

Joshua M. Thurman and Tomas Berl

Introduction

Disorders of water balance and serum Na (S_{Na}) are very common in hospitalized patients [1]. In health, water balance and plasma osmolality, and thereby S_{Na} , are tightly regulated by the kidney, which makes minute-by-minute adjustments to the composition of urine in order to maintain a near-constant plasma osmolality. The development of hyponatremia or hypernatremia may therefore reflect serious underlying illness and both conditions often suggest a poor prognosis for the underlying causative disease. Hypo- and hypernatremia are associated with increased morbidity and, equally vexing to the clinician, inappropriate correction may itself cause serious morbidity or mortality. A careful therapeutic approach as well as close attention to the patient's response are therefore important for the clinician caring for patients with these conditions.

Hypo- and hypernatremia are each the common manifestation of several distinct underlying diseases. Effective therapy depends upon an accurate evaluation of the underlying process and

different treatment strategies are often necessary, even when patients present with the same serum sodium level. A patient presenting with a S_{Na} of 115, for example, may be benefited or harmed by hydration with saline, depending upon whether the hyponatremia was caused by volume contraction, congestive heart failure, or the syndrome of inappropriate secretion of anti diuresis hormone (SIADH). Furthermore, water handling by the kidney can change quickly as the patient's condition changes. A patient who is volume contracted and is concentrating his or her urine at presentation may subsequently start excreting free water in response to rehydration. This patient's urine osmolality would initially be high but would fall in response to volume resuscitation. Perhaps the most important aspect of therapy, then, is continuous reassessment of patients and their response to therapy.

Normal Regulation of Water Balance

The serum sodium is determined by the total body sodium plus potassium and the total body water. Sodium is the primary extracellular osmole, so the serum sodium concentration usually reflects the osmolality of the extracellular fluid, and patients with disorders of water handling often present as hypo- or hypernatremic. Potassium is the primary intracellular osmole, and water equilibrates across cell membranes such that the intra- and extracellular osmolality will balance. The serum sodium concentration is,

J.M. Thurman, M.D. (✉)
Department of Internal Medicine,
University of Denver School of Medicine,
1775 Aurora Ct., M20-3103, Aurora, CO 80111, USA
e-mail: joshua.thurman@ucdenver.edu

T. Berl, M.D.
Department of Medicine, University of Colorado,
12700 E. 19th Ave., C281, Aurora, CO 80045, USA

therefore, primarily determined by the total body sodium, potassium, and water (2.1):

$$S_{\text{Na}} = \frac{(\text{TB}_{\text{Na}} + \text{TB}_{\text{K}})}{\text{TBW}}. \quad (2.1)$$

While this empirically derived relationship has undergone careful reanalysis by Nguyen and Kurtz [2], in large measure it predicts well changes in serum sodium concentration under most clinical circumstances. In the steady state each of these components is maintained. Therefore, daily losses must equal daily intake. The intake of both water and solute are inconstant, however. The average person consumes approximately 700–800 mOsm of solute and

1–3 L of water each day, but consumption is episodic. Water is also contained in food and generated by the oxidation of carbohydrates. In addition to their excretion in urine, water and solute are lost through the gastrointestinal tract, sweat, and water is lost through respiratory processes. In spite of variations in the intake and extra-renal losses of water and solute, the plasma osmolality is tightly maintained within 275–290 mOsm/kg. The primary mechanism by which the body maintains water balance in spite of variations in intake and losses is by adjusting the urine osmolality. The average daily U_{Osm} is determined by the intake of osmoles and the intake of water (2.2):

$$U_{\text{Osm}} = \frac{\text{Daily intake of osmoles}}{\text{Daily urine output}(\text{daily intake of water} - \text{non-renal losses})}. \quad (2.2)$$

The kidney can generate urine as dilute as 40–100 mOsm/kg [3] and as concentrated as 900–1,200 mOsm/kg [4]. Although this range tends to narrow with age, it still permits great flexibility in the renal response to the intake of food and water. If, however, the ratio of consumed osmoles and water exceeds this range, steady state can no longer be maintained and the total body water will increase or decrease (Fig. 2.1).

Serum sodium is determined by total body Na plus K and total body water (2.1), and the kidney could maintain serum sodium through its handling of either component. The active regulation of osmolality is primarily accomplished by regulation of the total body water, and it is useful to consider the renal handling of solute and water as separate functions. As water is gained or lost in relation to total body osmoles—decreasing or increasing the net plasma osmolality—the kidneys decrease or increase water reabsorption in the collecting duct. This response involves precise sensing of the plasma osmolality by osmoreceptors in

the hypothalamus, which control the production and release of the antidiuretic hormone, arginine vasopressin (AVP). AVP regulates insertion of water channels in the principal cells of the collecting duct [5]. As the number of channels increases and the cells become more freely permeable to water, it passes from the urine to the hypertonic medulla, thereby concentrating the urine and returning free water to the circulation.

Sodium handling by the kidney, in contrast, is regulated by the renin-angiotensin aldosterone system and by atrial natriuretic peptide, which respond to changes in the effective arterial blood volume. Retention or excretion of sodium in response to these systems is accompanied by retention or excretion of water, such that the net change is an isosmotic change of volume. However, changes in salt handling will affect the amount of filtered osmoles. Given the limits to the osmolality that the kidney can achieve, changes in the net amount of filtered osmoles will affect the limits of free water that the kidney is able to excrete (Fig. 2.1).

