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# 2 Disorders of Sodium Homeostasis

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## Key Points

1. Renal sodium excretion is the primary determinant of sodium homeostasis.
2. Changes in sodium concentration in extracellular fluid (ECF) are associated with disorders of water balance.
3. Hypovolemia refers to losses of salt and water from the ECF, whereas dehydration is defined as primarily water loss from ECF.
4. Hypervolemia results when fluid accumulates in the ECF at a higher rate than the output due to either sodium and water retention or abnormal sodium and water intake.
5. Activation of sympathetic nervous system, renin–angiotensin–aldosterone, and epithelial sodium channel contributes to renal sodium and water retention.

**Key Words:** Isovolemia; atrial natriuretic hormone; hypovolemia; hypervolemia; Starling’s forces; cirrhosis; congestive heart failure; renin–angiotensin system; nephrotic syndrome; dehydration

## 1. SODIUM REGULATION IN ISOVOLEMIA

Regulation of sodium and water homeostasis is one of the major functions of the kidney (1, 2). Sodium balance is the result of sodium intake, extra-renal sodium loss, and renal sodium excretion. Renal sodium excretion is the primary determinant of sodium homeostasis (2). Since sodium is a main cation of extracellular fluid (ECF), changes in sodium concentration are linked to changes in ECF volume (3) and are associated with disorders of water balance. The extracellular fluid compartment is subdivided into the intravascular and interstitial compartment, commonly referred to as a “third space.” The chemical composition and the interdependence of fluid compartments were discussed in Chapter 1: Water Homeostasis. Estimates of intravascular volume distribution indicate that 85% of blood circulates on the low pressure (venous side of the circulation) and an approximately 15% of blood is on the high pressure (arterial circulation) (4).

Although the term “effective circulatory volume” has been used in medical literature for decades, its definition remains unclear (4). Peters (5) referred to “effective blood

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volume” as that portion of the total circulating volume that is “somehow sensed,” and thus responds to too little or too much volume. In an underfilled body fluid compartment, there must be signals, coming from extra-renal locations promoting retention of sodium and water by the kidney, in response to a decreased effective blood volume (6). Since the kidney can normally regulate sodium and water (5, 7), if heart failure or cirrhosis is reversed (transplantation), the afferent signal for sodium and water retention in patients with heart failure and cirrhosis must come from extra-renal sites (6). Although low cardiac output was proposed to explain low effective circulatory volume (8), sodium and water retention still occur in high-output heart failure and in pregnant women, who also have an increased cardiac output (3).

The “underfilling hypothesis” was subsequently proposed (9). If 85% of the total blood volume is on the venous circulation (low pressure) and 15% of the total blood volume resides on the arterial circulation (high pressure), then an increase in total blood volume and an “underfilling” of the arterial circulation can occur, by an expansion of the venous compartment (10). Underfilling may also occur with low cardiac output (heart failure) or arterial vasodilatation (pregnancy, cirrhosis, sepsis). When arterial underfilling is the result of arterial dilatation or low cardiac output, the neurohumoral axis is stimulated and renal sodium and water retention occurs to maintain perfusion to vital organs (3). These mechanisms include activation of the renin–angiotensin–aldosterone system, activation of the sympathetic system, and nonosmotic vasopressin release (3), which initially maintain perfusion, although in patients with advanced edematous states, sodium and water retention leads to pulmonary edema and ascites (6). The high-pressure (arterial) circulation response to increase pressure and stretch is mediated by baroreceptors located in the aortic arch, left ventricle, carotid sinus, and juxtaglomerular apparatus (glomerular afferent arteriole) (6). Baroreceptors signal the appropriate areas in the brain leading to the release of arginine vasopressin (AVP) (6). In patients with congestive heart failure, who have hyponatremia and low osmolality along with detectable serum concentrations of AVP, there is a nonosmotic AVP release similar to the phenomenon in cirrhotic patients (11). When arterial “underfilling” is detected, secondary to low-output heart failure (arterial baroreceptor stretch) or arterial vasodilatation (high-output heart failure, cirrhosis), an increase in sympathetic tone and nonosmotic AVP release occurs (6). The increase in sympathetic tone stimulates the renin–angiotensin–aldosterone system (RAAS) through renal  $\beta$ -adrenergic stimulation and by an increase in sympathetic tone and RAAS to increase systemic vascular resistance compensating for arterial “underfilling” (6). The nonosmotic release of AVP stimulates the V1a receptors (V1aR) on vascular smooth muscle, which contributes to the compensatory response to arterial “underfilling” (6). The AVP receptors V2 on the collecting tubules, when stimulated, activate the adenylate cyclase and cyclic AMP, increasing the number of aquaporin-2 water channels in the apical membrane of the collective tubules, leading to an increased water reabsorption responsible for hyponatremia in patients with edematous states (6).

Low-pressure receptors located in the atria, in response to an increase in transmural atrial pressure, inhibit the release of AVP, decrease vascular resistance in the kidney, and increase water and sodium excretion (3). Atrial stretch associated with heart failure results in secretion of atrial natriuretic peptides such as C-terminal-ANP,

N-terminal-ANP, B-type natriuretic peptide (BNP). This increase in the synthesis of atrial natriuretic hormones in heart failure patients results in less retention of water, thereby decreasing edema by inhibition of RAAS and sodium absorption (3). Although in heart failure atrial pressure is increased, sodium and water retention occurs (3). This may be explained by “underfilling” that activates arterial stretch receptors, which in turn activate the sympathetic system and the renin–angiotensin–aldosterone system (RAAS) as well as nonosmotic vasopressin release, dominating the response, over the atrial pressure receptor reflex in patients with heart failure (3).

In the first trimester of pregnancy, the systemic arterial vasodilatation and decrease in blood pressure are associated with increased cardiac output (3). When arterial “underfilling” is detected, RAAS is activated, resulting in water and sodium retention and nonosmotic release of AVP (3). In this scenario, there is an increase in renal blood flow and glomerular filtration rate, which does not occur in patients with heart failure or cirrhosis (3). Estrogen upregulates endothelial nitric oxide synthase (eNOS), increasing nitric oxide, which may be also responsible for the systemic and renal vasodilatation observed in pregnancy (3).

