nd Ed, Little Brown and Co., Boston, 1982, p 86.

For this 6 kg infant with hyponatremic dehydration at 10%
Deficits for 24 h

Water	Pre-illness weight – Illness weight = 6.6–6 kg = 0.6 kg = 600 mL
Sodium	10 mEq × 6.6 kg = 66 mEq
Potassium	8 mEq × 6.6 kg = 53 mEq

Total First 24 h Requirements

The total amount of maintenance and deficit amounts are given 50% over the first 8 h and the remainder over the next 16 h.

Component of therapy	*Water*	*Sodium*	*Potassium*	*Hourly rate Round number up or down to the nearest 5 increment*
Acute phase	120	18 (154 mEq/L × 0.12 L)	0	Entire amount over 20–60 min
Maintenance	660	20	13	
Deficit	600	66	53	
Ongoing losses of diarrhea or vomiting*				
TOTAL	1280	104	66	
Emergent phase therapy	(120)	(18)		
FINAL THERAPY	1160	86	66	
Hours 1– 8	580	43	33	72 mL/h
Hours 9–24	580	43	33	36 mL/h

- From clinical experience the gastrointestinal losses tend to resolve or decrease significantly following the initiation of parenteral therapy. If it does continue these losses will need to be added to the ongoing loss row.
- For each liter of IV solution there would be 43 mEq/0.58 L = ~75 mEq/L for the 1st 8 h, then about 35 ml/h for the next 16 h.
- *Fluid selection – 5% dextrose + 0.45% isotonic saline + 40 mEq KCl/L*

Generally the final solution potassium concentration is about 30– 40 mEq/L (*it should not exceed 40 mEq/L* without close intensive care monitoring). Some clinicians have recommended using a lower concentration of 20–25 mEq/L since potassium stores will be replenished when the child restart oral feeds. The 5% dextrose provides 50 g of carbohydrate per liter of 50 g × ~4 calories/g = 200 calories. This would be about 20% of the daily caloric intake which is sufficient to prevent protein breakdown over a short treatment period (less than 1 week).

Approach 2: Direct Deficit Calculation

a. Sodium deficit: Fluid deficit (L) × 0.6 (sodium distribution factor) × normal serum sodium concentration = 0.6 L × 0.6 × 140 mEq/L = 50 mEq

b. Additional sodium = (Desired serum sodium – actual serum sodium) × 0.6 L/kg × kg body weight = (135 – 124 mEq/L) × 0.6 L/kg × 6.6 kg = 43.6 mEq*
c. Total sodium deficit = 50 + 43.6 = 94 mEq
d. Total potassium deficit = Fluid deficit (L) × 0.4 (potassium distribution factor) × normal intracellular potassium concentration = 0.6 L × 0.4 × 120 mEq/L = ~ 29 mEq

- In cases of isonatremic dehydration, the calculation is identical except the additional sodium deficit (b. above) is excluded from the calculation.

Total First 24 h Requirements

The maintenance is provided equally over the entire 24 h period, and deficit amounts are given 50% over the first 8 h (emergent phase is usually excluded from the 24 h calculations) and the remainder over the next 16 h.

Component of therapy	*Water*	*Sodium*	*Potassium*	*Hourly rate Round number up or down to the nearest 5 increment*
Acute phase	120	18 (154 mEq/L × 0.12 L)	0	Entire amount over 20–60 min
Maintenance	660	20	13	
Deficit	600	94	29	
Ongoing losses of diarrhea or vomiting*				
TOTAL	1280	132	42	
Emergent phase therapy	(120)	(18)		
FINAL THERAPY	1160	114	42	
Hours 1–8	520 mL	64	20	
	1/3 Maintenance = 220 mL	7	5	
	1/2 Deficit = 300 mL	57	15	
Hours 9–24	740 mL	71	22	
	2/3 Maintenance = 440 mL	14	8	
	1/2 Deficit = 300 mL	57	14	

- For the first 8 h, each liter of IV solution there would be 64 mEq/0.52 L = 123 mEq of sodium per liter = *Fluid selection – 5% dextrose + isotonic saline + 40 mEq KCl/L at a rate of 520 mL/7 h = ~75 mL/h*

- For the remaining 16 h, each liter of IV solution there would be 71 mEq/0.74 L = 95 mEq/L = *Fluid selection – 5% dextrose + 0.45% isotonic saline + 40 mEq KCl/L at a rate of 740 mL/16 h = ~45 mL/h*

The major difference in the two approaches is the provision of isotonic saline rather ½ isotonic saline in the first 8 h. Thereafter, the approaches are nearly identical. As stated above, using a lower intravenous potassium concentration of 20–25 mEq/L is also acceptable.

Signs and symptoms (Fig. 6b) attributable to hyponatremia include anorexia, weakness, lethargy, confusion, seizures, and coma. It seems appropriate here to point out that although hyponatremia is not unusual, the central nervous system (CNS) manifestations are fortunately quite uncommon. What protects the CNS from swelling whenever the osmolality falls (in situations of hyponatremia or in situations of decreasing osmolality when the serum osmolality starts above normal such as the correction of hypernatremia) are at least 5 physiological process recently reviewed by Chesney *(23)*. These processes include diminished ADH secretion unless volume contraction exists simultaneously; reduced movement of brain cell aquaporins (aquaporin-4) thus reducing water movement into brain cells; movement of ionic and nonionic osmolytes out of cells especially in the brain; existing mechanisms that regulate cell volume; and existing mechanisms that sense intracellular osmolality. The interchanges between these processes help keep the brain from swelling when the osmolality falls but they can be overwhelmed when the rate of water ingested by the patient or infused into the patient exceeds these regulatory controls. However, in situations with significant neurological symptoms (seizures, coma) associated with hyponatremia, a more rapid increase in the serum sodium and osmolality needs to be considered. Under those conditions, the use of a hypertonicsaline solution may be necessary. Three percent NaCl (500 mEq NaCl/L – 0.5 mEq/mL) is the preferred solution. The recommended change in serum sodium *should not* exceed 10 mEq/L/24 h (approximately 20 mOsm/kg H_2O/24 h – Na and Cl each contributes 10 mOsm/kg H_2O). To calculate the amount of sodium required to change the serum sodium concentration, the following equation can be used:

$$(\text{Desired [Na]} - \text{Measured [Na]}) \times \text{BW} \times 0.6$$

EX: To raise the serum sodium concentration from 123 to 130 mEq/L for a 10 kg child – (130–123) × 10 kg × 0.6 = 42 mEq

[Na] is the sodium concentration in mEq (or mmol/L). BW is bodyweight in kilograms and 0.6 represents the 60% of BW (except newborns and young neonates) that is water. The entire body water space is used for this calculation since sodium added to the extracellular space raises extracellular (ECF) osmolality drawing water from the intracellular space into the extracellular to equalize osmolality in the body fluid compartments. In most patients, 3% saline correction is only administered until symptoms are abated which usually occurs when the serum sodium is raised by approximately 5–10 mEq (osmolality – 10–20 mOsm/kg H_2O). Ultimately, patients can be corrected near the lower limit of the normal range for serum sodium – approximately 130 mEq/L. An infusion 6 mEq/kg/h (there is 0.5 mEq/mL in the 3% NaCl solution

which implies a delivery volume of 12 mL/kg/h) of a 3% NaCl solution will raise the serum sodium approximately 5 mEq/h.

3.4. Syndrome of Inappropriate Antidiuretic Hormone (SIADH) Release

In the classic description by Bartter and Schwartz, SIADH release includes hyponatremia and hypo-osmolality of the serum, a urine osmolality that is inappropriately greater than serum, normal renal, thyroid and adrenal function and increased urine sodium excretion *(24)*. Another way to view SIADH release is as a *non-physiologic* condition of AVP excess. Thus release of AVP due to hyperosmolality or volume depletion does not represent inappropriate ADH release because both represent physiologic release of AVP. So SIADH cannot occur in a state of negative water balance. SIADH release can be viewed as having three basic causes – (a) ectopic production, (b) exogenous administration of vasopressin, or (c) "abnormal" release of AVP from neurohypophysis. Table 8 lists some of the more common causes of SIADH release.

In SIADH AVP is released despite a normal or low serum osmolality. As noted above, the excess AVP results in a further reduction in serum sodium and osmolality only if the patient continues to consume water in excess to urine and insensible losses (sweating and respiration). Because patients are not volume depleted (in fact they are volume expanded), urinary sodium losses are high. SIADH release is associated with total body water expansion; high urine sodium concentration without evidence of heart, liver, or kidney diseases; and no edema. The diagnostic criteria for SIADH are listed in Table 9.