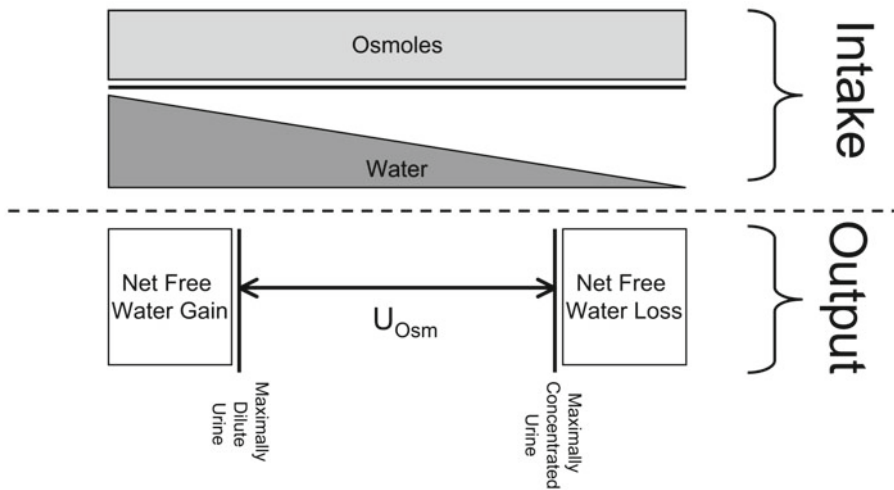


Fig. 2.1 Daily balance of solute and water. The body maintains water and solute balance by excreting an amount equal to the daily oral intake. As non-renal losses are fairly fixed, the concentration of the urine is adjusted so as to keep the net excretion equal to net intake. The amount

of overall solute and water consumed will therefore determine the concentration of the urine. If the balance of solute to water is too low or too high it may exceed the range of concentrations that the kidney can achieve, and hyponatremia or hypernatremia will ensue

Hyponatremia and Hypoosmolar States

Mechanisms of Hyponatremia

All patients with hyponatremia have consumed or received water in excess of the kidneys' ability to excrete it. If renal function is normal, this imbalance can occur because:

- AVP or, less commonly, an intrarenal AVP-independent mechanism limits the degree to which urine can be diluted.
- Inadequate intake and/or excretion of osmoles limits the amount of water that can be excreted.
- Water consumption exceeds even normal urinary dilution.

Because the kidneys can ordinarily excrete such a large volume of free water (approximately 20 L for normally functioning kidneys), hyponatremia due exclusively to polydipsia is rare, and hyponatremia usually occurs in patients with some limitation to their ability to excrete a water load. This may be due to a decrease in GFR, decreased NaCl reabsorption in the diluting segment of the nephron, or the presence of AVP [6].

Non-osmotic and Inappropriate Release of AVP

Typically, hypoosmolality causes full suppression of AVP release. For patients in whom the U_{Osm} is not maximally diluted (e.g., >100 mOsm/kg) one can assume that there is some AVP being released. Its presence in the setting of hyponatremia/hypoosmolality reflects that it is being released due to non-osmotic factors (i.e., decreased effective arterial blood volume) or it is being inappropriately released. By increasing the U_{Osm} , AVP limits the amount of water relative to solute that one can take in without retaining free water. For hyponatremic patients who are not maximally diluting their urine, the urine sodium concentration can help in the determination of the stimulus for AVP release as well as help guide therapy (Table 2.1). Urine sodium below 20 mEq/L is suggestive of a low effective arterial blood volume and non-osmotic release of AVP. Patients with a low urine sodium will likely retain sodium which is administered as part of their therapy. A urine sodium higher than 20 mEq/L, on the other hand, is more suggestive of SIADH. These patients are effectively euvolemic and will excrete administered sodium.

Table 2.1 Use of urinary osmolality and urinary Na in the evaluation of the hyponatremic patient

Volume status	Clinical setting	U_{osm} (mOsm/kg)	U_{Na}
Hypovolemic	Renal salt wasting <ul style="list-style-type: none"> • Diuretics • Mineralocorticoid deficiency • Salt-losing nephropathy • Bicarbonaturia • Ketonuria • Osmotic diuresis 	>100	>20 mEq/L
	Extrarenal Losses <ul style="list-style-type: none"> • Diarrhea • Vomiting • “Third space” 	>100	<10 mEq/L
Euvolemic	Polydipsia or Potomania Low solute intake	<100	↔
	SIADH Glucocorticoid deficiency Hypothyroidism Drugs	>100	>20 mEq/L
Hypervolemic	Congestive heart failure Nephrotic syndrome Cirrhosis	>100	<20
	Renal failure	>100	>20 mEq/L

Measurement of the urine electrolytes also helps to gauge how much free water is being lost in the urine. The main electrolytes in urine are sodium

and potassium, and their total concentration relative to the plasma sodium is used to measure the tonicity of the urine relative to plasma (2.3):

$$\text{Tonicity of urine relative to plasma} = \frac{(U_{Na} + U_K)}{S_{Na}} \tag{2.3}$$

If this ratio is less than one the urine is hypotonic relative to the plasma and electrolyte free water is being excreted, tending to correct the hyponatremia. Alternatively, if the ratio is greater than one the urine is hypertonic relative to plasma. This concentrated urine reflects a gain of electrolyte free water and will tend to exacerbate the hyponatremia (see (2.1)).