ECF volume and total body sodium are assessed by a thorough history, physical examination and measurement of serum sodium concentration and fractional urinary sodium excretion (12). If not corrected, sodium loss causes volume depletion (hypovolemia) and increased sodium intake leads to volume expansion (hypervolemia).

## 2. HYPOVOLEMIA

### 2.1. Definition and Pathophysiology

Hypovolemia occurs when the loss of fluid from the ECF exceeds the ability to replenish the deficit by enteral or parenteral sources. Decrease in effective circulating volume occurs due to losses from the gastrointestinal tract, kidneys, skin, respiratory system, or third-space sequestration (Table 1).

**Table 1**  
**Sources of ECF Volume Loss**

|                           |   |
|---------------------------|---|
| Gastrointestinal losses   | Vomiting, diarrhea, prolonged nasogastric suction, fistulas, ostomies, bleeding   |
| Renal losses              | Diuretics, salt wasting nephropathies, osmotic diuresis, adrenal insufficiency, central or nephrogenic diabetes insipidus |
| Skin losses               | Burns, extensive skin lesions, sweat losses in endurance exercise   |
| Respiratory losses        | Large pleural effusions, bronchorrhea   |
| Third space sequestration | Crush injuries, intestinal obstruction, acute pancreatitis, bleeding, sepsis, anaphylaxis                                 |

Volume depletion due to gastrointestinal losses generally leads to a hypotonic state. In addition, when replacement is hypotonic, this leads to hyponatremia and hypotonicity. The volume depletion stimulates the baroreceptors releasing AVP leading to fluid retention with an exacerbation of the hyponatremia. Prolonged loss of stomach contents results in loss of hydrogen and chloride ions resulting in a state of metabolic alkalosis (see Chapter 9). Since bicarbonaturia obligates excretion of sodium, patients with prolonged vomiting have a urine sodium concentration that may be paradoxically elevated. This is true at the start of the metabolic alkalosis but if losses and volume depletion persist patients have a paradoxical aciduria and they do not have ongoing bicarbonate losses, hence increasing serum bicarbonates. In this situation urine chloride concentration or fractional excretion of chloride is a more reliable marker of volume depletion. Hypokalemia is also commonly observed with vomiting and diarrhea (2).

Diuretics are known to cause hyponatremia. Thiazide diuretics act at the distal nephron by inhibiting sodium chloride reabsorption and are more likely to cause hyponatremia than the loop diuretics (73% vs. 8%; thiazides compared to furosemide) (3).

Salt wasting nephropathy is frequently found in children with tubular and interstitial diseases, such as medullary cystic kidney disease, obstructive uropathy, hypoplastic kidneys, and in patients with renal insufficiency. Salt wasting results from tubular epithelium injury causing aldosterone resistance, osmotic diuresis due to increased urea load on the remaining functioning nephrons, and an inability to “shut off” natriuretic forces (i.e., atrial natriuretic peptides) when sodium intake is reduced (13, 14).

Primary adrenal insufficiency leads to renal sodium wasting, hypovolemia, and hyperkalemia associated with an increased urine sodium concentration (Chapter 14). When patients ingest hypotonic fluids or are treated with hypotonic fluids intravenously, severe hyponatremia may develop (6).

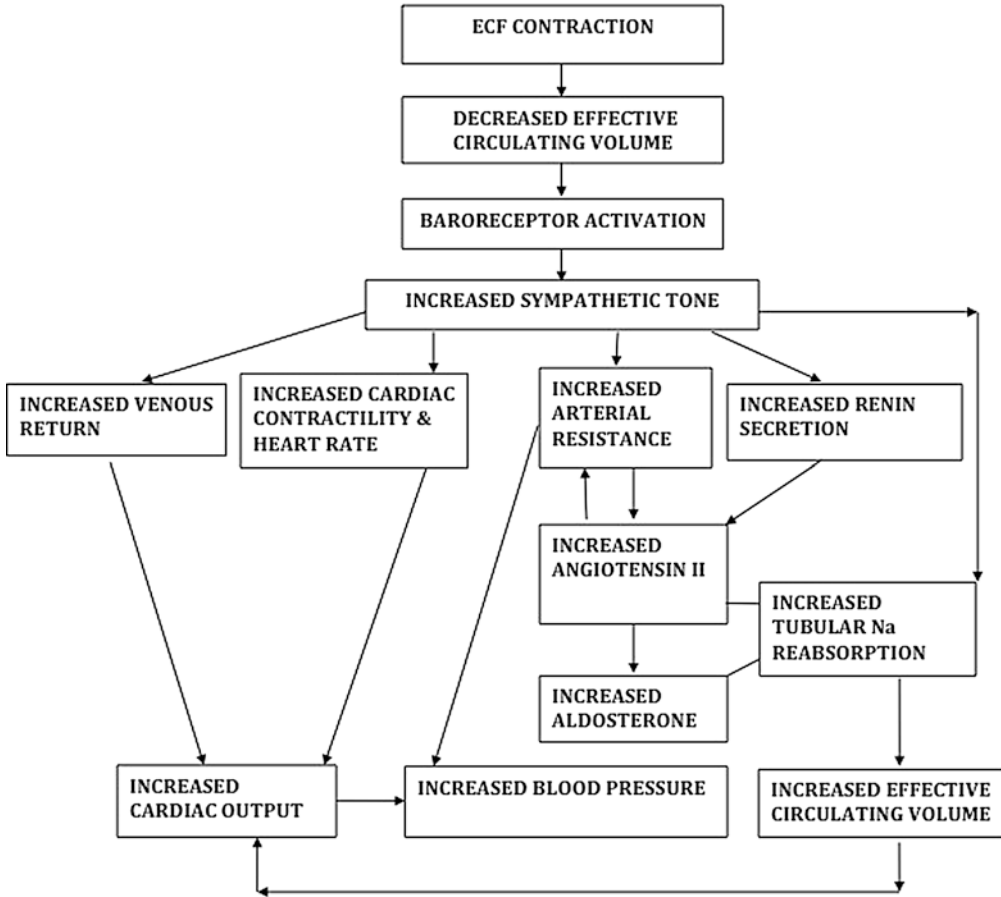
Vigorous endurance exercises like running a marathon may result in hyponatremia either due to excessive loss of sodium and chloride in the sweat or due to overhydration secondary to excessive hypotonic fluid ingestion, along with AVP secretion (due to osmotic and nonosmotic stimulation – decreasing water excretion) (15). The consensus statement of the Second Exercise Induced Hyponatremia conference recommends to drink liquids only when thirsty and to avoid weight gain during exercise to prevent hyponatremia (15).