The treatment of choice for SIADH release is to treat the underlying cause such as a direct therapy for ectopic AVP production, removal of an offending drug agent; or reduction in the dose or lengthening the interval of exogenous AVP administration. Since treatment of the underlying cause may not be possible, fluid restriction is often effective. The total fluid intake should be less than that excreted in urine and from insensible loss (approximately 40% of maintenance calculation). This therapy will raise the serum sodium by 2–3 mEq/L/24 h. Other proposed therapies for a more rapid increase in sodium (osmolality) include (a) doxycycline, a tetracycline derivative that interferes with the action of AVP but cannot be used in young children, (b) fludrocortisone, which increases sodium retention but leads to hypokalemia and hypertension, and (c) AVP antagonists. AVP antagonists appear effective in short-term trials but are untested in children *(25)*. Finally, prevention of hyponatremia by limiting water intake in situations where one might expect SIADH to occur, such as neurological surgery, is warranted.

Case Scenario 2. Patient with Meningitis and SIADH

A 10-month-old infant presents to the pediatric emergency room with a generalized tonic clonic seizure. The child had a fever to 39–40°C for the past 24–36 h, lethargy, vomiting, decreased oral intake, and less wet diapers. The child did not receive Prevnar (pneumococcal vaccine).

On examination the child appeared ill and irritable resisting any movement. Vitals signs were the following: blood pressure 94/58 mmHg; temperature of 39°C, respiratory rate of 40/min, and pulse of 175 beats/min. The weight was 10 kg. There were no

Table 8
Causes of SIADH

Tumors	*Chest disorders*	*CNS disorders*	*Drugs*
Bronchogenic	Infection	Infection/	Adenine
AdenoCarcinoma	TB	inflammatory	Arabinoside
Duodenum	Bacterial	TB meningitis	Amitriptyline
AdenoCarcinoma	Mycoplasma	Bacterial meningitis	Barbiturates
of pancreas	Viral	Encephalitis	Carbamazepine
Ca of ureter	Fungal	Head trauma	Chlorpropamide
Hodgkin's	Positive pressure	Subarachnoid	Clofibrate
Thymoma	ventilation	hemorrhage	Colchicine
Acute leukemia	Dec left atrial	Hypoxia–ischemia	Diuretics
Lymphosarcoma	pressure	Acute psychosis	Fluphenazine
Histiocytic	Pneumothorax	Brain tumor/mass lesions	Isoproterenol
lymphoma	Atelectasis	Miscellaneous	Morphine
	Asthma	Guillain–Barré	Nicotine
	Cystic fibrosis	syndrome	Tricyclics
	Mitral valve	Spinal cord	Vinblastine
	Commissuro-	lesions	Vincristine
	tomy	VA shunt Obstruction/	
	PDA ligation	hydrocephalus	
	Malignancy	Acute intermittent	
		porphyria	
		Cavernous sinus	
		thrombosis	
		Stress/extensive	
		exercise	
		(running a	
		marathon, etc.)	
		Idiopathic	

Ca – cancer; VA – ventriculo-atrial shunt
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focal neurological findings. The impression was meningitis, probably pneumococcal, and hyponatremia.

On admission the laboratory studies were as follows:

Sodium 126 mEq/L, chloride 95 mEq/L (normal 98–118 mEq/L), potassium 4 mEq/L (normal 4.1–5.3 mEq/L), bicarbonate (or total CO_s) was 19 mEq/L (normal 20–28 mEq/L or mmol/L), serum creatinine 0.3 mg/dL (normal ~0.3–0.5 mg/dL), blood urea nitrogen 6 mg/dL, uric acid of 2.4 mg/dL, blood glucose 85 mg/dL; white blood count was elevated at 26,000/mm^3 with 255 immature cells (bands). Lumbar puncture showed a protein concentration of 140 mg/dL, glucose of 30 mg/dL and 2000 leukocytes/mm^3 with more than 80% polymorphonuclear leukocytes. Blood and urine

Table 9
Diagnostic Criteria for SIADH

1)	Hypotonic hyponatremia
2)	Inappropriate urine osmolality compared to plasma osmolality. In patients with an medical condition associated with the occurrence of SIADH, a urine osmolality greater than maximal dilution (75–125 mOsm/L) and a low plasma osmolality is "inappropriate" to state of water balance
3)	Absence of thyroid, adrenal, cardiac, or renal disease
4)	Absence of volume contraction
5)	High urinary sodium concentration (increased FE_{Na})

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culture pending. Serum osmolality 262 mOsm/kg (this was a measured value, although the effective osmolality or tonicity is [2 × serum sodium + glucose/18 = 252 + 5 = 257]).

Urinalysis/chemistries: specific gravity of 1.018 (estimated osmolality = 720 mOsm/kg), no blood, protein, or glucose, small ketones; urine sodium 100 mEq/L, urine creatinine 15 mg/dL; fractional sodium excretion (FE_{Na}) – 1.6%.

3.5. Assessment

The clinical and laboratory information suggest meningitis with SIADH. The presentation of neurological findings with hyponatremia suggests this diagnosis. There is no evidence of volume depletion or expansion/excess of the extracellular fluid compartment. The presence of hyponatremia with a decreased serum osmolality (effective osmolality/tonicity) with a urine osmolality, which is not maximally dilute (<∼125 mOsm/kg) without evidence of renal, thyroid, or adrenal disease is consistent with SIADH. Additional information supports the diagnosis: a low serum uric acid and BUN in the face of clinical euvolemia, elevated FENa (>1%) – inconsistent with hypovolemia when the FE_{Na} should be <1%, lack of evidence of diuretic use, pseudohyponatremia (secondary to increased plasma proteins or lipids) or hypertonic hyponatremia (hyperglycemia or mannitol infusions).

3.6. Therapeutic Plan

SIADH will not resolve until the underlying disease process has significantly improved or resolved (treatment of meningitis will not be discussed). The approach is a three-step process.

1. Acute presentation (neurological manifestations such as coma, encephalopathy, and seizures).
   a. There are two approaches for *symptomatic presentation* that can be used to increase the serum sodium concentration/serum osmolality.
      Increase the serum sodium by 10 mEq/L or the serum osmolality by 20 mOsm/kg (10 mOsm from sodium and 10 mOsm from chloride) with the use of hypertonic or

3% saline (513 mEq/L of sodium or ~0.5 mEq/mL). Regardless of the approach, when the symptoms are improved the 3% infusion should be discontinued.

i. For sodium correction = 10 mEq/kg Na × body weight (BW) × 0.6 (distribution factor for sodium) = *6 BW = # of mEq to be infused.* Since there is 0.5 mEq Na/mL or 1 mEq/2 mL, *the amount of 3% saline to be infused over about 60–90 min would be 2 mL/mEq × 6 mEq × BW = 12 BW.*
ii. The alternative method is to provide 2–4 mL/kg /h to increase the serum sodium by 2–4 mEq/L/h.
iii. Furosemide has been used in a dosage of 0.5 mg/kg up to a maximum of 20 mg given intravenously which may enhance free-water excretion, increase the serum sodium concentration, and avoid ECF volume expansion/excess.

b. If the symptoms are absent or mild – *asymptomatic presentation,* a lower infusion rate of 0.5–2 mL/kg of body weight may be used which will increase the serum sodium from 0.5 to 2 mEq/L/h. Some centers will select to use isotonic saline in asymptomatic patients for patients with a serum sodium above 123–125 mEq/L.
c. In either case, the *serum sodium should be monitored every 2–3 h* to prevent overcorrection of the serum sodium concentration.
d. The *maximum serum sodium correction per 24 h should not exceed 10 mEq/L* (some clinicians limit the increase to 8 mEq/L/24 h).

3.7. Hyperosmolar Hyponatremia

In general, when the serum sodium is found to be below normal, serum osmolality is also below normal. However, as noted above, serum osmolality reflects the concentration of electrolytes (with sodium the major extracellular cation) and other osmolytes such as glucose and urea. The best example of a clinical situation where a low serum sodium is associated with an elevated serum osmolality is diabetes mellitus especially diabetic ketoacidosis.

Illustrative of this point is the following case scenario. A patient with Type 1 diabetes mellitus presents with a 3 day history of fever and abdominal pain. The patient complains of anorexia and nausea. As a result, the patient used less insulin. The patient is febrile, ill appearing, and weak with a respiratory rate of 20 and deep breaths, heart rate of 130 beats/min, and a blood pressure of 84/54 mmHg. Laboratory assessment includes serum sodium 125 mEq/L, potassium 3.8 mEq/L, chloride 90 mEq/L, bicarbonate 10 mEq/L, glucose 900 mg/dL, and urea 20 mg/dL. Urinalysis reveals a specific gravity of 1.035, pH 5, glucose 4+, ketones 3+, protein 1+, and no blood. At first glance the low serum sodium would suggest a low serum osmolality. However, if we use the formula above to estimate osmolality we would find 2× [Na] equals 250 plus glucose of 900/18 equals 50 plus a urea of 20/2.8 equals approximately 7 making the serum osmolality 307 – well above the normal range.