The urine can also be thought of as comprising two fractions—an isotonic fraction and a water

fraction. For example, if the ratio described by (2.3) is 0.5, the urine would be 50 % isotonic fluid and 50 % electrolyte free water. Together these fractions make a whole that has an electrolyte concentration half that of plasma. The rate of urine flow can then be measured to determine the electrolyte free water clearance and find the rate of electrolyte free water gain or loss. The electrolyte free water that is being excreted or retained is also a function of urine flow and defined by the following equation (2.4):

$$\text{Electrolyte - free water clearance} = \text{Urine flow} \times \tag{2.4}$$

For example, in the patient whose $U_{Na} + U_K$ is equal to 0.5 of the S_{Na} , half of the urine flow is electrolyte free water. If this patient is making 100 mL of urine an hour, the electrolyte free water clearance is 50 mL an hour. This calculation

allows one to predict the hourly change in total body water and plasma sodium.

As can be seen from (2.4), if the $U_{Na} + U_K > S_{Na}$, the electrolyte free water clearance will actually be negative. In this case, the urinary losses of

electrolytes exceed urinary losses of water and the production of urine is tending to exacerbate the hyponatremia even in the absence of water consumption. If one administered normal saline to a euvolemic patient with these urinary indices, the administered sodium would eventually be excreted (since the patient is euvolemic) in a more concentrated urine. This would result in a negative electrolyte free water clearance or a net gain in free water, further decreasing the serum sodium concentration.

Polydipsia and Inadequate Solute Intake

The kidney has a broad range of achievable osmolality, and regulation of the sense of thirst will also help maintain a balanced intake and excretion of solute and water. However, continued ingestion of too much water relative to intake of solute will exceed the diluting capacity of the kidneys, eventually leading to accumulation of total body water and hyponatremia (Fig. 2.1). Patients in whom hyponatremia is caused by excessive consumption of water should have a very dilute urine with full suppression of endogenous AVP. As can be deduced from (2.2) and Fig. 2.1, inadequate solute intake also limits the ability to excrete free water and can contribute to hyponatremia [7]. As with primary polydipsia, hyponatremia caused by inadequate solute intake (potomania) is also characterized by full suppression of AVP and maximally dilute urine. These two disorders can be distinguished by history or by collecting the urine and measuring the total osmoles.

Complications of Hypotonic Hyponatremia

Severe hyponatremia can cause significant morbidity. However, aggressive therapy is also associated with complications. The primary mechanism of injury during both the generation and the resolution of the hypoosmolar state is caused by the passage of water into or out of cells whose membranes are impermeable to some solutes but are freely permeable to water. Changes in the tonicity of the extracellular fluid cause an osmotic gradient across cell membranes and passage of water into or out of the cells. Because

the cells of the brain are contained within the fixed confines of the skull they are at great risk of injury and most of the symptoms of hyponatremia are neurologic.

Some adaptation to changes in tonicity can occur within 1–3 h. As plasma osmolality drops and cellular volume expands, interstitial pressure increases and forces extracellular fluid into the cerebrospinal fluid. The transfer of this extracellular fluid effectively relieves some of the elevation in intracranial pressure (ICP). This mechanism protects against mild, acute changes in hyponatremia but likely does not defend against more severe and long-standing hypotonicity. A second protective mechanism involves a reduction in intracellular solutes, a process that starts approximately 3 h after the onset of hypotonicity with the loss of cellular potassium. Adaptation proceeds through a decrease in the intracellular levels of organic solutes including glutamate, taurine, myo-inositol, and glutamine [8]. Although some of the decrease in the intracellular osmolytes occurs within 24 h, the loss of such solutes becomes more marked over the next several days and accounts for almost complete restoration of cerebral water. Because of the time required for full compensation, however, acute changes in the extracellular osmolality cause significant changes in cell volume.

Cerebral Edema

Severe acute hyponatremia is a medical emergency. If plasma osmolality drops too quickly the intracranial cells cannot adequately decrease the intracellular osmolytes, and water then crosses into the cells causing cerebral edema. This can be aggravated by the hypoxemia brought about by coexistent neurogenic pulmonary edema [9]. Precipitous changes in plasma osmolality can cause tentorial herniation and death. Even in otherwise healthy patients, failure to aggressively correct these patients is associated with high mortality rates [10]. Symptoms of hyponatremia, such as gastrointestinal complaints, lethargy, apathy, agitation, and cramps, most commonly occur with rapid decreases in serum sodium to below 125 mEq/L. Seizures and coma usually result from acute decreases to levels of approximately 110 mEq/L or less [11, 12]. When choosing goals

of therapy the clinician must weight the risks of overly rapid correction with those of inadequate correction. Patients with signs, symptoms, and risk factors for cerebral edema should be corrected more aggressively than those without.

The patients at greatest risk for cerebral edema are those in whom hyponatremia has developed over less than 48 h. This is because full adaptation to changes in tonicity requires 48–72 h. The magnitude of hyponatremia and its duration are, therefore, the most important factors to consider in planning the treatment goals.

Risk Factors for Severe Cerebral Edema

Hypoxia. The combination of hyponatremia and hypoxia may be particularly dangerous [9]. In experimental animals, hypoxia abrogates the volume adaptive response to hyponatremia, therefore resulting in increased brain edema [13].