Hypovolemia should not be considered synonymous with dehydration. Hypovolemic losses usually refer to losses of salt and water from the ECF, whereas dehydration is defined as primarily water loss from ECF, often resulting in hypernatremia, although these patients are also hypovolemic (3).

### **2.1.1. CARDIAC AND RENAL RESPONSES TO HYPOVOLEMIA**

Decrease in effective circulating volume elicits cardiac and renal responses to restore volume back toward normal. Initially hypovolemia results in decreased venous return to the heart sensed by the receptors in the atria and the pulmonary vessels, triggering activation of the sympathetic nervous system leading to selective vasoconstriction of the skin and skeletal muscle’s vasculature. Further volume loss causes a decrease in

cardiac output and fall in blood pressure activating the baroreceptors in the carotid sinus and aortic arch. Stimulation of the baroreceptors leads to activation of three major neurohormonal vasoconstrictor mechanisms: increase in sympathetic activity, activation of renin–angiotensin system, and release of arginine vasopressin. These act in concert to increase venous return, cardiac contractility, vascular resistance, and renal retention of sodium and water, leading to normalization of effective circulating volume (Fig. 1) (2).



**Fig. 1.** Hemodynamic responses induced by the sympathetic nervous system after effective circulating volume depletion. (Adapted from Rose BD and Post TW (40) with permission.)

**2.1.2. RENAL RESPONSE TO HYPOVOLEMIA**

Renal sodium excretion is altered with changes in effective circulating volume. In states of severe volume depletion the urine is almost devoid of any sodium. Glomerular filtration rate (GFR) and more importantly tubular reabsorption play a key role in sodium conservation. With decrease in effective circulating volume, there is increased circulating norepinephrine and angiotensin II concentrations leading to efferent

arteriolar constriction and increase in the filtration fraction, which is defined as the ratio of the glomerular filtration rate (GFR) to the renal plasma flow (RPF). An increase in filtration fraction results in increased protein concentration and increase in oncotic pressure in the efferent arterioles and peritubular capillaries surrounding the proximal tubules contributing to an increase in sodium and water reabsorption. The proximal tubule and distal tubule/collecting ducts are the primary sites of sodium reabsorption. Sodium reabsorption is regulated by increased norepinephrine and angiotensin II activity in the proximal tubule and increased aldosterone in the collecting ducts. If there is a defect in any of ECF regulation mechanisms, then the phenomenon of pressure natriuresis becomes important in maintaining sodium balance. The increase in sodium and water excretion occurs even with slight elevations of blood pressure. Decreased reabsorption in the proximal tubule and loop of Henle and increased release of vasodilating renal prostaglandins and nitric oxide (from the macula densa) are thought to lead to pressure natriuresis (1, 9).

### **2.1.3. SERUM SODIUM CONCENTRATION IN HYPOVOLEMIA**

Serum sodium concentrations under hypovolemic conditions depend upon a multitude of factors: from underlying etiology of hypovolemia, sodium and water content of the fluid lost, sodium content of the restoration fluid provided, and co-existing conditions. Restoration fluid provided in severe hypovolemia should be generally isotonic (0.9% saline) at first, until measurement of serum electrolytes is available, and then adjusted accordingly. Iatrogenic hyponatremia may develop during administration of hypotonic fluids. In secretory diarrheas the sodium content is similar to plasma, so serum sodium concentrations generally do not change. In osmotic diarrheas more water is lost than sodium, hypernatremia may develop if the thirst mechanisms are not intact. Low urine sodium concentration or fractional excretion of sodium (FENa) is always an indicator of decreased effective circulating volume, unless there is a defect in the kidney that precludes sodium reabsorption (10). In certain conditions like nephritic syndrome, heart failure, and cirrhosis, patients may develop edema, decreased effective circulating volume without total body water volume depletion. In these situations, the kidneys respond by increasing sodium and water reabsorption with a low FENa. Urine sodium concentrations can vary in hypovolemia based on the underlying etiology of the hypovolemic state (Table 2).

## **2.2. Symptoms and Signs of Hypovolemia**

Most of the symptoms are due to the underlying etiology of the hypovolemia. Loss of fluid from the ECF compartment results in decreased tissue perfusion, which produces similar symptomatology regardless of the underlying cause (Table 3).

## **2.3. Diagnosis**

Diagnosis of hypovolemia requires a detailed history and physical examination to elicit the etiology and extent of hypovolemia (Chapter 1). Laboratory tests help to con-

**Table 2**  
**Classification of Hypovolemic Disorders Based on Urine Sodium Excretion**  
**(Chapter 1)**

| <i>Low urine sodium concentration (UNa &lt; 10 mol/L)</i> | <i>Normal or increased urine sodium concentration (UNa &gt; 20 mmol/L)</i> |
|---|--|
| Vomiting  | Diuretics  |
| Diarrhea  | Osmotic diuresis (glucose, mannitol, urea)                                 |
| Nasogastric aspiration                                    | Mineralocorticoid deficiency   |
| Fistulae  | Postobstructive diuresis   |
| Ostomies  | Non-oliguric acute renal failure   |
| Gastrointestinal bleeding                                 | Salt wasting nephropathy   |
| Burns   | Bicarbonaturia   |
| Extensive skin lesions                                    | Ketonuria  |
| Heat exposure   |  |
| Cystic fibrosis   |  |
| Large pleural effusion                                    |  |
| Third space   |  |
| Crush injuries  |  |