What is the pathophysiology of hyperosmolar hyponatremia? Why is the serum sodium low in this condition? As the extracellular glucose concentration increases in the face of low available insulin, glucose cannot enter cells. The extracellular osmolality increases and provides an osmotic force for water to leave the intracellular space for

the extracellular space. No additional sodium is added to the extracellular space. This results in a decrease in the concentration of sodium in the extracellular space. There may also be some loss of sodium in urine but the major cause of a low serum sodium in diabetic ketoacidosis is the "dilutional effect" of glucose drawing water from the intracellular to extracellular space.

In a recent publication, the above observation was examined in patients treated for diabetic ketoacidosis. The authors found that during initial management when the serum glucose concentration fell and the serum sodium concentration rose [resulting in little change in osmolality] central nervous system morbidity was lower *(26)*. Recognizing that hyponatremia in this setting is associated with hyperosmolality, then managing the hyperosmolality carefully and in concert with serum glucose concentration will improve outcome in this type of clinical scenario.

3.8. Cerebral Salt Wasting

Cerebral salt wasting is far less understood cause of hyponatremia/hypo-osmolality. Cerebral salt wasting occurs within a few days of a central nervous system insult, such as a brain injury or brain surgery. Like SIADH release, hyponatremia and hypo-osmolality are noted. However unlike SIADH release, urine volumes are high (urine sodium concentration are very high), extracellular volume is contracted along with high measurable serum levels of natriuretic peptides (brain and cardiac), and low levels of renin and aldosterone despite volume contraction. Although both SIADH release and cerebral salt wasting can follow brain injury, differentiating the entities is important since one is treated with fluid restriction and in the other (cerebral salt wasting) fluid restriction could be detrimental (Table 10). Cerebral salt wasting should be considered in a child following brain injury or surgery with hyponatremia, when there is evidence of volume

Table 10
Differences Between SIADH and Cerebral Salt Wasting (CSW)

	SIADH	*CSW*
Weight	Increased	Decreased
Extracellular fluid volume	Increased	Decreased
Signs of dehydration	Not present	Present
Hematocrit	Normal	Increased
Serum sodium concentration	Decreased	Decreased
Plasma osmolality	Decreased	Decreased
Urine sodium concentration	Increased	Increased
Urine volume	Decreased	Increased
Plasma [arginine vasopressin]	Increased	Normal or decreased
Serum uric acid concentration	Decreased	Normal
Serum albumin concentration	Normal or decreased	Increased
BUN and serum [creatinine]	Both decreased	Both increased
Treatment	Fluid restriction	Isotonic saline

Modified with permission from Feld *(41)*. Adapted from Chonchol and Berl *(44)*, and Ingelfinger *(45)*.

contraction, very *high* urine output with urinary sodium losses >80 mEq/L and negative sodium balance, suppressed antidiuretic hormone (why this is true is unclear) and low plasma aldosterone concentration (along with low plasma renin activity) *(27)*.

The treatment of cerebral salt wasting includes providing salt and water – often very large sodium infusions while awaiting resolution, which usually occurs in 2–4 weeks. Other potential therapies include providing AVP while administering sodium and the use of fludrocortisone to help enhance sodium reabsorption. Additional potassium may also be needed with fludrocortisone administration.

4. HYPERNATREMIA AND HYPERTONICITY

4.1. Definition and Pathophysiology

Hypernatremia (serum sodium > 150 mEq/L) occurs less frequently than hyponatremia and reflects a net water deficit through water losses or inadequate water replacement. Since sodium is the predominant element in the serum osmolality formula, hypernatremia is always a state of increased effective tonicity or hyperosmolality. Infrequently, it results from a pure sodium gain. Protective mechanisms against the development of hypernatremia include the ability of the kidney to excrete concentrated urine through ADH release and an intact thirst mechanism leading to increased water intake (Fig. 7). Young infants have higher maintenance water requirements related to their large surface area for size and given their dependence on others to provide necessary fluids, they are particularly vulnerable to hypernatremia.

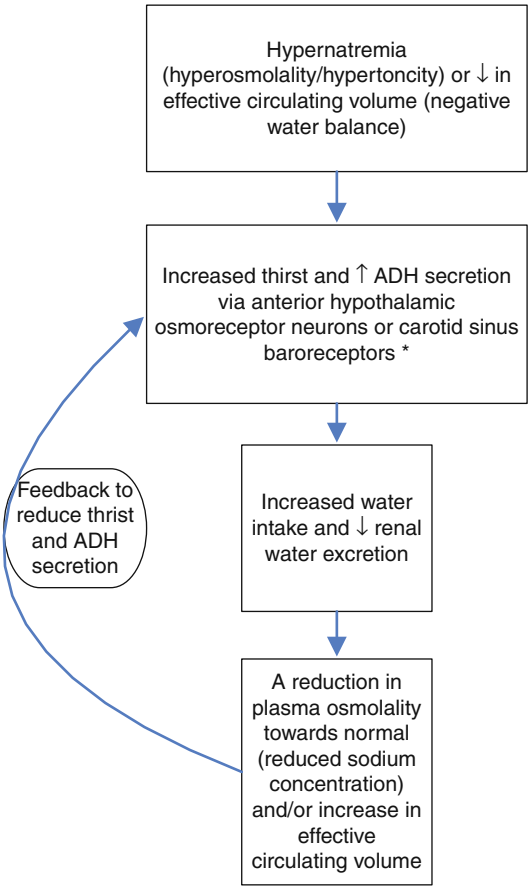
The consequences of hypernatremia are often severe due to cellular dehydration from water shifting from the intracellular to extracellular space in an attempt to reestablish osmotic equilibrium. The brain in infants and young children is particularly susceptible to injury because of its large water content.

4.2. Symptoms

The typical features of dehydration (Table 3) are often lacking due to the preservation of the intravascular volume at the expense of intracellular dehydration (Fig. 8). The signs and symptoms of hypernatremia are typically neurologic in nature from CNS injury and consist of irritability, high-pitched cry, seizures, lethargy, intense thirst, altered mentation and coma *(28, 29)*. In fatal cases, patients may experience intracranial hemorrhages, cranial thrombosis, and infarctions as the brain shrinks away from the meninges and calvarium, placing tension on bridging veins. In those infants and children who survive hypernatremic dehydration, rates of persistent neurologic impairment range from 11 to 15%.

4.3. Diagnosis and Causes

A variety of causes leading to free water losses result in hypernatremia if fluid intake or thirst is impaired (Fig. 9). Hypernatremia may result from either extrarenal water loss or renal water loss. Examples of non-renal water loss include insensible water losses through perspiration or the respiratory tract (hyperventilation, mechanical ventilation).



* The opposite scenario of hypoosmolality (hyponatremia) and/or increased effective circulating volume (positive water balance) would have the opposite effect. There would be decreased oral intake and water intake leading to water excretion to restore plasma osmolality and circulatory volume (water balance).

Fig. 7. Protective mechanisms against the development of hypernatremia.

Historically, acute infectious diarrhea is the most common cause of hypernatremia in children due to hypotonic fluid losses in stool in conjunction with low water intake or vomiting. In addition, osmotic diarrhea from enteral feeds in acutely or chronically ill infants/children or in those with neurologic impairment may also lead to hypernatremia. The presence of fever or elevated ambient temperatures accentuates the water losses (there is a 12% loss per degree increase in body temperature). Hypotonic fluid losses in these situations are accompanied by losses from the extracellular fluid volume compartment adding to the total body sodium as well as water deficit. Urine will have a high osmolality and urinary sodium concentration < 20 mEq/L.