Hospital-acquired hyponatremia in premenopausal women. Several reports suggest that menstruating women who develop acute hyponatremia while hospitalized are at greater risk of developing neurologic complications than men [10, 12, 14]. The incidence of hyponatremia appears to be similar for men and women in this setting, but women are more likely to develop symptoms or neurologic deficits. In a report in which 307 men developed postoperative hyponatremia, only one man had an outcome of permanent cerebral dysfunction or death [15]. In contrast, 33 of 367 women with hyponatremia had severe neurologic complications. The susceptibility of women to complications from hyponatremia may be due to differences in cellular adaptation to changes in osmolality in part related to hormonal differences [16].

Thiazide diuretics. Thiazide diuretics may predispose to the development of hyponatremia, and patients who develop thiazide-induced hyponatremia may be at higher risk for the development of neurologic complications. In one reported series, 12 of 129 patients who developed thiazide-induced hyponatremia died [17], highlighting the potential severity of thiazide-induced

hyponatremia. Thiazides reduce sodium chloride reabsorption in the distal tubule, the primary site for urinary dilution, thus decreasing the amount of electrolyte free water delivered to the collecting duct. Diuretics may also stimulate thirst. Loop diuretics may also induce volume depletion, but by interfering with the transfer of NaCl into the medullary interstitium they also reduce the gradient driving water reabsorption from the collecting tubules and thus are less likely to induce hyponatremia [18]. Certain patients seem to be particularly predisposed to develop hyponatremia on thiazides and develop recurrent hyponatremia when rechallenged. The patients most likely to develop hyponatremia due to thiazides appear to be the elderly, those with low body weight, and those with hypokalemia [19].

Children. Children are at risk for the development of hyponatremia in response to the administration of excessive hypotonic fluid [10]. Hyponatremia can result from overestimation of the fluid requirement as well as concurrent non-osmotic stimuli for the release of AVP, further limiting the patient's capacity for excretion of free water [20]. The susceptibility of children to neurologic sequelae may be due to limitation of space within the skull to accommodate brain edema, an inadequate degree of compensation, and delay in diagnosis and treatment.

Osmotic Demyelination Syndrome

In contrast to the risk of cerebral edema in the setting of acute hyponatremia, the correction of hyponatremia of longer duration (>48 h) is associated with an increased risk of osmotic demyelination syndrome (ODS). ODS is a life-threatening neurologic abnormality caused by demyelination, classically within the central basis pontis, but occurring also in extrapontine sites. Just as the rapid development of hypotonicity causes passage of water into the cells of the brain, overly rapid correction of hypotonicity induces an osmotic passage of water out of these same cells. Cells require several days to decrease intracellular osmolytes in response to a fall in extracellular

tonicity. Rapid correction causes cerebral dehydration by drawing water out of cells. This dehydration is enhanced by the delay in the aforementioned osmolytes' return to the brain. The downregulation of transporters during hypotonicity, such as SNAT2, may partially be responsible for this delayed restoration of solutes [21]. The overly rapid correction has been linked with the development of ODS [22]. Clinicians treating patients with hyponatremia thus face the dilemma of correcting hyponatremia quickly enough to avoid morbidity from cerebral edema without precipitating ODS.

Patients who are corrected overly rapidly may initially improve during therapy but show subsequent deterioration. In fact, the development of ODS can occur several days after the hyponatremia has been corrected [23]. The signs and symptoms of ODS classically include motor abnormalities potentially progressing to quadriplegia and respiratory paralysis, pseudobulbar palsy, lethargy, altered mental status, and coma, and it is often but not always fatal [24]. The diagnosis of ODS is confirmed by the presence of foci of demyelination on head magnetic resonance imaging (MRI), but these findings may lag behind clinical findings by several weeks. Thus early imaging may not reveal any pathology, and even later imaging may show no lesions. The diagnosis is primarily made on clinical grounds.

Risk Factors for Development of ODS

The risk of development of ODS is related to the severity and chronicity of the hyponatremia and the rate and magnitude of the correction. ODS is rarely observed in patients presenting with serum sodium greater than 120 mEq/L, and patients probably need to have been hyponatremic for at least 48 h [24]. Other risk factors for the development of ODS include alcoholism, malnutrition, hypokalemia, and severe hyponatremia (<105 mEq/L), as well as thiazide-induced hyponatremia in the elderly [24]. Catabolic patients, such as those with burns, may also be at increased risk [25].

Complications of Hyponatremia in CHF and Cirrhosis

Hyponatremia is a poor prognostic sign in both CHF [26] and cirrhosis [27]. This is probably because it reflects neurohormonal activation and thus reflects underlying circulatory derangements and disease severity. In patients with CHF, free water retention contributes to overall volume overload [28]. The development of hyponatremia may also limit the use of diuretics, thus impeding treatment. In addition to being a marker of disease, there is also evidence that hyponatremia itself contributes to worse outcomes. In a study in which patients were treated with a standard diuretic regimen versus high-dose furosemide combined with hypertonic saline, those that received the latter regimen achieved similar improvement in congestion but had improved serum sodium concentrations [29]. This group had fewer symptoms and had decreased mortality, indicating that correction of the serum sodium concentration may be of benefit in patients who achieve similar reductions in volume overload.