**Table 3**  
**Symptoms and Signs of Hypovolemia**

| <i>Symptoms</i>                              | <i>Signs</i>                                     |
|--|--|
| Abdominal pain                               | Weight loss                                      |
| Chest pain                                   | Decreased skin turgor/prolonged capillary refill |
| Confusion                                    | Dry mucus membranes                              |
| Decreased p.o. oral intake                   | Orthostatic hypotension                          |
| Decreased urine output                       | Sunken eyes                                      |
| Diarrhea                                     | Sunken fontanelle (in infants)                   |
| Disorientation                               | Tachycardia                                      |
| Fatigue                                      | Weak pulse                                       |
| Increased thirst                             |  |
| Irritability                                 |  |
| Muscle weakness                              |  |
| Postural dizziness                           |  |
| Salt craving (primary adrenal insufficiency) |  |
| Seizures                                     |  |
| Vomiting                                     |  |

firm the diagnosis and the co-existing electrolyte abnormalities. The most direct sign of volume depletion is weight loss. The severity of volume depletion can be assessed if the pre-illness and illness weight are known, using the formula

$$\% \text{ Dehydration} = (\text{pre} - \text{illness weight} - \text{illness weight}) / \text{pre} - \text{illness weight} \times 100$$

If the weights are not known, then other clinical signs can be used to approximate the severity of dehydration.

Laboratory tests help to confirm the diagnosis and the co-existing electrolyte abnormalities (Table 4).

**Table 4**  
**Laboratory Signs of Hypovolemia**

|                      |   |
|----------------------|---|
| Complete blood count | Elevated hematocrit, but possibly low if bleeding   |
| Serum chemistry      | Serum sodium, potassium, bicarbonate may be increased or decreased<br>Elevated plasma albumin (unless nephrotic syndrome) |
| Urine analysis       | High specific gravity and osmolality  |
| Urine electrolytes   | Usually less than sodium <20 mEq/L (unless renal sodium losses) Fractional excretion of sodium <1%                        |

The *goals* of treatment are twofold:

- restore normovolemia
- correct electrolyte abnormalities.

## **2.4. Hypovolemia Clinical Case Scenarios (See Case Scenarios in Chapter 1)**

### *Case Scenario One:*

A 9-month-old baby boy has been sick for the past 2 days. He has had fever for 2 days, temperature maximum of 103°F, four to five loose, non-bloody stools/day, decreased oral intake, and decreased activity. In the emergency room he refused to take any oral fluids for the past 12 h. He vomited 2 days ago, but not in the past 24 h. Parents deny any decrease in urine output.

On physical examination he is afebrile, BP 100/70 mmHg, HR 90/min, RR 26/min. His weight is 10 kg. Mucus membranes are moist, skin turgor is normal, capillary refill is <2 s, and he cries on physical examination with tears but is consolable. There is some urine in his diaper. No prior weight is available. Laboratory studies reveal a normal CBC, normal chemistries, and a normal urinalysis.

Clinical assessment of this baby suggests mild dehydration. He is given a trial of Pedialyte p.o. (250 ml over 2 h), which he is able to tolerate without further emesis in the next 2 h. He has one more episode of diarrhea in the ER, but no emesis. He has urine output as evidenced by a wet diaper.



### 2.4.1. MANAGEMENT

This is a 9-month-old baby boy with gastroenteritis and mild dehydration. He does not have any vomiting now, so he should be given a trial of p.o. oral rehydration fluids in the ED. As he tolerated the oral challenge he can be sent home with the following instructions to the family:

- Give Pedialyte 250 ml over the next 2 h (deficit correction for mild dehydration – 50 ml/kg over 4 h, he has already received half the correction in the ER).
- For every episode of diarrhea give 100 ml of Pedialyte (10 ml/kg/episode).
- Continue to encourage breast feeding and other foods the baby eats.
- If baby is not taking anything else by mouth, he will need 40ml/hr of Pedialate (maintenance requirement).
- If patient starts vomiting and unable to take p.o., then return to the ER.
- Monitor urine output and other signs of dehydration as explained, similar to Scenario in Chapter 1.

#### *Case Scenario Two:*

A 17-month-old boy with prune belly syndrome and chronic kidney disease presents to the ER with a 2 day history of fever, vomiting, and diarrhea. His mother reports a decreased urine output since the morning. He was seen in clinic a week ago and weighed 10 kg and had an estimated GFR of 50 ml/min/1.73 m<sup>2</sup>. In the ER he was irritable but consolable, had a blood pressure of 90/70 mmHg, HR 120/min, T 102°F, RR 28/min, and the weight was 9 kg. Physical examination showed a toddler with dry mucus membranes, decreased tears, sunken eyes, tenting of the skin, and a capillary refill of 2 s. Patient was given a 10ml/kg intravenous bolus of normal saline after his blood was sent for analysis. Initial reports showed a serum sodium of 125 mEq/L, K –3.7 mEq/L, HCO<sub>3</sub><sup>-</sup> 18 mmol/L, BUN/Cr 71/2.6, CBC showed anemia with hemoglobin of 9.8 g/dL, white count was normal. UA: SG 1010, pH 7.0, protein 100 mg/dL, large blood, no ketones or glucose, nitrite positive, leukocytes were positive, many WBCs and RBCs under high power field. Urine and blood cultures were sent.

### 2.4.2. MANAGEMENT

A 17-month-old boy with gastroenteritis, 10% dehydration, asymptomatic hyponatremia, worsening renal function (estimated GFR 20 ml/min), anemia, and a possible urinary tract infection.

