30 Water, Electrolyte, and Acid–Base Disorders

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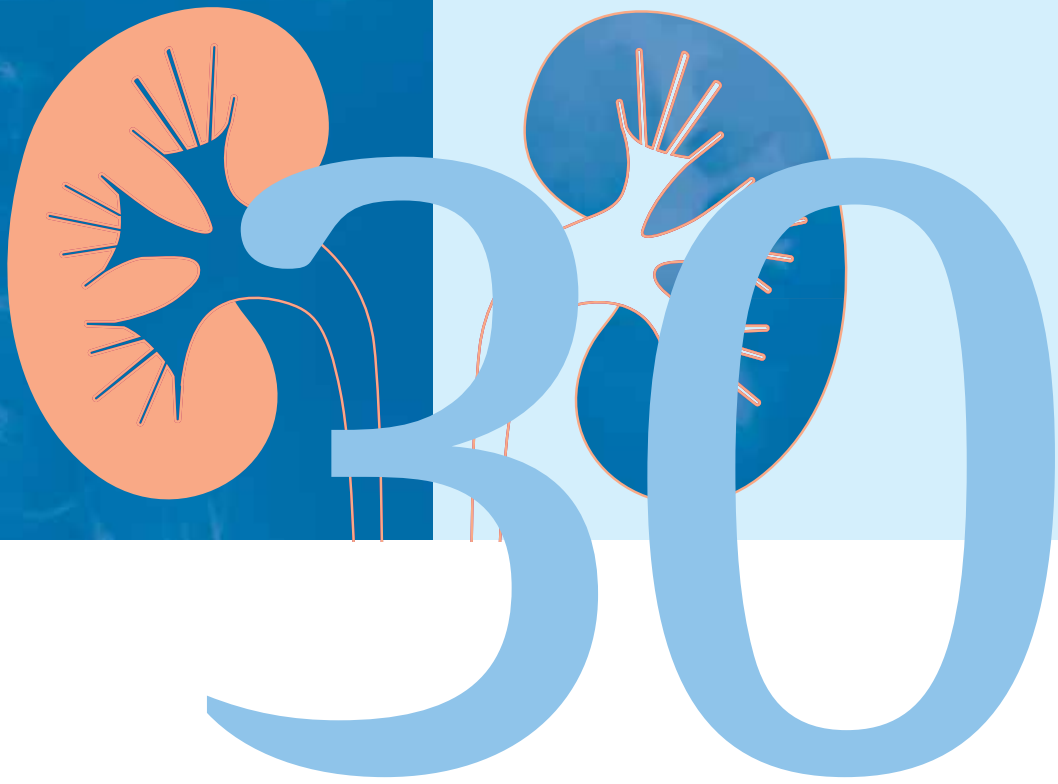


30.1 Disorders of Sodium and Water Homeostasis

Physiologic Principles

Disorders of sodium and water homeostasis result in changes of volume status, serum osmolality, and serum sodium concentration. Basic knowledge of physiologic principles is fundamental for understanding these disorders. Some of these principles are briefly described below.

Fluid Compartments

General Pathogenesis of Electrolyte Disorders. The human body consists of different fluid compartments, and each of them has a characteristic electrolyte profile (Tab. 30.**1**). Electrolyte disorders, which are usually measured in the serum, can occur by three different mechanisms (Fig. 30.**1**): by a *net change in intake*, by a *shift between different compartments*, and by a *net change in excretion*.

The kidney is the main organ responsible for excretion of electrolytes. Therefore, the differential diagnosis usually distinguishes between renal and extrarenal disorders of electrolyte excretion/loss. The renal excretion of a substance X can be estimated by determination of the fractional excretion (FE) in spot urine. The fractional excretion is defined as the amount of a substance X excreted via urine divided by the total amount of glomerular filtration of X. In this chapter the concentration of a substance X in the plasma/serum or in the urine is described as P_X or U_X, respectively. The fractional excretion of X can then be calculated as follows:

$$FE_X = \frac{(U_X \times P_{Creatinine})}{(P_X \times U_{Creatinine})}$$

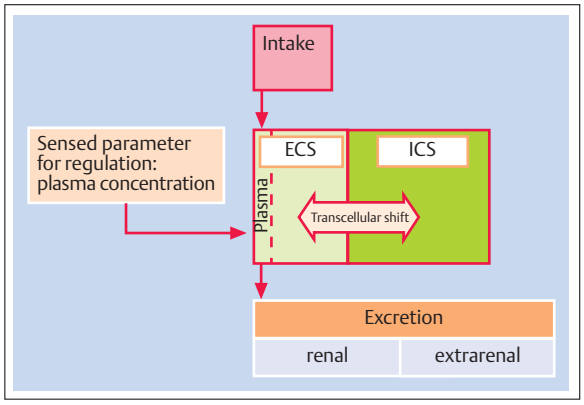


Fig. 30.**1** Fundamental pathogenesis of electrolyte disorders. Electrolyte disorders principally arise in three different ways: by altered intake, by internal shifts (mainly between intracellular space [ICS] and extracellular space [ECS]), and by altered excretion.

Size of Fluid Compartments. On average, the human body consists of 60% water and 40% solid substances. Based on a body weight of 70 kg, the total body water is distributed as follows (Fig. 30.**2**):

- *intracellular volume (ICV)*: 40% (28 L)
  - blood cells: 3% (2 L)
- *extracellular volume (ECV)*: 20% (14 L)
  - intravascular compartment (plasma): 5% (3.5 L)
  - interstitial compartment: 15% (10.5 L).

The *blood volume* consists of the combined volume of blood cells and plasma. It represents about 8% of body weight.

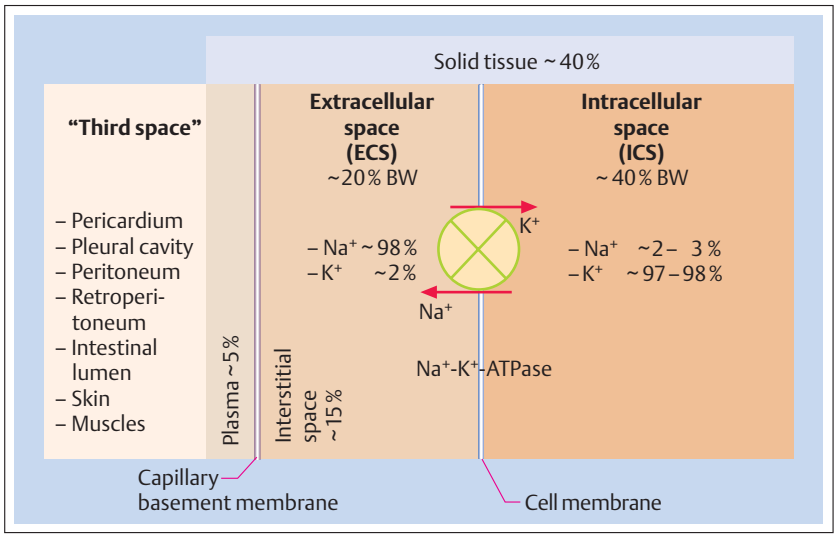


Fig. 30.**2** Distribution of water and cations in the adult body; water in percent of body weight (BW), cations in percent of total body stores.