In patients with cirrhosis it is also difficult to distinguish whether hyponatremia is simply a marker of worse disease or whether it contributes to the development of complications and worse outcomes. There is some evidence that the adaptation of brain cells with cirrhosis and hyponatremia adversely affects cell function, and that hyponatremia predisposes patients with cirrhosis to the development of hepatic encephalopathy [30].

Treatment of Symptomatic Hyponatremia

Calculation of the Free Water Excess

As can be surmised from (2.1) hyponatremia can occur either by decrements in solutes (the numerator) or increments in total body water (the denominator). In most instances the predominant process is one that leads to an increase in total body water with a modest decrease in total body sodium.

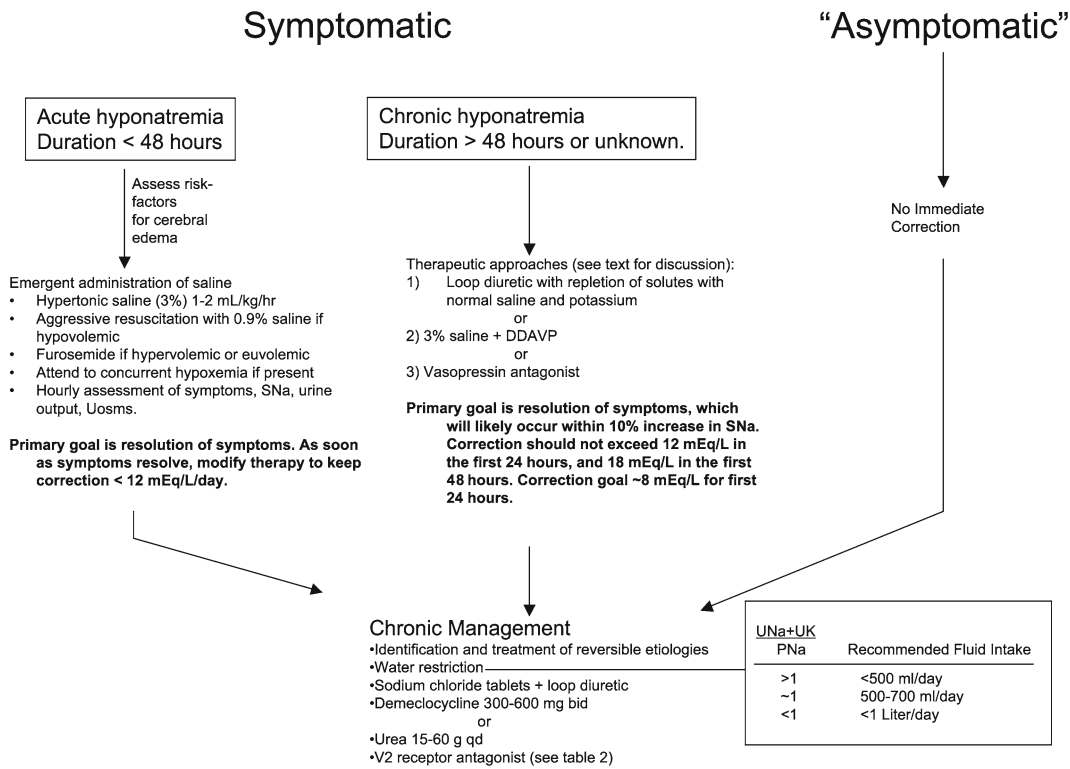


Fig. 2.2 Treatment of the patient with severe hyponatremia. Adapted with permission from Therapy of dysnatremic disorders, Joshua M. Thurman, Tomas Berl. In:

Wilcox CS, editor. Therapy in nephrology and hypertension, 3rd ed. WB Saunders; 2008

Even in hypovolemic states that are characterized by a decrease in body sodium, there is a relative

excess of body water. The free water excess can therefore be calculated as follows (2.5):

$$\text{Free water excess} = 0.6 \times \text{weight(kg)} \left[1 - \frac{(S_{Na})}{(\text{desired } S_{Na})} \right], \tag{2.5}$$

where $0.6 \times \text{weight}$ is taken as the total body water. For women the total body water may be approximated as $0.5 \times \text{weight}$.

In a 70 kg patient an increase in the S_{Na} by 10 % can be accomplished by removing the free water excess which can be estimated to be $0.6 \times 70 \text{ kg} \times (1 - 0.9) \approx 4 \text{ L}$. To accomplish this over 10 h will require 400 mL/h of electrolyte free water excretion.

Acute Hyponatremia

In view of the potentially life-threatening complication of acute hyponatremia as described

above there is a wide consensus that rapid correction of hyponatremia is indicated in patients in whom hyponatremia has developed over less than 48 h (Fig. 2.2). Generally, the presence of symptoms indicates that hyponatremia has developed too quickly for the adaptive mechanisms to compensate, and symptomatic patients have probably developed hyponatremia over a short period. Because patients who have acutely developed hyponatremia have not had time to adapt to the change in tonicity they also are at less risk of developing complications from correction of the hyponatremia (ODS) [24].

Goals of Therapy

Therapy should be initiated immediately in symptomatic patients, particularly in those at increased risk of complications, such as those with hypoxia, in whom, if present, intubation should be considered. For patients with hyponatremia of less than 48-h duration and/or risk factors for the development of cerebral edema, treatment is aimed at achieving a rapid increase in serum sodium.