FLUID AND SODIUM requirements for 24 h (deficit + maintenance + ongoing losses):

FLUID REQUIREMENTS for 24 h:

Deficit: 10 kg × 100 ml/kg = 1000 ml

Maintenance: 1000 ml

TOTAL fluid requirement = 2000 ml

SODIUM REQUIREMENTS: Na deficit in hyponatremia patient has two components:

- Na deficit independent of any volume deficit: Na required to normalize serum Na without replacing a volume loss

Deficit: (expected–observed serum sodium)  $\times$  0.6 (fraction of total body water)  $\times$  wt (kg)

- 10 kg non-dehydrated patient with Na 125 mEq/L: Na deficit = (135 mEq – 125 mEq)  $\times$  0.6  $\times$  10 = 60 mEq
- Na deficit associated with volume loss: Na concentration of deficit volume in isonatremic dehydration is 140 mEq/L: Na deficit = 140 mEq/L  $\times$  1 L (1000 ml) = 150 mEq
- Maintenance sodium: 3 mEq/100 ml = 30 mEq

Hence TOTAL sodium requirement = 60 + 140 + 30 mEq = 230 mEq.

The patient requires 2000 ml of fluid and 230 mEq of sodium in the next 24 h to correct his hypovolemia and hyponatremia. Half of the correction can be given in the first 8 h and the rest in the next 16 h. Initial fluid should have a higher sodium content. There is no need for rapid correction of sodium as patient is asymptomatic. Patient received a 100 ml bolus of normal saline (has 15.4 mEq sodium), which will be deducted from the total sodium requirements.

First 8 h: 900 ml of fluid and 120 mEq sodium = 0.78 NS  $\approx$  Normal saline

Next 16 h: 1000 ml of fluid and 100 mEq of sodium = 0.68 NS  $\approx$   $\frac{1}{2}$  Normal saline

So give D5 with NS for the first 16 h, and then change to D5 with  $\frac{1}{2}$  NS for the next 8 h.

- Monitor serum electrolytes every 3–4 h.
- Replace ongoing losses in addition to the above fluids. Diarrheal fluid usually is close to half normal saline and that can be used for ongoing losses.
- Once urine output is confirmed add potassium to the fluids as patient is losing potassium in the diarrheal fluid.
- If the serum bicarbonate is very low, some of the sodium can be added as sodium bicarbonate.

With the above regimen the patient's dehydration and hyponatremia were corrected in 36 h. He required IV antibiotics for an *Escherichia coli* UTI. His serum creatinine returned to baseline after 2 weeks.

### 3. HYPERVOLEMIA

#### 3.1. Definition and Pathophysiology

Hypervolemia results when fluid accumulates in the ECF at a higher rate than the output due to either sodium and water retention or abnormal sodium and water intake. Since the ECF volume compartment is largely determined by its quantity of  $[\text{Na}^+]$ , the most reliable way to assess the sodium content in the ECF compartment is to measure the plasma sodium concentration and to multiply this value by the estimated ECF volume (quantitative and clinical assessments of the ECF volume were provided in Chapter 1).

Sodium concentration in the ECF compartment (mEq/L) = Plasma sodium (mEq/L)  $\times$  ECF volume (liters) For example, if the serum sodium concentration is 140 mEq/L in 10 kg child, whose estimated ECF (ECF  $\approx$  0.2  $\times$  body weight) is 2 L, then the sodium content of ECF is 2 L  $\times$  140 mEq/L = 280 mEq. Another clinically useful method to assess changes in ECF volume is using hematocrit values. Hematocrit is defined as the ratio of red blood cells (RBCs) volume to the blood volume. Hematocrit = RBC volume/total blood volume. For example, assuming that patient has no bleeding, anemia or erythrocytosis, and that normal total blood volume is  $\sim$  80 ml/kg, if the normal hematocrit is 0.40, then normal blood volume in child with weight of 20 kg is 1600 ml, with RBC volume = 0.4  $\times$  1600 ml = 640 ml, and plasma volume = 0.6  $\times$  1600 ml = 960 ml. In contrast if the measured hematocrit is 0.50, and RBC volume remains the same (640 ml), his/her plasma volume would be reduced to from 960 ml to 800 ml (0.5  $\times$  1600 ml), or 16.6% (16).

Clinical hypervolemia may result in edema or hypertension. Edema is defined as the palpable swelling produced by expansion of the interstitial fluid volume. Edema is usually accompanied by weight gain if it results from increase in total body sodium content. Increased capillary permeability may be the main mechanism of edema in inflammatory states (i.e., insect bites), but the edema in these circumstances is usually localized. For generalized edema (anasarca) there are two main mechanisms that are required:

1. *Disruption of the Starling's forces* : It is an alteration in capillary hemodynamics favoring movement of fluid from the vascular space into the interstitium.

Net filtration =  $L_p S(\Delta \text{hydraulic pressure} - \Delta \text{oncotic pressure})$ , or

Net filtration =  $L_p S[(P_{\text{cap}} - P_{\text{int}}) - (\pi_{\text{cap}} - \pi_{\text{int}})]$

where  $L_p$  is the measure of unit porosity and  $S$  is the surface area,  $P_{\text{cap}}$  is the hydraulic pressure in the capillary,  $P_{\text{int}}$  is the hydraulic pressure of the interstitium,  $\pi_{\text{cap}}$  is the oncotic pressure in the capillary, and  $\pi_{\text{int}}$  is the oncotic pressure in the interstitium (17). In a physiologic state edema does not form since the forces along the capillary are balanced so that any net fluid filtration into the interstitial space does not exceed the ability of the lymphatic system to remove it. Situations favoring edema formation are increased capillary permeability, decreased capillary oncotic pressure, increased capillary hydraulic pressure, increased interstitial oncotic pressure, and impairment of lymphatic drainage.

2. *Sodium and water retention by the kidney*: Retention of water most commonly occurs due to conditions that impair renal sodium excretion (6). These conditions result in increase in ECF volume and are characterized by high concentrations of plasma arginine vasopressin, despite hypotonicity (the exception is renal insufficiency where high urea concentration contributes to increased tonicity) (18, 10). Table 5 lists these conditions.