Renal water loss is accompanied by polyuria due to the inability to conserve water appropriately. Polyuria can either result from the excretion of a large solute load, i.e.,

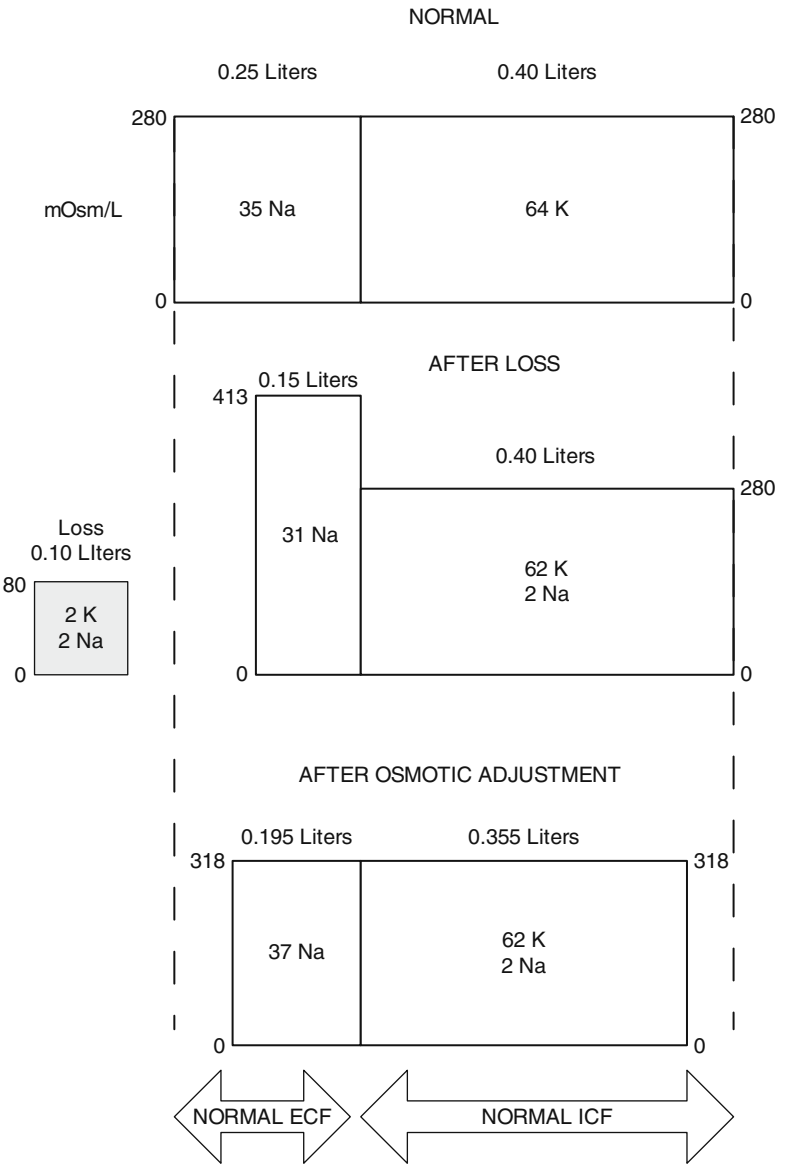


Fig. 8. Effects of a hypotonic loss on volume and composition of body fluids in hypertonic dehydration. The normal situation is altered after the loss followed by an osmolar readjustment with a resulting higher osmolality in both the ECF and ICF. Reproduced with permission from Winters *(39)*.

glucose, or from the excretion of very dilute urine. Evaluating the urine osmolality assists in distinguishing between these two clinical settings (Fig. 10). Osmotic diuresis occurs with poorly controlled diabetes and resulting glucosuria, administration of mannitol for cerebral edema, or excessive urea excretion seen in those receiving hyperalimentation with high protein content or those with a high catabolic rate. Urine osmolality will exceed >300 mOsm/L with a urine sodium concentration >20 mEq/L. In

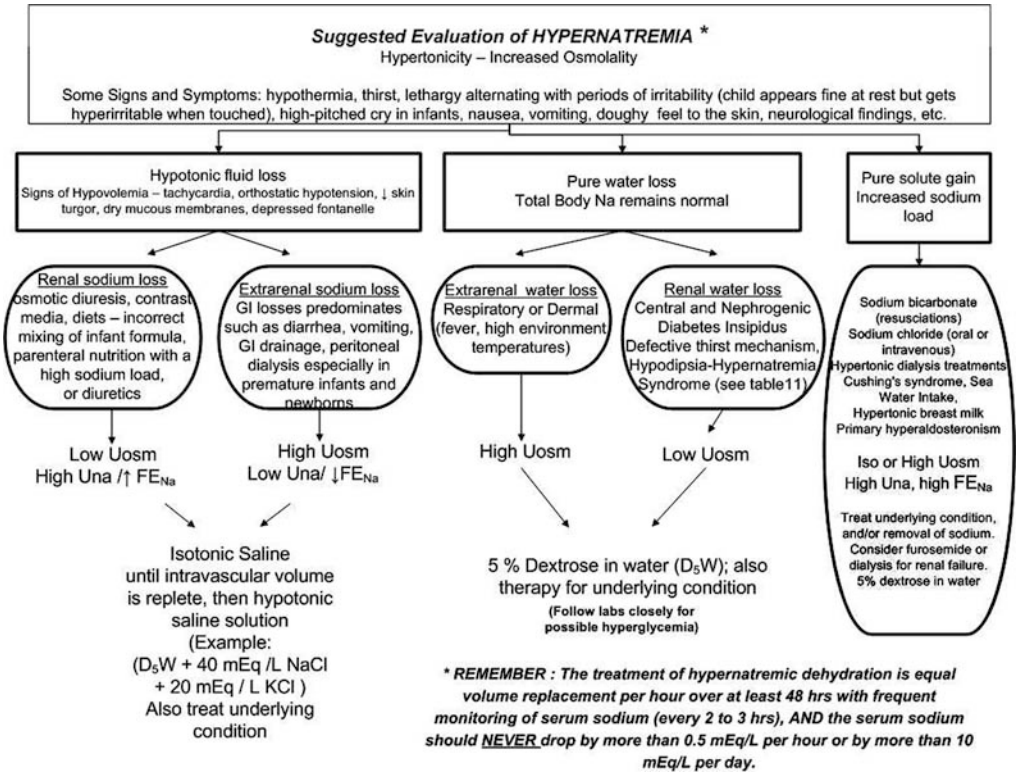


Fig. 9. Suggested evaluation of hypernatremia.

contrast, the polyuria from diabetes insipidus results from the inability of the kidney to excrete concentrated urine due to either deficient vasopressin secretion (central diabetes insipidus) or renal resistance to vasopressin (nephrogenic diabetes insipidus). In contrast to osmotic diuresis, the urine osmolality in diabetes insipidus is <150 mOsm/L and a low sodium concentration in face of an elevated serum sodium levels.

Central diabetes insipidus (DI) may be idiopathic or may result from trauma, infections, neoplasms, intracranial hemorrhages, neurosurgical procedures, or granulomatous conditions as seen with sarcoid and histiocytosis X *(30)* (Table 11). It is characterized by excessive polydipsia and polyuria and the inability to concentrate urine despite a hypovolemic stimulus. A strong preference for cold fluids is a unique feature of this form of polyuria. Diminishing urine volume and increasing urine osmolality in response to exogenous vasopressin confirms the diagnosis of central DI. Intramuscular injections of vasopressin have been replaced by desmopressin delivered either by intranasal or oral routes with the former having greater potency due to absorption *(31)*.

Nephrogenic DI is characterized by the inability to concentrate urine due to unresponsiveness of the distal renal tubule to circulating vasopressin *(32–34)*. There are two different receptors for ADH: the V1 (AVPR1) and V2 (AVPR2) receptors with the latter being located on the X-chromosome (Xq-28). Familial nephrogenic DI that accounts for 90% of all hereditary forms occurs with an X-linked mode of inheritance due to