Table 30.**1** Electrolyte profiles in various fluid compartments (in mEq/L)

Ions	Plasma	Interstitial fluid	Intracellular fluid
Cations			
Sodium	142	145	12
Potassium	4.3	4.4	140
Calcium (ionized)	2.5	2.4	4
Magnesium (ionized)	1.1	1.1	34
Anions			
Chloride	104	117	4
Bicarbonate	24	27	12
Phosphate	2.0	2.3	40
Proteins	14	0	50
Others	5.9	6.2	84

In particular clinical situations sequestration of large volumes of fluid is observed in serous cavities (pleural, pericardial, peritoneal space) or in traumatized tissue (muscle, retroperitoneal space). This is described as a *transcellular third space*. Under physiologic conditions, this volume is negligible, but it can consist of several liters of fluid in certain disease states, and therefore, considerably influence volume homeostasis.

Each fluid compartment has a characteristic electrolyte profile, which is summarized in Tab. 30.**1**. Under physiologic conditions, the sum of osmotic and oncotic pressure is identical in all the compartments, which allows stable volume homeostasis. However, it is important to understand that the regulation of volume and osmolality are fundamentally different and independent of each other. Each of these is regulated by different hormone systems.

Principles of Osmoregulation

Intracellular and extracellular spaces are separated by the cell membrane, which is permeable to water and urea, but impermeable to electrolytes and proteins. The osmotic pressure within a compartment can be determined by the total concentration of all soluble constituents and is described as serum *osmolality*. In the steady state it is identical in all the compartments and highly correlated with the serum sodium concentration. The osmolality (Osm) is tightly regulated (285–290 mOsm/L) and can be approximately calculated by the following formula:

$$P_{Osm} = (2 \times P_{Na}) + P_{Glucose} + P_{urea}$$

If there is a considerable difference between calculated and effectively measured osmolality, this is referred to as an *osmotic gap*. Substances which are not included in the formula above (e.g., alcohol, glycol, and certain drugs) may be responsible for this difference (see Metabolic Acidosis, below).

Feedback Loop of Osmoregulation. The feedback loop of osmoregulation is shown in Fig. 30.**3**. Osmolality is sensed in specialized cells of the hypothalamus (afferent part of the loop). Regulation of osmolality then occurs via a change in water intake and water excretion in the kidney. Two effector mechanisms are mainly responsible (efferent part of the loop):

- Hyperosmolality *stimulates thirst* and leads to increased water intake.
- Hyperosmolality induces the *secretion of vasopressin* (antidiuretic hormone [ADH]) in the hypothalamus. Vasopressin activates the vasopressin receptor type 2 (V_2 receptor), which reduces renal water excretion. In contrast, hypoosmolality suppresses vasopressin secretion, which leads to activation of water channels (aquaporins) in the collecting duct and increased water excretion.

The daily urine output can be regulated between 0.5 and 15–20 L, which allows stable serum osmolality, independent of water intake. Variability of serum osmolality remains within ± 2 %.

Principles of Volume Regulation

Feedback Loop of Volume Regulation. The maintenance of the extracellular volume (ECV) to allow for stable circulation and adequate perfusion of vital organs is one of the most fundamental principles of water homeostasis. The feedback loop of volume regulation is depicted in Fig. 30.**4**. Since the ECV cannot be measured directly, it is determined indirectly by *arterial baroreceptors*, which are located in the carotid sinus, aortic arch, and left ventricle (afferent part of the loop). These receptors

Fig. 30.**4** Scheme of the feedback loop of volume regulation. ▷ ANP = atrial natriuretic peptide.