In sodium retaining disorders secondary to systemic arterial vasodilatation (cirrhosis), the compensatory mechanism includes increase in shortening fraction due to the reduced cardiac afterload (19). However, with uncompensated arterial underfilling, there

**Table 5**  
**Hypervolemic Disorders Associated with Impaired Sodium Excretion by the Kidneys**

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*Increased ECF volume*

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Renal insufficiency  
Cirrhosis  
Congestive heart failure  
Nephrotic syndrome

---

is a stimulation of sympathetic nervous system and humoral system (vasopressin release and renin–angiotensin–aldosterone system) resulting in sodium and water retention by the kidney (20).

Accidental or iatrogenic sodium load may be the result in hypervolemia. This condition may self-correct if the renal function is normal. In edema associated with primary hyperaldosteronism, aldosterone initially induces sodium and water retention, followed by a spontaneous diuresis (aldosterone escape), which partially lowers the extracellular fluid volume toward normal (19, 21). This response is induced by the volume expansion (21).

### **3.1.1. HEART FAILURE**

Heart failure (HF) is a complex syndrome that results from structural or functional cardiac disorder that impairs heart ventricle to fill or eject blood (22). In healthy individuals, increase in total blood volume is associated with increase in sodium and water excretion by the kidney (23). However, in patients with heart failure, the water and sodium excretion depends on the integrity of the arterial system, not the total body volume (23). As mentioned previously, 85% of the total blood volume circulates in the venous system; therefore in the states of low cardiac output that causes arterial underfilling, the increase in total body volume occurs mainly in the venous circulation (23). When there is an increase in sodium reabsorption in the proximal tubule secondary to the arterial underfilling and neurohumoral activation, there is decreased delivery of sodium to the distal collecting tubule (site of action of aldosterone and natriuretic peptides). Therefore in patients with heart failure there is an escape from the sodium–water retaining effect of aldosterone and natriuretic peptides (23). When the neurohumoral axis is stimulated, secondary to decreased distention of the arterial baroreceptors, renal sodium and water retention occurs as a compensatory mechanism to maintain adequate tissue perfusion (3). There is an adrenergic discharge, leading to the activation of the renin–angiotensin–aldosterone system (RAAS) (23). The adrenergic response and the elevation of angiotensin II activate the receptors in the proximal tubule, resulting in the increased absorption of sodium in the proximal tubule and decreasing the delivery

of sodium to the distal collective tubule (23). The adrenergic discharge is also responsible for the release of the nonosmotic release of AVP, which is responsible for heart failure-induced hyponatremia (16, 23–25). As mentioned earlier AVP causes activation of the V2 receptors in the collecting tubule, increasing the number of aquaporin-2 water channels, but the V1a receptors in the smooth muscle are also activated, leading to constriction of the coronary vessels, proliferation of cardiac myocytes, therefore, increasing ventricular wall stress, dilatation, and hypertrophy (22).

The activation of RAAS and the sympathetic nervous system is the normal response to low cardiac output, which occurs in patients with heart failure (22). This neurohormonal activation of RAAS and the adrenergic discharge increases the afterload by increasing peripheral vascular resistance and the retention of sodium, potassium, and water, enhancing the preload (22).

Angiotensin II contributes to the retention of sodium and water by

1. Stimulating the release of aldosterone, causing the reabsorption of sodium in the distal tubule/collecting duct
2. Renal efferent arteriolar constriction, causing a decreased renal blood flow by increasing the renal filtration fraction (1)
3. Stimulation of thirst through central nervous system mechanism

An increase in filtration fraction results in an increase in oncotic pressure (increased protein concentration) in the efferent arterioles and peritubular capillaries around the proximal tubules (1). This increase in the oncotic pressure has been proposed to increase the absorption of sodium and water in the proximal tubules (1). Angiotensin II also stimulates myocyte hypertrophy and fibrosis, contributing to the deterioration of the heart function. Therefore, treatment with angiotensin convertase inhibitors (ACEi) that inhibit the conversion of angiotensin I to angiotensin II improves cardiac remodeling (23).

The natriuretic peptides, atrial natriuretic peptide (ANP) and brain natriuretic peptide, or B-type natriuretic peptide (BNP), are elevated in patients with heart failure (1). These hormones have natriuretic properties, vasorelaxant properties, and renin–aldosterone inhibiting properties (1). BNP is produced by the ventricular myocardium as a response to stretching of the myocardium; its effects, vasodilatory and natriuretic, oppose the actions of aldosterone and angiotensin II (26). Atrial natriuretic peptide (ANP) is primarily released from the atria in response to volume expansion. ANP triggers an increase in intracardiac pressure (27), which is thought to play a counterbalancing role in congestive heart failure, limiting the accumulation of edema. ANP increases the glomerular filtration rate (GFR) without raising renal blood flow (28) and directly reduces sodium reabsorption in the inner medullary collecting duct, activating cyclic GMP closing sodium channels in the luminal membrane that normally allow luminal sodium to enter the tubular cell (29, 30).

Renal prostaglandins do not regulate sodium excretion by the kidney in healthy individuals (1). Prostaglandin activity is elevated in heart failure patients and is correlated with the severity of the disease and degree of hyponatremia (1). The exact role of

prostaglandins in the sodium handling by the kidney in edematous states, similar to heart failure, is not clear (1).

### 3.1.2. CIRRHOSIS (SEE CHAPTER 12)

Cirrhosis is commonly caused by hepatitis C or alcoholism in adults and in children it is due to cholestasis, inborn errors of metabolism, and chronic hepatitis. Ascites is the most common complication of cirrhosis (31). Splanchnic vasodilatation is the main factor contributing to ascites (9). In cirrhosis portal hypertension is produced, most importantly, by nitric oxide, and to a lesser extent, prostaglandins leading to splanchnic arterial vasodilatation (32). In these situations there is an up-regulation of endothelial nitric oxide synthase (eNOS) (6). In experimental cirrhosis in rats, inhibition of eNOS until normal vascular resistance is achieved results in a reversal in the elevation of plasma AVP, renin, and aldosterone concentrations (33). Splanchnic vasodilatation has only a small effect on the effective circulatory volume (ECV), which is maintained within normal limits secondary to increased cardiac output and plasma volume. These effects happen early in the onset of cirrhosis. In the late stages of cirrhosis, splanchnic arterial vasodilatation causes the ECF volume to decrease markedly and, subsequently, the arterial blood pressure to fall (31). The dilated circulation acts as an “underfilled” compartment, stimulating the activation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, maintaining the arterial blood pressure resulting in sodium and water retention. Portal hypertension and splanchnic arterial vasodilatation alter the intestinal capillary pressure and permeability, facilitating the leaking and accumulation of retained fluid within the abdominal space (31). As the disease progresses, there is an impairment in renal excretion of free water, causing dilutional hyponatremia, and renal vasoconstriction, leading to the hepatorenal syndrome (31).