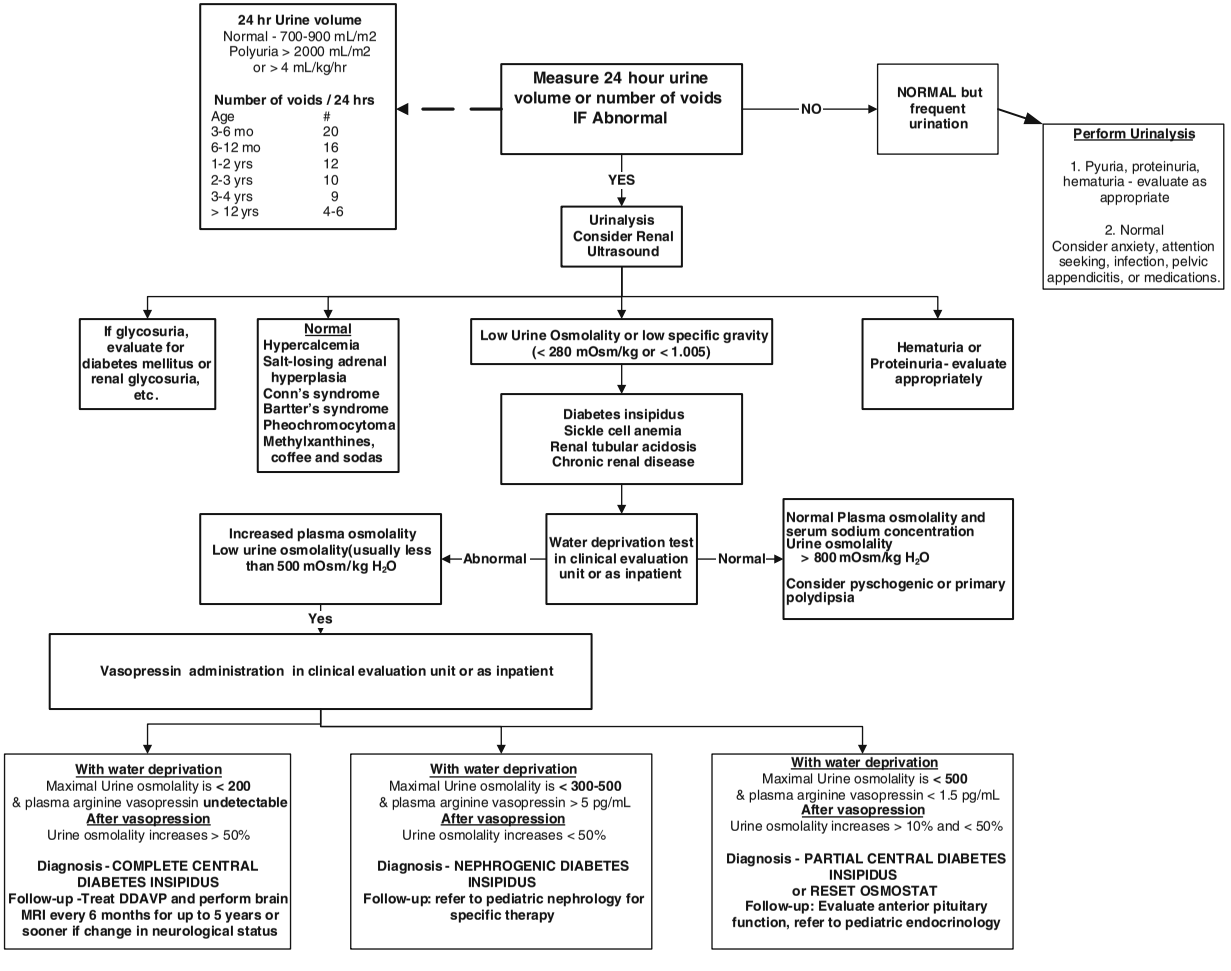


Fig. 10. Suggested evaluation of polyuria. Reproduced with permission from Silverman LA, Endocrinology in Feld *(41, p. 188).*

Table 11
Causes of Central and Nephrogenic Diabetes Insipidus

Central diabetes insipidus	*Nephrogenic diabetes insipidus*
Idiopathic	***Congenital***
Hereditary – autosomal recessive or dominant	ADH receptor – X-linked
Head trauma or skull fracture	Aquaporin defect
Supracellular or intracellular tumors (craniopharyngioma, glioma, pinealoma)	***Renal Disease***
Granulomatous disease – sarcoid, TB,	Obstructive uropathy
Wegener's granulomatosis, syphilis	Renal dysplasia
Histiocytosis	Medullary cystic disease
Guillain–Barré syndrome	Pyelonephritis and reflux nephropathy
Sickle cell disease	Polycystic disease
Cerebral hemorrhage, thrombosis or aneurysm	Uric acid nephropathy
Ischemic encephalopathy – cardiac arrest or shock	***Systemic disease with renal involvement***
Infection – meningitis or encephalitis	Sickle cell disease
Associated with cleft lip and palate	Sarcoidosis
Leukemia or lymphomas	Amyloidosis
Anorexia nervosa	Multiple myeloma
	Sjögren disease
	Medications
	Aminoglycosides
	Amphotericin
	Diuretics
	Isophosphamide
	Lithium
	Methicillin
	Methoxyflurane
	Phenytoin
	Vinblastine
	Miscellaneous
	Hypokalemia
	Hypercalcemia
	Excessive water intake or decreased protein intake

Reproduced with permission from Feld *(41)*.

mutations in the gene *AVPR2* gene, resulting in the loss of function or dysfunction of the V2 receptor. The disease presents in the neonatal period with polyuria, excessive thirst, poor weight gain, unexplained fever, and recurrent episodes of hypernatremic dehydration. A less common form of nephrogenic DI is seen with an aquaporin-2 gene mutation, which encodes the vasopressin-regulated water channel, aquaporin-2 (*AQP2*), in renal collecting ducts. Mutations in the *AQP2* gene may have either an autosomal dominant

or recessive mode of inheritance. Molecular genetic testing is available to distinguish between the two forms of diabetes insipidus. Testing is particularly important where there is a known history of families with X-linked nephrogenic DI and prenatal mutation analysis can be performed. Acquired forms of nephrogenic DI are more common than the hereditary forms. Typically, causes in the pediatric population include chronic kidney disease from cystic kidney disease, renal dysplasia, obstructive uropathies, or chronic pyelonephritis; and with metabolic disturbances as seen with hypokalemia and hypercalcemia.

Unlike central DI, administration of vasopressin will not affect urinary volume or osmolality in situations of nephrogenic DI. Paramount to dealing with a child with NDI is to ensure unrestricted amounts of water. Therapeutic management is aimed at decreasing urinary volume through a low osmolar load (low protein and low sodium diet – 0.7 mEq/kg/day). Additionally, hydrochlorothiazide (1–2 mg/kg/day) acts to block sodium reabsorption in the distal tubule leading to a modest extracellular fluid volume contraction and consequently increased proximal tubular reabsorption of water (Table 12). Long-term monotherapy with hydrochlorothiazide commonly results in hypokalemia. This potentially serious complication can be avoided by the addition of amiloride. Indomethacin (0.75–1.5 mg/kg/d) can provide further reduction of urinary volume. Collectively, these maneuvers diminish free-water clearance by approximately 50%. Early recognition of this condition averts recurrent episodes of hypernatremic dehydration, hyperthermia, and mental retardation, which are well-described complications.

Least commonly observed as a cause of hypernatremia is sodium gain. Administration of hypertonic sodium bicarbonate solutions in situations of cardiopulmonary resuscitation (less common), inadvertent fluid boluses with hypertonic sodium chloride solutions, and seawater drowning can lead to hypernatremia. Boiled skim milk, once commonplace in the treatment of infants with diarrhea, resulted in hypernatremia *(35*, *36)*. Large outbreaks of hypernatremia have been reported in the past due to improper preparation of powdered infant formulations. Urine studies show normal or high osmolality and urinary sodium excretion >20 mEq/L.

4.4. Treatment

The objectives of managing hypernatremia involve identifying the underlying cause, limiting further water loss, and replacing the water deficit. Evaluation of volume status is critical to the therapeutic management of patients with hypernatremia. In addition, ongoing water losses through insensible losses, diarrhea, or polyuria must be taken into account.

When hypernatremia is accompanied by depletion of extracellular volume, restoring this space with isotonic solution (normal saline, lactated Ringer's solution, 5% albumin) takes precedence regardless of the serum sodium concentration. Treatment of hypernatremia requires cautious lowering of serum sodium by no more than 0.5 mEq/L/h or 10 mEq/24 h. In states of hypernatremia, fluid shifts out of brain cells to establish osmotic equilibrium leading to cellular shrinkage. Too rapid of a correction of serum sodium results in osmotic water movement back into brain cells leading to cerebral

Table 12
Suggested Management of Diabetes Insipidus

Central diabetes insipidus
Desmopressin acetate (DDAVP, vasopressin)
- *Oral*
  - ≤12 years: Initial: 0.05 mg once a day or twice daily; titrate to desired response (range 0.1–0.6 mg daily or twice daily)
  - >12 years: 0.05 mg twice daily; titrate to desired response (range 0.1–1.2 mg divided 2–3 times daily)
- *Intranasal solution*
  - Children 3 months to ≤ 12 years: Initial 5 mcg/day divided 1–2 times/day (range 5–30 mcg/day)
  - Children > 12 years: Initial 5–40 mcg/day divided 1–2 times/day
- *Subcutaneous*
  - Children > 12 years: 2–4 mcg/day divided 1–2 times/day

Some of the adverse reactions: Desmopressin acetate: facial flushing, palpitations, headache, dizziness, hyponatremia, nausea, abdominal cramps, rhinitis, nasal congestion, etc.; vasopressin: circumoral pallor, vertigo, water intoxication, abdominal cramps, nausea, flatus, wheezing, diaphoresis, etc.

Nephrogenic Diabetes Insipidus
- Salt restriction ≤ 100 mEq/d (2.3 g sodium)
- Protein restriction ≤ 1 g/kg/day*
- Diuretics
  - Hydrochlorothiazide (HCTZ) 1–2 mg/kg/day divided 1–2 times/day
  - Amiloride 0.2–0.4 mg/kg/day
- Indomethacin 0.75–1.5 mg/kg/day
- Ample fluid via mouth or G-Tube; if necessary intravenous such as 5% dextrose with ¼ (0.225%) isotonic saline to achieve normal or high normal serum sodium concentrations.

Some of the adverse reactions: Hydrochlorothiazide: hypotension, headache, hypokalemia, hyperglycemia, hyperlipidemia, hyperuricemia, metabolic alkalosis, muscle weakness, etc. Amiloride: headache, dizziness, hyperkalemia, hyperchloremic metabolic alkalosis, nauseas, diarrhea, vomiting, abdominal pain, weakness, muscle cramps, etc. Indomethacin: fatigue, hyperkalemia, epigastric or abdominal pain, gastrointestinal bleeding, ulcers, renal failure, etc.