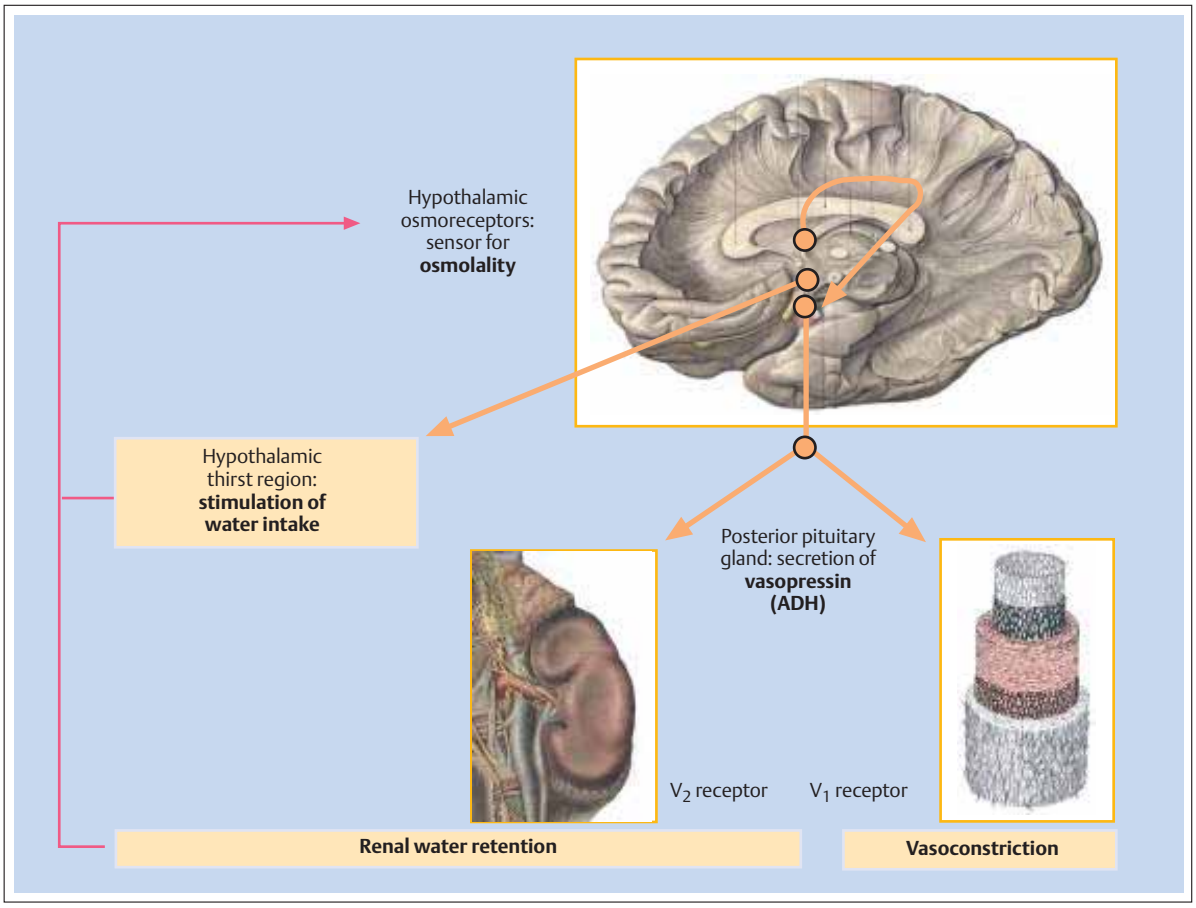
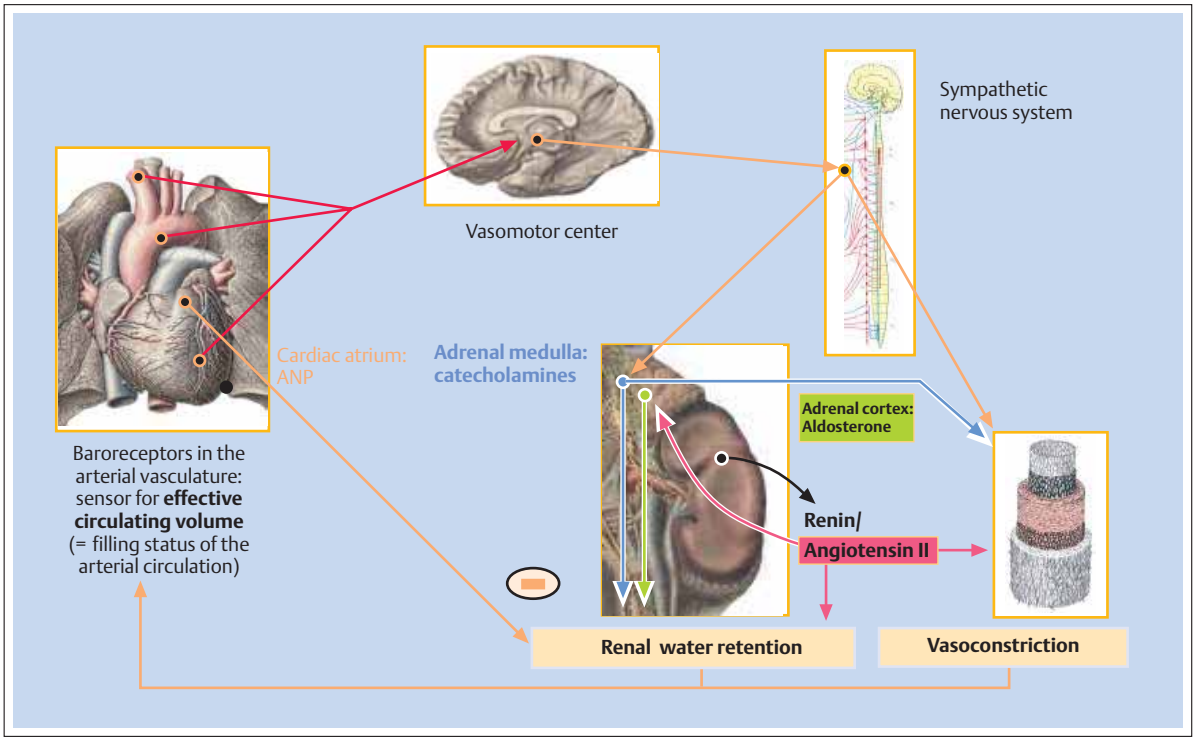


Fig. 30.**3** Scheme of the feedback loop of osmoregulation. V_1/V_2 receptor: vasopressin receptor type 1 (on blood vessels) and 2 (on collecting duct cells).



measure the *effective circulating volume*, therefore the filling status of the arterial circulation, which is determined by ECV and vascular tonus. Under physiologic conditions ECV and the effective circulating volume are highly correlated, but in certain pathophysiologic situations they can be highly discrepant (e.g., edematous disorders with an increase of ECV, but a decrease in the effective circulating volume).

The ECV is determined by the *total body sodium*, which is mainly located in the ECV. An increase of total body sodium leads to volume expansion, whereas a decrease leads to volume contraction. Therefore, volume regulation occurs mainly by variation of renal sodium excretion (efferent part of the feedback loop). The following hormone systems regulate renal sodium excretion:

➤ Hypovolemia activates baroreceptors, which stimulate the *sympathetic nervous system*, which leads directly and indirectly to secretion of catecholamines and consecutive increase of vascular tone. In addition, catecholamines increase sodium reabsorption in the proximal tubule.

➤ Hypovolemia leads to renal hypoperfusion, which triggers *renin* secretion in the juxtaglomerular apparatus of the kidney. Renin stimulates the synthesis of bioactive angiotensin II and ultimately aldosterone. *Angiotensin II* is a potent vasoconstrictor and also stimulates sodium reabsorption in the proximal tubule. In contrast, *aldosterone* leads to sodium reabsorption and potassium secretion in the collecting duct.

➤ Hypervolemia induces secretion of *atrial natriuretic peptide* (ANP) in the heart. ANP leads to renal sodium excretion by increasing glomerular filtration and inhibition of sodium reabsorption in the proximal tubule.

Overview of Volume and Osmoregulation

The fundamental principles of volume and osmoregulation are summarized in Tab. 30.**2** and can be described as follows:

- **The kidney regulates the ECV via renal sodium excretion.** The clinical parameter is the urine sodium concentration U_{Na}. Volume contraction leads to sodium retention. Volume expansion leads to increased natriuresis.
- **The kidney regulates serum osmolality via renal water excretion.** The clinical parameter is the serum sodium concentration P_{Na}. Hyperosmolality leads to renal water retention. Hypoosmolality leads to increased renal water excretion.