Initial sodium administration should increase the serum sodium by approximately 2 mEq/L/h. A rapid increase in the serum sodium can be achieved by administering hypertonic saline (3 % saline contains 513 mEq/L of Na). Hypertonic saline is often started at 1–2 mL/kg/h. Studies in patients with impending trans-tentorial herniation have revealed that an increase in serum sodium by 5–6 mEq/L is sufficient to reverse the herniation and reduce ICP by 40 % [31]. This was achieved with 30 mL of 23.4 % saline. The primary goal for the administration of hypertonic saline is not the restoration of a sodium deficit but the rapid reversal of potentially life-threatening cerebral edema.

It must be noted that if the urine electrolyte free water clearance (2.4) is negative, the excretion of urine represents a net gain in free water. This point is critical to consider in the treatment of patients with euvolemic hyponatremia. Although normal saline is hypertonic relative to the plasma, it will eventually be excreted in a more concentrated form and will exacerbate the hyponatremia. Even if the urine electrolyte free water clearance (2.4) is negative, as long as $U_{Na} + U_K < 513$ mEq/L (the sodium concentration of 3 % saline) the urine is more dilute than 3 % saline. The ultimate excretion of the sodium will then result in a net decrease in total body water. If $U_{Na} + U_K = 250$ mEq/L, for example, the sodium in any administered 3 % saline will be excreted in a urine only half as concentrated, and half of the resultant urine volume will be a free water loss.

Chronic Symptomatic Hyponatremia

For patients in whom the duration of hyponatremia is unknown or is longer than 48 h, or in whom there are risk factors for the development of ODS, initial therapy is aimed at achieving rapid resolution of symptoms, but care must be

taken not to exceed well-defined goals [24]. Several general principles should guide the therapeutic approach.

- For patients with chronic hyponatremia cerebral water is increased by approximately 10 %, so a 10 % increase in serum sodium (or 10 mEq/L) should be sufficient for resolution of symptoms.
- If the duration is unknown or is longer than 48 h, as soon as symptoms resolve care should be taken not to overcorrect the serum sodium. At that point the hourly correction rate should not exceed 0.5 mEq/L/h. The cumulative limit of correction should be no more than 12 mEq/L/day or 18 mEq/L over 2 days, and a more appropriate goal of correction is approximately 8 mEq/L over 24 h.
- If patients exceed these goals, or if the rate and osmolality of the urine indicate that they will overcorrect (e.g., if the patient is making a large volume of hypotonic urine), then hypotonic fluid or dDAVP should be administered to control the rate of change and even to lower the S_{Na} concentration and keep the net correction within the desired range [32, 33].
- Restriction of free water: While patients with symptomatic hyponatremia should have free water restriction, the rate of correction achieved by this means is too slow in the symptomatic patient and other corrective measures must also be employed.

Therapeutic Approach

The overall goal of therapy is to remove free water from the patient with chronic symptomatic hyponatremia, and to prevent ODS. Several different strategies can be employed to achieve this, each with certain advantages. We describe three general approaches below.

Loop diuretics with sodium and potassium repletion. Loop diuretics cause excretion of electrolyte free water with a salt concentration approximating half-normal saline (e.g., ~75 mEq/L of $Na^+ + K^+$). Therefore, in patients who are euvolemic and receiving intravenous saline, furosemide can be used to prevent exacerbation of volume overload and to also increase electrolyte free water excretion. If the $U_{Na} + U_K$ after furosemide is ~75 mEq/L,

for example, one could titrate the dose to maintain approximately 300 mL/h of urine output. This urine would contain 150 mL/h of electrolyte free water. Depending upon the free water excess, one could increase or decrease these rates to change the rate of correction.

This approach offers control over the balance of water and electrolytes. It is, however, labor intensive as it involves frequent monitoring of urine volume and sodium and potassium losses. Likewise, it necessitates equally frequent decisions regarding the composition of the repletion fluid in order to achieve the desired rate of correction. It can also cause over-correction of hyponatremia, although this can be countered by the administration of free water. When properly conducted this approach results in neutral solute balance and net negative water balance, resulting in an increase in the serum sodium concentration.

Hypertonic saline and DDAVP. Hypertonic saline (e.g., 3 % saline at 1–2 mL/kg/h) will increase the S_{Na} . If reversible causes of hyponatremia (e.g., dehydration) are concurrently reversed, resulting in a water diuresis, the correction may be overly rapid. Some investigators, therefore, have recommended administering hypertonic saline concurrently with DDAVP to patients with chronic symptomatic hyponatremia [34, 35]. This approach addresses the concern of overly rapid correction, particularly in settings in which hyponatremia is transient. On the other hand, it runs the risk of worsening the underlying hyponatremia if the patient is not carefully monitored. Because this approach could lead to positive sodium balance, it may not be advisable for patients with marginal cardiac function. Furthermore, it does not directly address the need to achieve negative water balance.

Vasopressin antagonists. A third therapeutic approach is to give patients with chronic symptomatic hyponatremia a vasopressin antagonist. These drugs are likely to result over the ensuing hours in the excretion of a dilute urine. The S_{Na} should therefore be monitored at least every 4 h after administering these agents. Once the S_{Na} has increased by 6–8 mEq/L the urine output can be

matched with D5W to prevent further correction. Two vasopressin antagonists are currently available on the market [36, 37]. In a report on 18 patients who received conivaptan, the drug resulted in a mean increase in S_{Na} of 8 mEq/L in 24 h [37].