*Caution in infants and young children

edema with the potential complications of seizures, cerebral herniation, and death. Water deficit in hypernatremia can be calculated by the following equation:

$$\text{Water deficit} = \text{TBW} \times ([Na^{+}_{(\text{measured})}] - [Na^{+}_{(\text{desired})}]/[Na^{+}_{(\text{desired})}])$$

where TBW is total body water, $[Na^{+}_{(\text{measured})}]$ is the measured sodium concentration, and $[Na^{+}_{(\text{desired})}]$ is the desired sodium concentration.

Total body water (TBW) is 0.6 × body weight in kilograms.

For example, to estimate the water deficit in a 10 kg infant with a serum sodium of 160, first calculate the total body water of a 10 kg infant, which is estimated at 6 L (TBW = 0.6 × 10 kg). The water deficit can then be calculated as follows:

$$H_2O\,\text{deficit} = \text{TBW} \times (\text{Actual Serum [Na]} - \text{Desired Serum [Na]})/\text{Desired Serum [Na]}$$
$$H_2O\,\text{deficit} = 6\text{L} \times (160 - 145)/145 = 0.6\text{L}$$

REMEMBER, in the first 24 h, fluid calculations should be adjusted to include the replacement of the free-water deficit, ongoing losses plus maintenance requirements.

A patient with hypernatremia due to pure water losses and euvolemia needs replacement with 5% dextrose solution in water (D_5W). If the hypernatremia has developed over a short course of time (<24 h), then rapid correction does not risk the development of cerebral edema. As noted above, if hypernatremia is secondary to central DI, administration of a vasopressin analogue is indicated (Table 12).

Treatment of hypernatremia due to sodium gains is targeted at removal of excess sodium through administration of diuretics such as furosemide or by dialysis if there is associated renal impairment.

Case Scenario 3. Hypernatremia with Sodium and Water Deficits = Hypovolemia

A 6-month-old infant presents to her pediatrician in December with a 4-day history of fever (up to 40°C), along with mild upper respiratory symptoms. On the evening and night prior to presentation, she began to have diarrhea and emesis with cessation of formula and solid foods. The child had a wet diaper this morning.

On examination, the child appeared quiet but became irritable during the exam, mucous membranes were mildly dry, and the skin felt doughy. Vitals signs were the following: blood pressure 85/58 mmHg, temperature of 39°C, respiratory rate of 40/min, and pulse of 175 beats/min. The weight was 7.5 kg. A previous weight about 2 weeks ago was 8.4 kg. There were no other significant findings and the child appears to have good turgor and skin elasticity.

With the magnitude of dehydration, high fever, and irritability, the decision by the clinician was to initiate parenteral fluid replacement rather than oral rehydration therapy. The child was admitted to the hospital with diagnosis of dehydration. On admission, the laboratory studies were as follows:

Sodium 162 mEq/L, chloride 126 mEq/L (normal 98 –118 mEq/L), potassium 4 mEq/L (normal 4.1–5.3 mEq/L), bicarbonate (or total CO_2) was 12 mEq/L (normal 20–28 mEq/L or mmol/L), serum creatinine 1 mg/dL (normal ~0.3–0.5 mg/dL), blood urea nitrogen 29 mg/dL, blood glucose 85 mg/dL; complete blood count was normal without immature cells.

Urinalysis/chemistries: specific gravity of 1.030, no blood, protein or glucose, small ketones; urine creatinine 30 mg/dL and sodium 30 mEq/L;

Fractional excretion of sodium (FE_{Na})

([urine sodium × serum creatinine]/[serum sodium × urine creatinine] × 100%) =
([30 mEq/L × 1 mg/dL]/[161 mEq/L × 30 mg/dL]) = 0.62%
Normal values for $FE_{Na} = \sim 1 - 2\%$;decreased renal perfusion
(dehydration, decreased intravascular volume) < 1%

4.5. Assessment

The clinical and laboratory information suggest *hypernatremic dehydration.* In many cases there is extrarenal losses from diarrhea and vomiting with predisposing factors being young age, fever, curtailment of oral intake and possibly, high solute fluids such as concentrated or improper preparation of formula or other fluid with a high sodium content. The child has lost proportionally more water than sodium or a relatively hypotonic fluid loss. The result is a higher extracellular fluid osmolality, which results in a fluid shift from the intracellular fluid compartment to the extracellular fluid compartment. This provides for better organ perfusion compared to iso- or hyponatremic dehydration of comparable degrees. The child on examination appears better perfused and provides a history of urine output rather than oliguria. This may lead to an underestimate of the degree of dehydration. In this case, the magnitude of the dehydration is about *10% or moderate*. The pre-illness weight was ~8.3 kg with a current weight of 7.5 kg or a 0.8 kg loss over the last week. Estimated guidelines for vital signs at this age: the normal respiratory rate for children is approximately 36; normal pulse is about 130 (standard deviation is ~45) beats/min; normal blood pressure is approximately 89/54 mmHg.

As noted above, the decision by the clinician was to initiate parenteral fluid replacement rather than oral rehydration therapy. The relative contraindications for oral rehydration therapy would include a young infant less than 3–4 months of age, the presence of impending shock or markedly impaired perfusion (increased capillary refill – turgor), inability to consume oral fluids due to intractable vomiting, marked irritability or lethargy/unresponsiveness or the judgment of the clinician.

4.6. Therapeutic Plan

1. Volume deficit, electrolyte calculations: Traditionally, treatment has been divided into three phases: an emergent or acute phase – isotonic saline; replacement phase – over 24 h unless there are on-going losses, which are not replaced adequately in the first day of treatment; and the maintenance phase – day 2 continuing to home management. However, in hypernatremic dehydration, the hyperosmolality results in the formation of idiogenic osmoles (organic and inorganic) such as taurine, glutamate, glutamine, urea, and inositol within the brain cells to assist in maintaining osmotic equilibrium between the two fluid compartments. If the adjustment in osmolality (lowering) occurs to quickly in the extracellular compartment, the osmotic changes will result in the brain cells to swell with resultant neurologic manifestations such as hemorrhage.

Emergent or acute phase – This may need to be prolonged in cases of more significant volume depletion. In some cases of hypernatremic dehydration the emergent phase is not necessary. If there are significant findings of decreased perfusion or hypotension, then therapy would be reasonable. Otherwise the process is for a slow restoration of the serum sodium concentration in order to allow the idiogenic osmols to dissipate over a few days. Similar to other forms of dehydration, if it is necessary to reestablish circulatory volume to prevent prolonged loss of perfusion to the key organs such as kidney, brain, gastrointestinal tract, etc., the fluid choices would be isotonic (0.9%) saline (normal saline) or another isotonic/hypertonic solution such as 5% albumin, Ringer's lactate, or a plasma preparation. With the availability of isotonic saline, this is the usual fluid choice.

Acute – Repletion/Replacement/Restoration Phase – Over 48 h; in this period the daily fluid/electrolyte maintenance requirements and deficit calculation are derived from standard estimates. Even though there are objective clinical signs of dehydration and estimated volume deficits, subjectivity will always to be a factor. For hypernatremic dehydration there are two basic rules – *slow correction and close monitoring*. Slow correction means that the serum sodium concentration should not be reduced by more than about 10 mEq/day. Correct the patient over 48 h for a serum sodium concentration of less than 165 mEq/L; correct the patient over 72 h for values above 165 mEq/L.

1. Maintenance fluid/electrolyte calculations for 24 h: Since the patient has a serum sodium concentration of 161mEq/L, the correction is over 2 days so 2 days of maintenance fluids needs to be added to the total fluid requirements for 48 h.

Calculations based on daily caloric requirements

Body weight (BW) in kg	*Caloric needs Calories/kg BW*	*Water needs mL/100 calories used per day – each mL equals about 1 calorie**	*Electrolyte needs mEq/100 calories used per day (alternate method is mEq/kg/day)*	*Calories derived from glucose/dextrose*
3–10	100	100	Sodium = 2.5–3 mEq (or 3 mEq/kg)	5 g/100 calories used
11–20	1000 + 50 calories/kg for each kg above 10	1000 + 50 mL/kg for each kg above 10	Potassium = 2–2.5 mEq (or ~2 mEq/kg)	
>20	1500 + 20 calories/kg for each kg above 20	1500 + 20 mL/kg for each kg above 20		

*Kidney losses are about 45–75 mL/100 calories expended; sweat losses usually 0; stool losses are about 5–10 mL/100 calories expended, and insensible losses (skin ~30 mL + respiratory ~15 mL) is about 45 mL/100 calories expended – 100 mL of total daily water losses = 100 calories expended per day or *1 mL = 1 calorie.*

For this 8.3 kg infant
Maintenance requirements for 48 h

Water	100 mL/kg × 8.3 kg = 830 mL × 2 days = 1660 mL
Sodium	3 mEq/100 mL × 830 mL = 25 mEq × 2 days = 50 mEq
Potassium	2 mEq/100 mL × 830 mL = 17 mEq × 2 days = 34 mEq

There are two approaches to replace the deficit. Both have a similar intravenous rate and time period (at least 48 h), they only differ in the method of calculation.