Therefore, disorders of sodium and water homeostasis can be classified as follows:

- extracellular volume contraction (with primarily normal serum sodium concentration)
- extracellular volume expansion (with primarily normal serum sodium concentration)
- hyponatremia
- hypernatremia.

Table 30.**2** Overview of volume and osmoregulation

	Volume regulation	Osmoregulation
What is measured? (input)	– effective circulating volume	– plasma osmolality
Sensor (afferent part of the loop)	– arterial baroreceptors (left ventricle, aortic arch, carotid sinus)	– hypothalamic osmoreceptors
What is regulated? (output)	– renal sodium excretion	– renal water excretion – water intake
Effector (efferent part of the loop)	– proximal sodium reabsorption via catecholamines and angiotensin II – sodium reabsorption in the collecting duct via aldosterone	– water retention in the collecting duct via vasopressin – water intake via stimulation of thirst

Disorders of Volume Homeostasis (Extracellular Volume Contraction and Expansion)

Definition, Diagnosis, and Clinical Features

Increase or Decrease of Total Body Sodium and Water to the Same Extent. Disorders of volume homeostasis lead to expansion or contraction of the ECV, which manifests in the typical cardiopulmonary symptoms of hypovolemia or fluid overload. These disorders are particularly frequent in clinical routine, and therefore the clinical evaluation of the volume status of a patient is of utmost importance for differential diagnosis. Chest radiograph and certain laboratory parameters can give some additional guidance. These symptoms and signs are summarized in Tab. 30.**3**.

Clinical Features. *Volume contraction* manifests with orthostatic hypotension, tachycardia, collapse of central veins, dry skin and mucosal surfaces, oliguria, and disorientation. In contrast, *volume expansion* leads to hypertension, increased body weight, peripheral edema, dyspnea, and crackles over the base of the lungs.

Diagnosis. In the case of volume expansion an increased heart size, pulmonary congestion, and pleural effusions can be seen in the *chest radiograph*. In intensive care units measurement of the central venous pressure allows reliable assessment of volume status.

Laboratory parameters can be helpful in the case of volume contraction. An increase of hematocrit or serum albumin level is not very reliable by itself, but can be used for follow-up investigations under therapy. Since volume contraction leads to renal sodium retention, a decrease in urine sodium level is a reliable parameter for a volume deficit. In spot urine, U_{Na} is usually < 20 mmol/L and $U_{Osm} > 600$ mOsm/L. The *fractional excretion of sodium, FE_{Na}*, allows differentiation between prerenal and parenchymal acute renal failure in the oliguric patient and is below 1 % in the case of volume depletion. FE_{Na} is calculated as follows:

$$FE_{Na} = \frac{(U_{Na} \times P_{Creatinine})}{(P_{Na} \times U_{Creatinine})}$$

Table 30.**3** Signs of extracellular volume contraction or expansion

	Volume contraction	Volume expansion
Clinical signs		
cardiopulmonary system	– orthostatic hypotension (> 15–20 mmHg systolic) – orthostatic increase in heart rate (> 15–20 beats/min) – collapsed central veins (at 45° back inclination) – shock in case of severe volume depletion	– hypertension – distended central veins, positive hepatojugular reflux – pulmonary congestion on auscultation
skin and mucosal surfaces	– reduced skin turgor – dry mucosal surfaces	– peripheral edema – increased body weight
Chest radiograph		
heart	– small heart silhouette	– heart silhouette ↑
lungs and pleura		– diffuse pulmonary vasculature, peribronchial cuffing, lung edema – pleural effusion
Laboratory parameters		
blood	– hematocrit ↑ – serum albumin ↑	– hematocrit ↓ – serum albumin ↓
urine	– $U_{Na} < 20$ mmol/L – fractional sodium excretion $FE_{Na} < 1$ %	
Hemodynamics		
pressures	– central venous pressure ↓ – pulmonary–capillary wedge pressure ↓ – mean arterial pressure ↓	– central venous pressure ↑ – pulmonary–capillary wedge pressure ↑ – mean arterial pressure ↑
cardiac output	– cardiac output ↓	– heart failure: cardiac output ↓ – others: cardiac output ↑
peripheral resistance	– peripheral resistance ↑	– peripheral resistance ↓

Table 30.**4** Differential diagnosis of volume depletion

Extrarenal causes (U_{Na} < 20 mmol/L)	Renal causes (U_{Na} > 20 mmol/L)

– Insufficient salt and water intake
– Fluid sequestration in the third space
  – crush injury, rhabdomyolysis
  – internal bleeding
  – pancreatitis, peritonitis, ileus, sepsis
– Gastrointestinal loss
  – vomiting, nasogastric tube
  – diarrhea, fistulas
  – bleeding
– Skin loss
  – intense sweating
  – burns
– External bleeding
	– Osmotic diuresis
	  – severe hyperglycemia
	– Drugs
	  – chronic diuretic abuse
	– Renal salt wasting
	  – tubulointerstitial nephropathies
	  – postobstructive diuresis
	  – renal tubular acidosis
	  – congenital salt-wasting disorders (Bartter syndrome etc.)
	– Mineralocorticoid deficiency (see Tab. 30.**12**)

Table 30.**5** Differential diagnosis of volume expansion

ECV ↑, effective circulating volume ↑	ECV ↑, effective circulating volume ↓

– Primary renal disease
  – acute glomerulonephritis
  – acute and chronic renal failure
– Mineralocorticoid excess (see Tab. 30.**11**)
	– Edematous disorders with secondary hyperaldosteronism
	  – heart failure
	  – nephrotic syndrome
	  – liver cirrhosis
	  – severe hypoalbuminemia (nutritive)

Extracellular Volume Contraction (with Primarily Normal Serum Sodium)

Volume contraction with consecutive decrease in the effective circulating volume occurs with combined net loss of sodium and water. Three basic mechanisms can be responsible and are not mutually exclusive:

- *insufficient intake* of sodium and water
- fluid shift with *sequestration* in the third space
- increased renal or extrarenal *loss*.

Renal loss occurs in the context of primary renal diseases with tubulointerstitial damage, but also indirectly as a consequence of osmotic diuresis and in all forms of mineralocorticoid deficiencies (see Disorders of Potassium Homeostasis, p. 907). The differential diagnosis of volume depletion is summarized in Tab. 30.**4**.