In general, all patients must be monitored closely for evidence of over- or under-correction. If the rise in S_{Na} indicates over-correction, the serum sodium exceeds the noted limits, and the serum sodium should be lowered. As a general rule, the S_{Na} should be monitored frequently. The urine output and vital signs should also be continually monitored. The U_{Osm} and urine electrolytes can be monitored periodically, particularly if DDAVP or a vasopressin antagonist is used.

Hypovolemic patients. Therapy can begin with the rapid administration of normal saline to achieve volume resuscitation. This will achieve partial correction of the serum sodium and may also stop the release of AVP leading to self-correction of the hyponatremia. These patients also need to be monitored to prevent excessively rapid correction. The same caution as to correction rates described in euvolemic patients needs to be exercised in this population.

Hypervolemic patients. The primary goal in hypervolemic patients is removal of free water. However, symptomatic patients require Na administration as well as water restriction to ensure a timely correction. Saline should typically be accompanied by furosemide to achieve a negative salt balance. If salt balance is maintained, the loss of free water in the urine will be the mechanism of correction of the S_{Na} .

Treatment of “Asymptomatic” Hyponatremia

At the outset it should be noted that some have questioned whether there are hyponatremic patients who are truly asymptomatic, as even mild hyponatremia may be associated with subtle neurologic impairments. A study of 122 such patients revealed that they frequently had gait

unsteadiness, attention deficits, and a 67-fold increased risk for falls [38]. The recently described association of hyponatremia with osteoporosis [39] may also contribute to the increased risk of fractures in this population [40]. The initial assessment of “asymptomatic” patients with hyponatremia involves consideration of the same issues—the duration of hyponatremia, underlying cause of hyponatremia, patient’s volume status, and quantitative assessment of how the patient is currently handling sodium and water. Since these patients almost always have chronic hyponatremia there is no urgency to treat them rapidly. Even without symptoms some risk stratification must be done. Hyponatremia is often a sign of underlying disease severity. Furthermore, the clinical manifestations may be subtle, such as mild gait imbalance. Even the asymptomatic patient, therefore, warrants careful consideration. In general, patients with $S_{\text{Na}} < 125$ or elderly patients who are at risk of falls should probably be treated. Patients with $S_{\text{Na}} < 120$ should be observed in the hospital with their labs repeated frequently enough to feel comfortable that the sodium level is correcting at the desired rate.

Hypovolemic Hyponatremia

Patients are classified as hypovolemic based upon their clinical history, physical examination, and a low urine sodium (e.g., < 20 mEq/L). Hypovolemic patients with asymptomatic hyponatremic should receive volume resuscitation with normal saline. The saline will be hypertonic relative to the patient’s serum, but several liters of normal saline will not cause a rapid rise in the serum sodium level as the change in tonicity will be equilibrated through the total body water. The other, perhaps more significant, effect on the serum sodium will be the fall in non-osmotic release of AVP. As patients become volume replete they may then begin excreting hypotonic urine resulting in auto-correction of the serum sodium. This can result in overly rapid correction of the serum sodium and necessitate administration of hypotonic fluids or dDAVP. Patients with other causes of hyponatremia, such as SIADH, may become volume depleted, thus presenting with two stimuli for

AVP release. This should become apparent if the patient remains hyponatremic after the volume resuscitation is complete. In that case they can subsequently be managed as euvolemic hyponatremia.

Hypervolemic Hyponatremia

Patients can appear clinically hypervolemic yet have non-osmotic release of AVP. This can occur because of a low effective arterial blood volume as is seen in patients with advanced heart failure or advanced cirrhosis. The hyponatremia reflects neurohormonal activation due to the hemodynamic abnormalities seen with both diseases, and this is often indicated by a low urine sodium (e.g., < 20 mEq/L). Consequently, hyponatremia due to either congestive heart failure or cirrhosis signifies severe underlying disease and is a poor prognostic sign. By definition, these patients have an excess of total body sodium and administration of saline is often not a therapeutic option. These patients frequently require natriuretic agents. In this regard, loop diuretics are preferable as they increase electrolyte free water clearance, while thiazides limit free water clearance. Some patients may present after being over-diuresed or after developing relative hypovolemia due to other causes such as diarrhea, however, and the clinical decision may be made to administer saline to a patient who is hypervolemic. The patients may be hypotensive or have an elevated creatinine. In those circumstances the administered volume may also improve the serum sodium concentration just as it does for hypovolemic patients.

The S_{Na} in patients with hypervolemic hyponatremia does not usually fall below 120 mEq/L. Chronic therapies are often unpleasant for patients, and there is no clear evidence to support a specific target. Most commonly therapy involves limiting intake of free water. The non-osmotic release of AVP in these patients limits their ability to excrete free water. One can calculate the electrolyte free water losses in the urine (2.4). Limiting the free water intake to less than the losses results in a net free water loss, correcting the hyponatremia, but adherence to this regimen is difficult and variable.