Approach 1: Use Table Below

Deficit replacement of water and electrolytes: in most circumstances the acid–base disorder is a simple metabolic acidosis, which does not require bicarbonate replacement unless there is severe tissue/impaired circulatory compromise such as shock (generally 15% dehydration). In general there is only partial replacement of potassium deficits, which are fully corrected over 2–4 days following resumption of oral intake.

Type of dehydration based on serum [Na] in mEq/L*	*Water (mL/kg)*	*Sodium (mEq/kg)*	*Potassium (mEq/kg)*
Isonatremic [Na] 130–150	120	10	8
Hyponatremic [Na] < 130	100	10–12	8
Hypernatremic [Na] > 150	100	4	2

*Isonatremic dehydration is the most common accounting for 70–80% of infants and children; hypernatremic dehydration accounts for about 15%, and hyponatremic dehydration for about 5–10% of cases. Adapted from Winter RW: Principles of Pediatric Fluid Therapy, 2nd Ed, Little Brown and Co., Boston, 1982, p 86.

For this 8.3 kg infant with hypernatremic dehydration at 10%

Deficits

Water	Pre-illness weight – Illness weight = 8.3 – 7.5 kg = 0.8 kg = 800 mL
Sodium	4 mEq × 8.3 kg = 33 mEq
Potassium	2 mEq × 8.3 kg = 17 mEq

2. Total 48 h Requirements

The total amount of maintenance (2 days) and deficit amounts are given equally over the 48 h period with frequent monitoring of electrolytes in order to adjust the intravenous rate or sodium concentration based on the rate of decline of the serum sodium concentration.

$$\text{Fluid selection} - \ 5\% \text{ dextrose } + 1/4 \textit{ isotonic saline}(\sim 30 - 40 \text{ mEq/L of Na}) + 20 \text{ mEq KCl/L at } 50 \text{ mL/h given equally over } 48 \text{ h}.$$

Generally the final solution potassium concentration is about 20 mEq/L, it should not exceed 40 mEq/L without close intensive care monitoring. The 5% dextrose provides 50 g of carbohydrate per liter of 50 g × ~4 calories/g = 200 calories. This would be about 20% of the daily caloric intake, which is sufficient to prevent protein breakdown over a short treatment period (less than one week).

Component of therapy	*Water*	*Sodium*	*Potassium*	*Hourly rate Round number up or down to the nearest 5 increment*
Maintenance – 2 days	1660	50	34	
Deficit	800	33	17	
Ongoing losses of diarrhea or vomiting*				
TOTAL	2460	83	51	50 mL/hr

* From clinical experience the gastrointestinal losses tend to resolve or decrease significantly following the initiation of parenteral therapy. If it does continue, these losses will need to be added to the ongoing loss row.

Approach 2: Use a Free-Water Deficit Calculation
Total 48 h Requirements

The total amount of maintenance (2 days) and deficit amounts are given equally over the 48 h period with frequent monitoring of electrolytes in order to adjust the intravenous rate or sodium concentration based on the rate of decline of the serum sodium concentration.

$$\text{Water deficit} - 4\,\text{mL/kg} \times \text{body weight} \times (\text{Ideal Serum [Sodium]} - \text{Actual serum [sodium]})$$

Component of therapy	*Water*	*Sodium*	*Potassium*	*Hourly rate Round number up or down to the nearest 5 increment*
Maintenance – 2 days	1660	50	34	
Water deficit 4 mL × 8.3 kg × (162–145 mEq/L)	564			
Sodium deficit 0.56 L × 0.6 × 140 mEq/L		47		
Potassium deficit 0.56 L × 0.4 × 120 mEq/L			26	
Ongoing losses of diarrhea or vomiting*				
TOTAL	2224	97	60	46 mL/h

Table 13
Treatment Summary for Dehydration

Body weight (kg)	*Water needs mL/100 calories used per day – each mL equals about one calorie**	*Sodium need mEq/100 calories used per day (alternate method is mEq/kg/day)*	*Potassium needs mEq/100 calories used per day (alternate method is mEq/kg/day)*
A. Maintenance			
3–10	100 mL/kg	Sodium = 2.5–3 mEq (or	Potassium = 2–2.5 mEq (or
11–20	1000 + 50 mL/kg for each kg above 10	3 mEq/kg)	~2 mEq/kg)
>20	1500 + 20 mL/kg for each kg above 20		
B. Type of Dehydration based on serum [Na] in mEq/L Calculations do not include an emergent therapy phase			
	Water (mL/kg)	Sodium (mEq/kg)	Potassium (mEq/kg)
B.1. Isonatremic [Na] 130–150 mEq/L – Provide maintenance needs plus one of the following			
Approach 1	100 mL/kg	10 mEq/kg	8 mEq/kg
Approach 2	Based on % dehydration Dry weight × %	Fluid deficit (L) × 0.6 × 135 mEq/L	Fluid deficit (L) × 0.4 × 120 mEq/L
Fluid selection: 5% dextrose +1/3 (0.33%) isotonic saline + 40 mEq KCl /L OR *5% dextrose + 1/2 (0.45%) isotonic saline + 40 mEq KCl/L* *Rate: ½ of the maintenance and ½ fluid deficit delivered over 8 h and the remainder over the next 16 h*			
B.2. Hyponatremic [Na] < 130 mEq/L – Maintenance plus one of the following			
Approach 1	100–120 mL/kg	10–12 mEq/kg	8 mEq/kg
Fluid selection – 5% dextrose + 0.45% isotonic saline + 40 mEq KCl /L			
Approach 2	Based on % dehydration Dry Weight × %	Fluid deficit (L) × 0.6 × 140 mEq/L	Fluid deficit (L) × 0.4 × 120 mEq/L

PLUS sodium deficit – (desired sodium (135) – actual sodium) × 0.6 L/kg × BW kg

First 8 h, Fluid selection: 5% dextrose + isotonic saline + 40 mEq KCl/L; In both approaches the Fluid Selection for the next 16 hrs (9–24 h) is 5% dextrose + ½ isotonic saline + 40 mEq KCl/L

B.3. Hypernatremic [Na] > 150 mEq/L

Approach 1	100 mL/kg	4 mEq/L	2 mEq/L

Fluid selection: 5% dextrose + ¼ isotonic saline (~30–40 mEq/L of Na) + 20 mEq KCl/L
1st 24 h: 24 h of Maintenance + ½ deficit
2nd 24 h: 24 h of Maintenance + ½ deficit with close monitoring of serum sodium every 2–3 h.

Approach 2	4 mL × (actual – desired mEq Na/L) × BW kg	Fluid deficit (L) × 0.6 × 140 mEq/L	Fluid deficit (L) × 0.4 × 120 mEq/L

1st 24 h: 24 h of Maintenance + ½ deficit
2nd 24 h: 24 h of Maintenance + ½ deficit
Fluid selection – 5% dextrose + 1/4 isotonic saline (~40 mEq/L of Na) + 30 mEq KCl/L
(some recommend using 5 dextrose with ½ isotonic saline + potassium)

4 mL/kg is derived from the relationship as follows: How much water is required to reduce 1 mEq of sodium?

$$\begin{gathered} 145\,\text{mEq}/1000\,\text{mL} = 145 + \text{X}/1000\text{mL} = 6.9\,\text{mEq}; 6.9\,\text{mEq} \\ \times 0.6\,(\text{distribution factor}) = 4\,\text{mL} \end{gathered} \tag{37}$$

$$\text{Water Deficit} - 4\,\text{mL} \times (162 - 145\,\text{mEq Na/L}) \times 8.3\,\text{kg} = 560\,\text{mL}$$

SodiumDeficit: $0.56\text{L} \times 0.6 \times 140\,\text{mEq/L}$

PotassiumDeficit: $0.56\text{L} \times 0.4(\text{distributionfactorforpotassium}) \times 120\,\text{mEq/L}$ (intracellular[K])

- From clinical experience the gastrointestinal losses tend to resolve or decrease significantly following the initiation of parenteral therapy. If it does continue these losses will need to be added to the ongoing loss row.
- 1st 24 h: 24 h of Maintenance + ½ deficit = 880 mL + 282 mL = 1162 mL; Na = 25 mEq (maintenance) + 24 (deficit) = 49 mEq; K = 17 (maintenance) + 13 (deficit) = 30 mEq.
- 2nd 24 h: 24 h of Maintenance + ½ deficit = 880 mL + 282 mL = 1162 mL; Na = 25 mEq (maintenance) + 23 (deficit) = 48 mEq; K = 17 (maintenance) + 13 (deficit) = 30 mEq.
- Fluid selection – 5% dextrose + ¼ isotonic saline (~40 mEq/L of Na) + 30 mEq KCl /L at 46 mL.