Extracellular Volume Expansion (with Primarily Normal Serum Sodium)

If the net intake of sodium and water overcomes excretion, the ECV expands. ECV expansion over 2–4 L leads to peripheral edema. Based on pathophysiology, two fundamentally different situations can be distinguished (Tab. 30.**5**):

- *concomitant increase* of ECV and the effective circulating volume as a consequence of increased sodium and water intake and/or reduced renal excretion
- increase of ECV associated with *reduced* effective circulating volume in the context of classical edematous disorders (heart failure, liver cirrhosis, nephrotic syndrome).

Volume expansion, as a consequence of *increased intake*, occurs in the context of infusion therapy, but usually only in situations where *excretion is also reduced*. This is mainly the case in patients with acute or chronic renal failure. The renin–angiotensin–aldosterone system is suppressed in these patients, and they are hypertensive due to an increase in the effective circulating volume. The same is the case in patients with primary mineralocorticoid excess (e. g., Conn syndrome). These diseases are usually associated with disorders in potassium homeostasis (see below).

In the case of *classical edematous disorders* a primary underfilling of the arterial circulation is observed. In the case of heart failure this is a consequence of reduced cardiac output, whereas in patients with nephrotic syndrome it is due to hypoproteinemia and consecutive fluid shifts into the interstitial space. In the case of liver cirrhosis, the reduced effective circulating volume occurs as a consequence of splanchnic vasodilatation and ascites. All of these patients have an activated renin–angiotensin–aldosterone system (*secondary hyperaldosteronism*), and they manifest with hypotension due to a reduction of the effective circulating volume. Renal hypoperfusion and hyperaldosteronism lead to renal sodium and water retention, and therefore, edema formation. Concomitant hyponatremia is often observed, because the reduction of the effective circulating volume leads to nonosmotic stimulation of vasopressin secretion. This is particularly dangerous in the context of therapy with thiazide diuretics (see below).

Disorders of Water Homeostasis and Osmoregulation (Hyponatremia and Hypernatremia)

Definition, Diagnosis, and Clinical Features

Increase or decrease of the serum sodium concentration represents disorders in water homeostasis and osmoregulation. *Hyponatremia* (P_{Na} < 135 mmol/L; severe: < 125 mmol/L) occurs due to an excess of water, and *hypernatremia* (P_{Na} > 145 mmol/L; severe: > 155 mmol/L) due to a water deficit, always in relation to the concomitant total body sodium. Both disorders can be associated with a net increase or decrease of total body water. For differential diagnosis, it is therefore of critical importance to also assess the volume status of such patients (see above).

Diagnosis. Until recently, the serum sodium concentration was measured by means of flame photometry of total plasma samples (therefore including plasma lipids and proteins). As a consequence, massive hyperlipidemia (e. g., with triglycerides) or hyperproteinemia (e. g., with paraproteins) led to artificially low sodium concentrations due to expansion of total plasma volume (so-called *pseudohyponatremia*). The serum osmolality is normal in these cases. With the introduction in laboratories of ion-selective electrodes, for determining ion concentrations, this discrepancy has disappeared.

The accumulation of *osmotically active, nonpermeable substances* in the extracellular space leads to a net shift of water from the intracellular to the extracellular space as an attempt to correct hyperosmolality. The serum sodium concentration decreases; so-called *translocation hyponatremia.* In these patients serum osmolality is increased. The most important clinical example is severe hyperglycemia. Finally, it is important to notice that the accumulation of *osmotically active, permeable substances* does not alter the serum sodium concentrations, since these substances distribute equally between the intracellular and the extracellular space, but the serum osmolality is increased. The most important clinical example is the accumulation of urea in the context of azotemia. Tab. 30.**6** shows an overview of these particular situations and underlines the importance of measuring serum osmolality in patients with unclear hyponatremia.

Clinical Features. Disorders of serum osmolality and serum sodium lead to a volume shift between the intracellular and the extracellular space. As a consequence, cellular swelling occurs with hyponatremia and cellular shrinking with hypernatremia. Because the brain is located in a fixed volume, it is primarily affected by shifts in cellular volume due to disorders in serum sodium concentration or quick therapeutic correction measures. *Neurologic and psychiatric symptoms and signs* are therefore very typical in both situations, e. g., headache, nausea and vomiting, confusion, delirium, lethargy, and eventually coma. Hyponatremia is also associated with muscle weakness, whereas hypernatremia results rather in spasticity and hyperreflexia.

> Acute brain edema is observed with acute hyponatremia and also with a too rapid correction of severe hypernatremia, and can result in the death of the patient.

Hyponatremia (P_{Na} < 135 mmol/L)

Hyponatremia indicates water excess in the extracellular space. For differential diagnosis the volume status has to be considered at the same time. Three different clinical situations can be distinguished as follows (Tab. 30.**7**):

- *hypovolemic hyponatremia:* deficiency in total body water and sodium with an excess loss of salt compared to water

Table 30.**6** Osmotically active substances, serum sodium, and serum osmolality

	Group 1	Group 2	Group 3
Serum osmolality	normal	increased	increased
Serum sodium	decreased	decreased	normal
Examples	– lipids (hypertriglyceridemia) – proteins (paraproteinemia)	– glucose – mannitol – glycine – maltose (with intravenous immunoglobulin)	– urea (azotemia) – alcohols (methanol, ethanol, isopropanol) – glycols (ethylene glycol)
Classification	isotonic hyponatremia, "pseudohyponatremia"*	hypertonic hyponatremia, "translocational hyponatremia"	hyperosmolality with normal serum sodium

* Observed with older methods of sodium measurement such as flame photometry; is not currently a problem with ion-selective electrodes.