The hepatorenal syndrome results often in irreversible renal failure with a very poor prognosis. However, the hepatorenal syndrome is a functional, rather than a structural type of renal failure, as liver transplantation can reverse the syndrome. There is evidence to support the hypothesis that primary arterial vasodilatation explains the retention of sodium and water, and the ascites in cirrhotic patients (6). In the splanchnic circulation, there is an elevated concentration of V1a receptors. Therefore, when terlipressin (V1a agonist) and albumin are provided for about 1 week, the hepatorenal syndrome is reversed in more than half of cirrhotic patients (6).

Increased sodium reabsorption in the proximal and distal tubule in cirrhotic patients and in heart failure patients is secondary to activation of the neurohormonal system promoting sodium and water retention, endogenous increased reabsorption by the nephron segments, and loss of tubuloglomerular feedback (the mechanism increasing glomerular filtration rate when the distal tubule is reached by a reduced sodium load) (1). An increase in renal vascular resistance and filtration fraction is frequently observed in decompensated cirrhotic patients (1). For this reason, decreased hydrostatic pressure and increased oncotic pressure in the peritubular spaces may be responsible for the increased sodium and water reabsorption seen in cirrhosis (1).

Evidence suggests that inhibition of aldosterone with spironolactone, or the removal of aldosterone source (the adrenal gland), results in natriuresis consistent with the increased levels of aldosterone contributing to water and sodium retention in the distal tubule of cirrhotic patients (1).

Nonosmotic release of vasopressin plays an important role in water and sodium retention in cirrhotic patients. The increased secretion of vasopressin is the major factor responsible for the inability to excrete water and sodium in the cirrhotic rats (34). When cirrhotic patients present with ascites and/or edema, they may have an abnormal response to fluid administration, contrary to cirrhotic patients without ascites or edema, who can excrete water and sodium adequately (1). Two possible explanations are as follows:

- a) Nonosmotic release of vasopressin.
- b) Decrease in water and sodium delivery to the distal tubule since interventions that improve the delivery of sodium and water to the distal tubule of cirrhotic patients, like infusion of albumin with saline, mannitol, or water immersion, improve water and sodium excretion (1).

Similar to patients with heart failure, the escape of the aldosterone effect and the resistance to natriuretic peptides in cirrhotic patients are mediated by the decreased delivery of water and sodium to the distal tubule (1).

### 3.1.3. NEPHROTIC SYNDROME

The principal clinical presentation of nephrotic syndrome is edema, and its pathogenesis remains controversial (35). The classical theory is that edema formation is secondary to a decrease in plasma oncotic pressure due to loss of albumin in the urine, causing water to shift into the interstitial space secondary to decreased oncotic pressure. That reduces the intravascular volume leading to renal hypoperfusion and stimulation of the renin–angiotensin–aldosterone (RAA) system, leading to increased reabsorption of sodium, especially at the distal segments of the nephron. This hypothesis is not fully supported by clinical findings. Plasma volume has been shown to be decreased only in some children with minimal change disease, particularly during the initial phase of a relapse, but absent in others and almost always absent in adults with nephrotic syndrome (36). Studies have failed to demonstrate elevation of RAAS hormones, and increased sodium reabsorption is still present when albumin or ACEi were given to suppress the renin production. It has been postulated that there is an intrinsic nephron abnormality with increased activity of Na/K-ATPase leading to retention of sodium. Patients with nephrotic syndrome can have several types of intrinsic renal lesions (1). The nephron site responsible for the increased sodium reabsorption in nephrotic patients is not clear. From clinical and animal studies, the distal nephron seems to be the site of the increased sodium retention, although increased sodium retention in the proximal tubule occurs in selected cases (1). If oncotic and hydrostatic pressures are the primary physical forces in the peritubular capillaries responsible for the renal water and sodium retention, it is likely they act at the level of the convoluted proximal tubule (1). The low filtration fraction, elevated renal plasma flow, and normal vascular resistance observed in patients

with nephrotic syndrome suggest that other factors, besides the oncotic and hydrostatic pressures, must be involved in the enhanced sodium retention (1). The role of natriuretic peptides in patients with nephrotic syndrome is not clear yet, as well as other humoral factors such as kinins and prostaglandins (1).

In rats with nephrosis induced by aminonucleosides, the decreased plasma volume, normal GFR, and edema could be prevented with the removal of the adrenal glands (1). In contrast patients with nephrotic syndrome induced by nephrotoxic serum have increased plasma volume, low GFR, and edema independently of the adrenal glands (1). Meltzer et al. (37) identified two groups of patients with nephrotic syndrome. One group with hypovolemia and with stimulation of RAAS was characterized by minimal change disease and normal GFR (37). The other group included patients with hypervolemia who had low or normal plasma renin activity and aldosterone level; this group was characterized by chronic glomerulopathy and low GFR (37). Patients with nephrotic syndrome and low GFR usually show enhanced sodium retention (37).

Contrary to heart failure and cirrhosis patients, hyponatremia is not commonly associated with nephrotic syndrome (1). Elevated serum lipid concentration may cause *pseudohyponatremia*. Abnormal water excretion has been shown in children with nephrotic syndrome (38) and increased levels of vasopressin also contribute to the retention of water (39). Water immersion and albumin infusion can reduce the plasma concentration of vasopressin and induce diuresis in these patients (1).