In both approaches, it is strongly suggested to monitor serum sodium concentration every 2–3 h and adjust the fluid rate and sodium concentration as appropriate. In cases of severe hypernatremic dehydration with marked circulatory compromise or shock, it is reasonable to provide 5% dextrose with ½ isotonic saline without potassium for the first 24 h. If circulatory status is restored, then a lower intravenous concentration of sodium can be used and potassium can be added, if appropriate, to the solution *(37)*.

Two other viewpoints that are in the literature: Laurence Finberg has suggested the use of 2.5% dextrose with 25 mEq/L of sodium plus 40 mEq/L of KCl and one ampule of 10% calcium gluconate per 500 mL of intravenous fluid to prevent hypocalcemia. The rate would be about 6–7 mL/kg/h.

Some have suggested using a higher sodium concentration – 0.45% isotonic saline or even isotonic saline to restore extracellular fluid volume then moving to a lower sodium containing solution to restore the water deficit. This approach may also reduce the possibility of dropping the serum sodium too quickly and preventing neurological problems.

Table 13 provides a summary of the treatment for Isonatremic, hyponatremic, and hypernatremic dehydration.

REFERENCES

1. Gamble JL. Chemical Anatomy Physiology and Pathology of Extracellular Fluid. Harvard University Press, 1950.
2. Winters RW. The Body Fluids in Pediatrics. Little, Brown & Co, Boston, 1973, p. 102.
3. Verney EB. The antidiuretic hormone and the factors which determine its release. Proc R Soc London 135 (Series B) (1947) 25.

4. Robertson GL. Antidiuretic hormone: Normal and disordered function. Endocrinol Metab Clin N Am (2001) 30:671.
5. Gauer OH, Henry JP. Circulatory basis of fluid volume control. Physiol Rev (1963) 43:423.
6. Baylis PH, Robertson GL. Arginine vasopressin response to insulin-induced hypoglycemia in man. J Clin Endocrinol Metab (1981) 53:935.
7. Robben JH, Knoers NVAM, Deen PMT. Cell biological aspects of vasopressin type-2 receptor and aquaporin-2 water channel in nephrogenic diabetes insipidus. Am J Physiol Renal Physiol (2006) 291:F257–F270.
8. Borgnia M, Nielsen S, Engel A, Agre P. Cellular and molecular biology of aquaporin water channels. Annu Rev Biochem (1999) 68:425.
9. Kim SW, Gresz V, Rojek A, et al. Decreased expression of AQP2 and AQP4 water channels and Na, K, ATPase in kidney collecting duct in AQP3 null mice. Biol Cell (2005) 97:765–778.
10. Ecelbarger CA, Kim GH, Wang W, et al. Vasopressin mediated regulation of epithelial sodium channel abundance in the rat kidney. Am J Physiol Renal Physiol (2000) 279:F46–F53.
11. Sands JM. Molecular mechanisms of urate transport. J Membr Biol (2003) 191:149–163.
12. Robillard JE, Matson JR, Sessions C, et al. The dynamics of vasopressin release and blood volume regulation during fetal hemorrhage in the lamb fetus. Pediatr Res (1979) 13:606.
13. Popjavuori M, Raivio KO. The effects of acute and chronic perinatal stress on plasma vasopressin concentrations and renin activity at birth. Biol Neonate (1985) 47:259.
14. Wiriyathian S, Rosenfeld CR, Arant BS, et al. Urinary arginine vasopressin: Pattern of excretion in the neonatal period. Pediatr Res (1986) 20:103.
15. Vander A. Control of sodium and water excretion: Regulation of extracellular volume and osmolality. In: Renal Physiology, 3rd edition. McGraw-Hill Inc., New York: 1985, pp. 136–4016.
16. Keoppen BM, Stanton BA. Regulation of body fluid osmolality: Regulation of water balance. In: Renal Physiology, 2nd edition. Mosby-Year Book Inc., St. Louis: 1997, pp. 90–91.
17. Finberg L, Kravath RE, Hellerstein S. Composition – Chemical Anatomy. In: Water and Electrolytes in Pediatrics: Physiology, Pathology, and Treatment, 2nd edition. 2WB Saunders Company, Philadelphia: 1993, pp. 11–16.
18. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics (1957) 19:823–832.
19. Moritz ML, Ayus JC. Prevention of hospital acquired hyponatremia, a case for using isotonic saline. Pediatrics (2003) 111:227–230.
20. Friedman AL, Ray PE. Maintenance fluid therapy. What it is and what it is not. Pediatric Nephrol (2008) 23:677–680.
21. Verbalis JG, Goldsmith SR, Greenberg A, et al. Hyponatremia treatment guideline 2007: Expert Panel Recommendations. Am J Med (2007) 120:S1–S21.
22. Hirschorn N. The treatment of acute diarrhea in children: an historical and physiological perspective. Am J Clin Nutr (1980) 33:637.
23. Chesney RW. The role of the kidney in protecting the brain against cerebral edema and neuronal cell swelling. J Pediatr (2008) 152:4–6.
24. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion if antidiuretic hormone. Am J Med (1967) 42:790.
25. Chen S, Jalandhara N, Batlle D. Evaluation and management of hyponatremia: an emerging role for vasopressin receptor antagonists. Nature Clin Pract (2007) 3:82.
26. Hoorn EJ, Carlotti APC, Costa LAA, McMahon B, et al. Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. J Pediatr (2007) 150:467–473.
27. Kappy MS, Ganong CA. Cerebral salt wasting in children: The role of atrial natriuretic hormone. Adv Pediatr (1996) 43:271–307.
28. Finberg L. Hypernatremic (hypertonic) dehydration in infants. N Eng J Med (1973) 289:196–198.
29. Finberg L. Pathogenesis of the lesion in the central nervous system in hypernatremic states: I. Clinical observations of infants. Pediatrics (1959) 23:40–45.
30. Greger NG, Kirkland RT, Clayton GW, et al. Central Diabetes Insipidus: 22 years' experience. AJDC (1986) 140:551–554.

31. Richardson DW, Robinson AG. Desmopressin. Ann Intern Med (1985) 103:228.
32. Knoers N, Monnens LAH. Nephrogenic diabetes insipidus: clinical symptoms, pathogenesis, genetics and treatment. Pediatr Nephrol (1992) 6:476–482.
33. Deen PMT, Knoers N. Vasopressin type-2 receptor and aquaporin-2 water channel mutants in nephrogenic diabetes insipidus. Am J Med Sci (1998) 316:300–309.
34. Kirchlechner V, Koller DY, Seidl R, et al. Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. Arch Dis Child (1999) 80:548–552.
35. Anand SK, Sandborg C, Robinson RG, et al. Neonatal hypernatremia associated with elevated sodium concentration of breast milk. J Peds (1980) 96:66–68.
36. Colle E, Ayoub E, Raile R. Hypertonic dehydration (hypernatremia): The role of feedings high in solutes. Pediatrics (1958) 22:5.
37. Hochman HI, Grodin MA, Crone RK. Dehydration, diabetic ketoacidosis and shock in the pediatric patient. Pediatric Clin NA (1979) 26:803–826.
38. Czernichow P, Friedman AL, Kappy M. Posterior Pituitary and Water Metabolism. In: Principles and Practice of Pediatric Endocrinology, Kappy M, Allen D, Geffner M (eds.), 1st edition, Charles C. Thomas Co., Springfield, IL: 2005, pp. 815–856.
39. Winters RW. Principles of Fluid Therapy. Abbott Laboratories, North Chicago: 1970.
40. Feld LG. Hyponatremia in infants and children: A practical approach. J Nephrology (1996) 9:5.
41. Feld LG. Nephrology. In: Fast Facts in Pediatrics, 1st edition, Feld LG, Meltzer AJ (eds.), Elsevier, Amsterdam, 2006, p. 451.
42. Cogan MG. Fluid & Electrolytes: Physiology & Pathophysiology. Appleton & Lange, Norwalk: 1991, p. 85.
43. Robertson GL. Thirst and Vasopressin. In: The Kidney Physiology and Pathophysiology, 4th edition, Alpern RJ, Hebert SC (eds.), 1985, pp. 1131–1135.
44. Chonchol M, Berl M. Hyponatremia. In: Acid–Base and Electrolyte Disorders, DuBose TD, Hamm LL (eds.), WB Saunders, Philadelphia: 2002, p. 233.
45. Ingelfinger JR. Diabetes Insipidus, SIADH and Cerebral Salt Wasting. In: Current Pediatric Therapy, Burg F, Ingelfinger JR, Polin R, Gershon AA (eds.), WB Saunders, Philadelphia: 2006, p. 1002.