Table 30.**7** Differential diagnosis of hypotonic hyponatremia

Hypovolemic hyponatremia	Euvolemic hyponatremia	Hypervolemic hyponatremia
Third space – crush injury, rhabdomyolysis – pancreatitis, peritonitis, ileus, sepsis **Extrarenal loss** – *skin*: severe burns – *gastrointestinal tract:* vomiting with metabolic alkalosis, diarrhea **Renal loss** – *osmotic diuresis*: glucosuria, ketonuria, bicarbonaturia – *diuretics*: mainly thiazides! – *renal salt wasting*: interstitial nephropathies, cystic kidney diseases, proximal renal tubular acidosis, congenital tubular disorders – cerebral salt wasting – mineralocorticoid deficit (see Tab. 30.**12**)	**Excessive water intake** – primary psychogenic polydipsia **Syndrome of inappropriate ADH secretion (SIADH)** – *CNS diseases*: tumors, inflammatory conditions (meningitis, encephalitis, abscess), brain trauma, ischemic or hemorrhagic stroke, Guillain–Barré syndrome, acute psychosis – *malignancies*: lung and pancreas carcinoma, lymphomas – *pulmonary diseases*: inflammatory conditions (pneumonia, abscess, tuberculosis, aspergillosis), asthma, cystic fibrosis, respiratory insufficiency – *drugs*: ADH analogues (desmopressin DDAVP, oxytocin), chlorpropamide, vincristin, cyclophosphamide, carbamazepin, tricyclic antidepressive and antipsychotic drugs, NSAIDs – postoperative state, other stress and/or painful situations **Endocrine diseases** – glucocorticoid deficit – hypothyroidism **Reset osmostat** – pregnancy – chronic malnutrition	**Edematous diseases with secondary hyperaldosteronism** – cardiac failure – nephrotic syndrome – liver cirrhosis **Acute and chronic renal failure**

- *euvolemic hyponatremia:* moderate excess in total body water without edema formation and clinically normal volume status
- *hypervolemic hyponatremia:* excess of total body water and sodium with retention of more water than salt.

It is important for the understanding of hypovolemic hyponatremia, as well as hypervolemic hyponatremia (in the context of edematous disorders with secondary hyperaldosteronism), to know that a decrease in the effective circulating volume leads to *nonosmotic* stimulation of vasopressin secretion. This is an expression of the body's priority for volume regulation over osmoregulation. In these cases, the main therapeutic principle is correction of the volume status or the effective circulating volume (e. g., treatment of low cardiac output), whereas euvolemic hyponatremia is mainly treated by water restriction.

Hypovolemic Hyponatremia

Causes. Either renal or extrarenal losses of sodium and water can be responsible for this disorder. For differential diagnosis U_{Na} is a good parameter to measure:

- U_{Na} < 20 mmol/L suggests extrarenal losses via gastrointestinal tract, via skin with severe burns, or into a third space with sepsis, pancreatitis, or peritonitis.
- U_{Na} > 20 mmol/L suggests renal sodium and water loss. Main causes are either secondary due to osmotic diuresis, mineralocorticoid deficiency (see below), or diuretics. Alternatively, this condition can occur in the context of primary renal diseases (interstitial nephritis, polycystic kidney disease, or nephropathy in the contest of analgesic abuse).

Diuretics. In clinical settings, hypovolemic hyponatremia is most often observed following the use of diuretics. It mainly occurs when the dosage of these drugs is not adjusted with reduced water and salt intake or when increased losses occur in the context of acute diseases (e. g., diarrhea). Risk is highest with the use of thiazide diuretics. *Thiazide diuretics* block sodium transport in the distal tubule. As for all other diuretics, urinary dilution is compromised due to sodium loss. However, the interstitial concentration gradient is unchanged, since it is built up in the loop of Henle. In contrast, loop diuretics block sodium transport directly in the loop of Henle and therefore interfere with urinary dilution and concentration by inhibiting the establishment of an interstitial concentra-

tion gradient. If hypovolemia results in nonosmotic vasopressin stimulation, water retention is much more efficient in the context of thiazide medication than with loop diuretics, which can result in severe hyponatremia in very short time!

Euvolemic Hyponatremia

Causes. The most frequent cause of this disorder is the so-called syndrome of inappropriate anti-diuretic hormone (ADH) secretion (SIADH, Schwartz–Bartter syndrome). The differential diagnosis includes diseases of the central nervous system, pulmonary diseases, malignancies, and drugs, which stimulate ADH secretion or mimic the effect of ADH. The common denominator in all these situations is impaired water excretion due to enhanced vasopressin activity. The typical laboratory signs are:

- hyponatremia
- low serum osmolality
- impaired urinary dilution ($U_{Osm} > 300$ mOsm/L)
- hypouricemia.

Low serum uric acid is a sensitive parameter for the distinction of SIADH and subclinical volume depletion (e. g., in the context of diuretics or a renal or cerebral salt-wasting syndrome). The latter is associated with hyperuricemia.

It is important to recall that any *postoperative state* is associated with inappropriate ADH secretion. Therefore, volume repletion with glucose or hypotonic salt infusion immediately after an operation bears a high risk of acute severe hyponatremia. Young women after gynecologic or obstetric operations represent a patient group with a particularly high risk!

Differential Diagnosis. For diagnosis of SIADH, certain *endocrine disorders* should be excluded, particularly hypocortisolism and hypothyroidism. The pathogenesis of hyponatremia in these diseases is unclear. Another condition with identical laboratory results constellation to SIADH is called *reset osmostat*. These patients have stable mild hyponatremia in the range of 125–130 mmol/L. Typical causes are pregnancy (via human chorion gonadotropin secreted in the placenta) and chronic malnutrition.

Diagnostic Approach to Hyponatremia

The differential diagnosis in patients with hyponatremia is depicted in Fig. 30.**5**. The most important parameters are the serum osmolality, assessment of volume status, urinary osmolality, and urinary sodium concentration.