Summarizing, a fall in GFR, changes in oncotic and hydrostatic pressures, stimulation of sympathetic nervous system and RAAS, and nonosmotic release of vasopressin are involved in the retention of sodium and water in the nephrotic syndrome (1).

#### 3.1.4. TREATMENT

Diuretics are usually effective in reducing edema of congestive heart failure, although effective fluid removal should be carefully monitored (26). Patients with heart failure should be treated with diuretics as part of their initial therapy (27). Loop diuretics are most often used (furosemide, bumetanide, torsemide). Patients who are chronically treated with loop diuretics usually require a higher dose in the acute setting (27). The addition of a thiazide diuretic potentiates the effects of the loop diuretics.

In patients with cirrhosis and ascites, fluid accumulation in the peritoneal cavity is sufficient to cause discomfort (11). Free water excretion by the kidney and GFR are normal in most patients and the serum sodium and creatinine concentrations are within normal limits (11). Usually, a negative sodium balance and, subsequently, loss of peritoneal fluid are easily achieved with diuretics, in patients with mild to moderate volume ascites (28). The diuretic of choice is spironolactone or amiloride (11). Furosemide is used with caution, because the risk of renal failure secondary to excessive diuresis and hypovolemia (11), and the response to treatment should be monitored by evaluation of urine output and changes in body weight (11). The measurement of urine sodium may be helpful to assess the response to diuretics (11). An important part of the therapy of cirrhotic ascites is the avoidance of non-steroidal anti-inflammatory drugs (NSAID). These medications inhibit the synthesis of renal prostaglandins, and this leads to renal vasoconstriction, a lesser response to diuretics, and increased risk of acute renal



insufficiency (29). In children with nephrotic syndrome, diuretics should only be given for severe edema and in the absence of intravascular volume depletion. Dietary sodium restriction (less than 2 g/day in adults) is also recommended (31), since diuretic effects may be overcome by high sodium intake. Non-adherence to a low-sodium diet is often linked to diuretic failure. Another reason for diminished diuretic effectiveness in edematous states may be reduced absorption of oral diuretics due to gastrointestinal mucosal edema. Reduced blood flow to the kidneys in states with decreased ECF decreases the amount of sodium delivered to the loop of Henle, and thus loop diuretic effectiveness. In addition in hypoalbuminemic states loop diuretics that are albumin bound are less effectively delivered to the site of action. Patients with anasarca or diuretic resistance may be treated with furosemide (1–2 mg/kg per dose) together with 25% albumin (0.5–1 g/kg) IV infusion, given over 4 h once to twice a day with careful monitoring of urine output and respiratory status, as IV albumin has been associated with pulmonary edema (30). Albumin binds furosemide improving its delivery to site of action in the ascending loop of Henle increasing sodium excretion. Albumin also prevents intravascular volume depletion. Spironolactone (1.0–3.5 mg/kg/day, adult maximal dose 400 mg), thiazide diuretics, and amiloride (0.2–0.625 mg/kg/day, adult maximal dose 20 mg) may be used in combination with a loop diuretic (31).

### *Case Scenarios (See Scenarios in Chapter 1)*

1. A 7-year-old girl presents to the emergency department with vomiting and cough for 3 days. The mother also reports weight loss, approximately 4 kg over the last 4 months and the development of bilateral lower extremity edema over the past week. The girl is urinating, but less than usual. She was a full-term neonate, born by uneventful normal spontaneous vaginal delivery. The child was diagnosed with acute lymphoblastic leukemia at 4 years of age. The medical records indicate the use of doxorubicin and methotrexate as part of the consolidation chemotherapy, and she has responded very well to the treatment and is in remission. Past family history is significant for maternal grandmother with insulin-dependent diabetes mellitus, on dialysis. Initial exam shows a thin 8-year-old girl, 10th percentile for weight and 25th percentile for height, jugular venous distention is noted to the angle of the jaw when seated at 90°, an S3 gallop and ventricular heave, tachypnea, diffuse rales, and 3+ pitting edema to the mid-calf bilaterally are present. Electrocardiogram reveals sinus tachycardia, left atrial enlargement, and T-wave abnormalities. All these findings are clinically diagnostic of left heart failure. The girl's symptoms improve after the initial treatment with intravenous furosemide 1 mg/kg twice a day for 24 h and she is transferred to the cardiology service. Her echocardiogram demonstrates severe global hypokinesis and a 20% ejection fraction.

Doxorubicin is a drug well known for its cardiac toxicity. The girl's treatment is likely the etiology of her heart failure. The compensatory mechanisms associated with low cardiac output, secondary to left heart failure, include up-regulation of sympathetic tone and the renin–angiotensin axis, causing increased release of vasopressin, aldosterone, and atrial natriuretic peptide, leading to sodium and water retention, resulting in volume expansion.

2. A 12-year-old boy with history of steroid-sensitive nephrotic syndrome, diagnosed when he was 6 years old, presents to the emergency department with the chief complain of

abdominal distention and edema of lower extremities. Mother reports that 5 days ago, the boy had cold symptoms that included runny nose, non-productive cough, and low-grade fever that resolved. Two siblings had the same symptoms and recovered. The boy noticed the swelling of both legs 3 days ago. On physical examination, the boy has no fever and is normotensive. Weight is 55 kg; the last weight according to mom in the pediatrician office 3 weeks ago was 48 kgs. There is pitting edema of both legs to the level of the knees, and generalized abdominal distension, flank fullness, and shifting dullness, consistent with ascites. Urine analysis shows a specific gravity of 1.025, no blood detected, and 3+ protein. Urine protein to creatinine ratio is 7. Basic metabolic panel shows normal renal function and electrolytes.

Albumin 25% – 1 g/kg – is infused over 4 h and furosemide 1 mg/kg is also given 2 h into infusion and at the end of the infusion. The boy voids approximately 500 ml and abdominal distention improves; he is also started on prednisone 60 mg/m<sup>2</sup> for probable steroid responsive nephrotic syndrome.

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