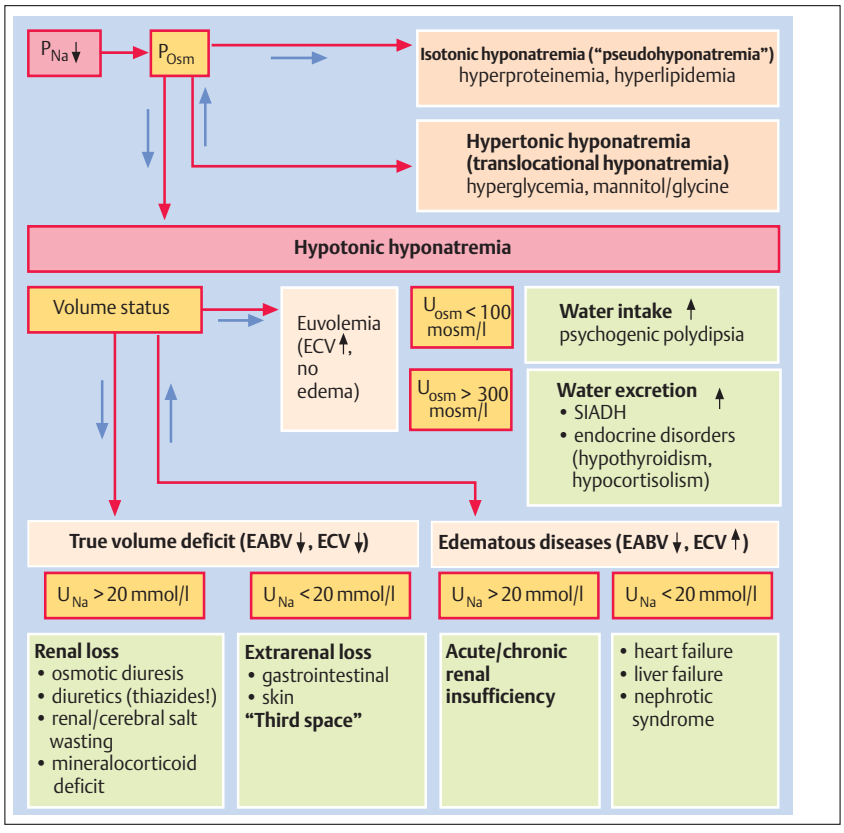


Fig. 30.**5** Diagnostic approach to hyponatremia. ECV = extracellular volume, EABV = effective arterial blood volume.

Table 30.**8** Differential diagnosis of hypernatremia

Hypovolemic hypernatremia	Euvolemic hypernatremia	Hypervolemic hypernatremia
Extrarenal losses – *skin*: intense sweating, severe burns – *gastrointestinal loss*: diarrhea, fistulas and tubes **Renal losses** – *osmotic diuresis*: severe hyperglycemia with diabetes mellitus, osmotic and loop diuretics – *renal salt wasting*: interstitial and cystic nephropathies, polyuria after obstruction or acute renal failure	**Reduced water intake** – patients with no access to water (children, severely ill and elderly patients) – disturbed thirst sensation (hypothalamic organic lesion) **Extrarenal losses** – *lungs*: hyperventilation with metabolic acidosis, fever and mechanical ventilation – *skin*: intense sweating **Renal losses with central diabetes insipidus** – *congenital/genetic*: *dominant:* vasopressin gene mutation *recessive*: Wolfram syndrome (DIDMOAD: diabetes insipidus, diabetes mellitus, optic atrophy, deafness) – *acquired*: CNS diseases (trauma, tumor, inflammatory and granulomatous diseases, aneurysm, Guillain–Barré syndrome) **Renal losses with nephrogenic diabetes insipidus** – *congenital/genetic*: *X-linked:* vasopressin V_2 receptor gene mutation *recessive:* aquaporin 2 gene mutation – *acquired*: interstitial nephropathies (analgesics, cystic kidney diseases, obstruction, myeloma kidney, sarcoidosis), chronic renal insufficiency, electrolyte disorders (hypokalemia, hypercalcemia), drugs (lithium, tetracyclines, amphotericin) **Renal losses with gestational diabetes insipidus (placenta-derived vasopressinase secretion)**	**Increased salt intake** – hypertonic infusions (e. g., $NaHCO_3$) – hypertonic dialysis – NaCl tablets **Endocrine diseases** – primary hyperaldosteronism – hypercortisolism

SIADH should be distinguished from *primary polydipsia*. Water intake > 15–20 L per day exceeds the renal capacity for water excretion and will lead to hyponatremia. This condition is easily distinguished from SIADH by measurement of the urinary osmolality, which is below < 100 mOsm/L in the case of polydipsia, but > 300 mOsm/L in the case of SIADH.

Hypervolemic Hyponatremia

This condition is usually associated with *edematous disorders* e. g., heart failure, nephrotic syndrome, and liver cirrhosis. The pathogenesis includes secondary hypoaldosteronism and nonosmotic stimulation of vasopressin secretion, as a consequence of reduced effective circulatory volume, and results in low U_{Na}. The differential diagnosis is usually easy in the clinical context of a given patient.

Hypernatremia (P_{Na} > 145 mmol/L)

Hypernatremia indicates water deficit in the extracellular space in relation to the total body sodium and is always associated with hyperosmolality. Similar to hyponatremia, we can distinguish three different conditions based on the volume status of the patient. The differential diagnosis is summarized in Tab. 30.**8**:

- *hypovolemic hypernatremia:* deficiency in total body water and sodium with an excess loss of water compared to sodium
- *euvolemic hypernatremia:* moderate excess in total body sodium without edema formation and clinically normal volume status
- *hypervolemic hypernatremia:* excess of total body water and sodium with retention of more salt than water.

Hypernatremia is a rare disorder, since the thirst mechanism is a very efficient compensation of water loss through skin, gastrointestinal tract, and respiration. Therefore, mainly patients with impaired access to free water intake (e. g., small children, elderly, severely ill patients) and patients with hypothalamic lesions affecting the thirst mechanism are affected.

Hypovolemic Hypernatremia

Either *renal or extrarenal causes* can lead to this disorder, which is characterized by an excess of water loss compared to salt loss. Extrarenal losses occur via the gastrointestinal tract (diarrhea, vomiting, fistulas) or the skin (sweating, burns) and are associated with U_{Na} < 20 mmol/L. Renal losses are observed in the context of ketoacidosis or hyperosmotic diabetic coma, but also with primary renal diseases (e. g., postobstructive renal disease or the polyuric phase of acute renal failure).

Euvolemic Hypernatremia

If only water is lost with stable total body sodium, the volume status remains stable. Water shifts occur from the intracellular to the extracellular space in order to maintain ECV and the effective circulatory volume. In the differential diagnosis a differentiation is made between inadequate water intake and renal and/or extrarenal water losses.

Causes. As described above, *inadequate intake* is only seen in patients with impaired access to free water ("too small, too old, too sick") and in patients with hypothalamic lesions affecting the thirst mechanism. Extrarenal water losses occur via the *lungs* and the *skin* (hyperventilation with metabolic acidosis, fever, sweating), whereas renal losses are caused by various forms of *diabetes insipidus*. These two situations can be distinguished by measurement of U_{Osm}. In the case of extrarenal losses urine is concentrated, with U_{Osm} > 800 mOsm/L, whereas in the case of diabetes insipidus urine is diluted, with U_{Osm} < 300 mOsm/L.

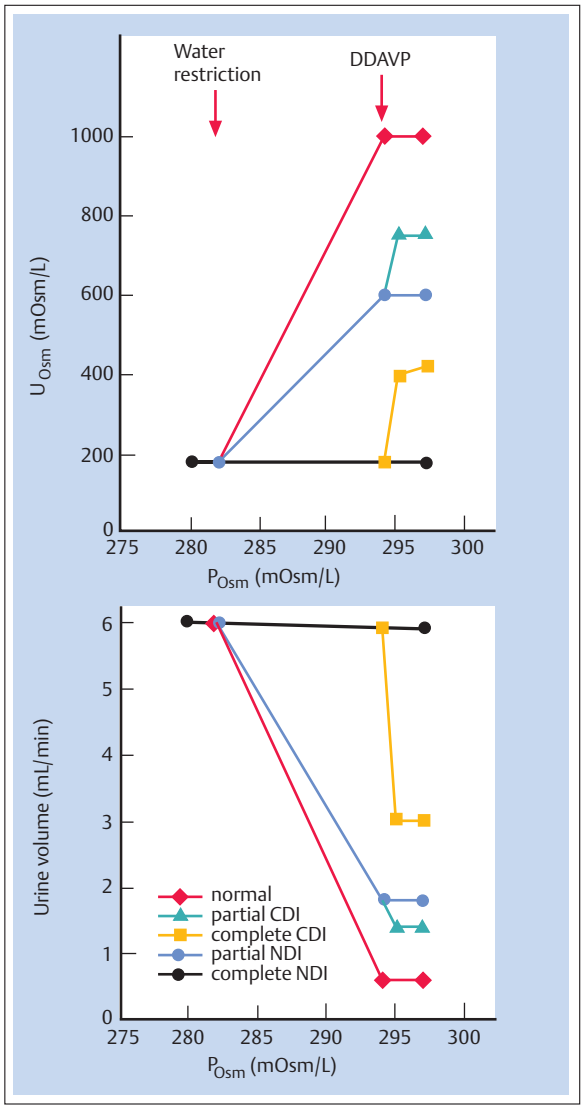


Fig. 30.**6** Scheme for interpretation of a thirst test. The thirst test is used for differential diagnosis between central (CDI) and nephrogenic (NDI) diabetes insipidus. The change of urine osmolality and urine volume is shown after a period with water restriction and subsequent application of a synthetic analogue of vasopressin (DDAVP).

Diabetes Insipidus. Diabetes insipidus is caused by a lack of vasopressin activity and results in polyuria and polydipsia. We can distinguish between *central diabetes insipidus* (CDI) with a lack of *ADH secretion* and *nephrogenic diabetes insipidus* (NDI) with a lack of *ADH effect* at the target organ. The former occurs as a congenital form (e. g., mutation in the vasopressin gene) or acquired in the context of central nervous system diseases. It can be corrected with exogenous application of vasopressin (e. g., the synthetic desmopressin, DDAVP). In contrast,

NDI does not respond to desmopressin. It also occurs as a congenital disease (mutations in the genes for the vasopressin receptor or the water channel). Acquired forms of NDI are observed with various chronic renal diseases (e. g., interstitial and cystic nephropathies), in the context of electrolyte disorders, e. g., hypokalemia and hypercalcemia, and it can also be caused by certain drugs (e. g., lithium). A particular form of diabetes insipidus is described during *pregnancy*, when placental secretion of an enzyme, called vasopressinase, can lead to accelerated degradation of vasopressin.

The differential diagnosis between central and nephrogenic diabetes insipidus can be made by experimental increase in serum osmolality by water restriction and subsequent application of 5 IU vasopressin ("thirst test").

Typical results of such a test are shown in Fig. 30.**6**.

Hypervolemic Hypernatremia

This disorder is mostly caused by *iatrogenic infusion* of hypertonic salt solutions. This can occur by excess of $NaHCO_3$ in the context of metabolic acidosis or cardiopulmonary reanimation, but also with hypertonic dialysis.

Endocrine disorders, e. g., hyperaldosteronism or hypercortisolism, should also be considered.

Diagnostic Approach to Hypernatremia

The differential diagnosis in patients with hypernatremia is depicted in Fig. 30.**7**. The most important parameters are assessment of the volume status, urine osmolality, and urine sodium concentration.

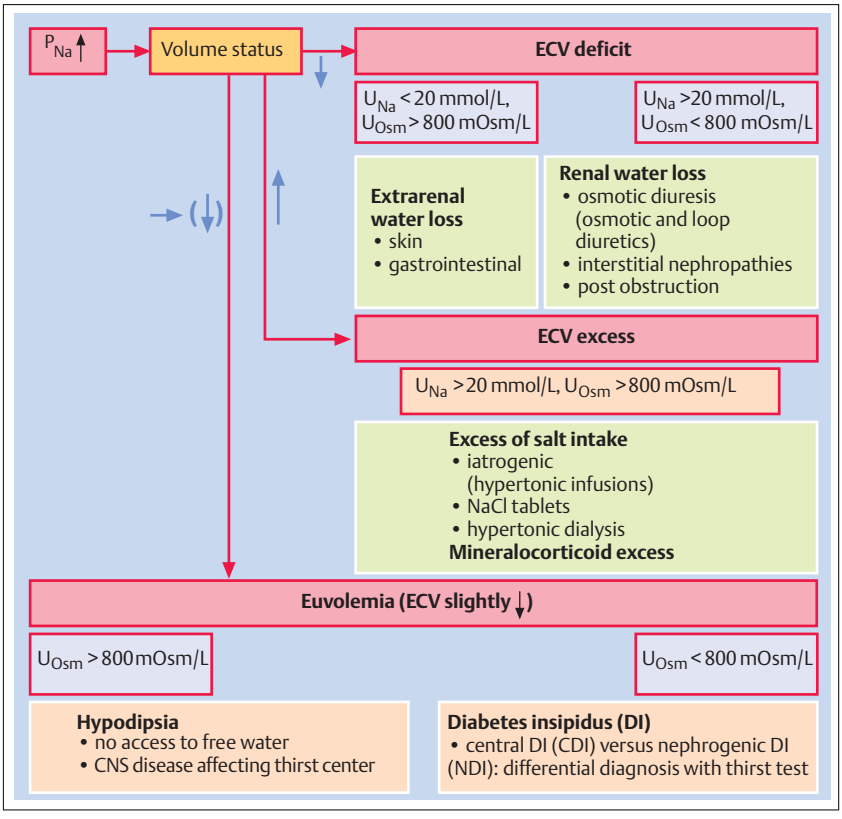


Fig. 30.**7** Diagnostic approach to hypernatremia.