Table 2.2 Non-peptide AVP receptor antagonists

	Tolvaptan	Lixivaptan	Satavaptan ^a	Conivaptan
Receptor	V ₂	V ₂	V ₂	V _{1a} /V ₂
Route of administration	Oral	Oral	Oral	IV
Urine volume	↑	↑	↑	↑
Urine osmolality	↓	↓	↓	↓
Na excretion	↔	↔ low dose ↔↑ high dose	↔	↔

Adapted with permission from Ellison D, Berl T. *N Engl J Med.* 2007;356(20):2064–72

^aNot under further development

Table 2.3 Chronic medical therapy for diabetes insipidus

Etiology	Drug	Dose
Complete central diabetes insipidus	dDAVP	10–20 μ(mu)g intranasally every 12–24 h Start at 0.05 at bid, and titrate dose to effect
Partial central diabetes insipidus	dDAVP	
	Aqueous vasopressin	5–10 U SQ every 4–6 h
	Chlorpropamide	250–500 mg/day
	Clofibrate	500 mg tid–qid
Nephrogenic diabetes insipidus	Carbamazepine	400–600 mg/day
	Thiazide diuretics	Conventional doses
	NSAIDs	Conventional doses
	Amiloride (for lithium-induced DI)	5 mg qid

Adapted with permission from Thurman JM, Berl T. *Therapy of dysnatremic disorders.* In: Wilcox CS, editor. *Therapy in nephrology and hypertension*, 3rd ed. WB Saunders; 2008

Vasopressin Antagonists

Because free water restriction can be difficult for patients and may not be effective in all settings, the recent development of vasopressin antagonists may provide a more easily tolerated treatment (Table 2.2). The vasopressin antagonists are a group of small molecule antagonists that block the action of AVP at its receptors. One of the antagonists, conivaptan, antagonizes both the V_{1a} and V₂ receptors. The others currently available selectively block the V₂ receptor. Blockade of both the V_{1a} and V₂ receptors causes a vasodilatory effect (through antagonism of V_{1a}) and an aquaretic effect (through antagonism of V₂). This could make conivaptan appropriate for the treatment of congestive heart failure, where the vasodilatory effect may be beneficial [41], but inappropriate for disorders such as cirrhosis. Conivaptan has been shown to decrease pulmonary capillary wedge pressure but the effect could be related to volume loss rather than a change in cardiac function [42]. Because the action of the other antagonists is limited to the V₂ receptor,

and given that non-osmotic release of vasopressin is the primary cause of free water excess in these conditions, the V₂ selective antagonists specifically target the underlying cause of hyponatremia in these diseases. The oral V₂ antagonists Lixivaptan [43] and Tolvaptan [44, 45] have been used effectively to induce a water diuresis in patients with CHF (Table 2.3).

A number of studies have reported that the vasopressin antagonists raise the serum sodium in patients with cirrhosis. Lixivaptan has been used by several different investigators, all of whom reported increases in the serum sodium [46–48]. While the drug may have a small effect on sodium excretion in these patients, it seems to raise the S_{Na} in patients with cirrhosis primarily through its aquaretic effects [48]. Dilutional hyponatremia in cirrhotic patients may predispose them to hepatic encephalopathy, and a worse outcome before and after liver transplantation [49, 50], but no studies have yet demonstrated a clinical benefit from treatment with V₂ antagonists.

Euvolemic “Asymptomatic” Hyponatremia

Hyponatremia in clinically euvolemic patients is usually caused by the SIADH, drugs, or endocrinopathies (see Table 2.1). The discontinuation of the drugs and treatment of the underlying endocrine disorder is necessary. Normally functioning kidneys have a very large capacity to excrete free water, so hyponatremia usually involves factors limiting the full excretion of water. Conversely, even patients with severe SIADH require the intake of water in order to become hyponatremic. For these reasons, therapy of patients with asymptomatic euvolemic hyponatremia begins with free water restriction. Measurement of the urine osmolality and calculation of the electrolyte free water clearance permit assessment of whether AVP is present, the rate at which the patient will correct their serum sodium if they stop oral intake of water, and estimation of the free water restriction necessary to start correcting their serum sodium. Alternatively, empiric free water restriction can be instituted based upon urine free water clearance (Fig. 2.2). In addition to the compliance limitation, it is evident that when $U_{Na} + U_K$ exceeds S_{Na} essentially no degree of water restriction is likely to be beneficial [51].

In “asymptomatic” patients, the acute administration of intravenous saline is unnecessary. For chronic control of the serum sodium, increasing the intake of dietary osmoles increases the amount of free water a patient can safely consume (2.2). This can be achieved with salt tablets or with urea tablets, although salt tablets induce thirst and urea tablets are considered unpleasant and frequently unpalatable. Loop diuretics induce production of a dilute urine and can increase patients’ ability to excrete free water, but may cause hypovolemia in patients who present as euvolemic. Thus, concurrent NaCl administration is necessary.

Lithium and demeclocycline cause nephrogenic diabetes insipidus. By impeding the renal response to AVP these drugs can be useful in the treatment of SIADH. Demeclocycline is usually started at 300–600 mg twice a day, and achieves its maximum aquaretic effect in about 2 weeks. Free water restriction can be eased during this time period, and rechecking the urine electrolytes permits a revised determination of the amount of

free water that a patient can safely consume. Demeclocycline is not recommended in pregnant women or children, and it can cause photosensitivity. It can also cause gastrointestinal discomfort and renal dysfunction, particularly if there is concomitant hepatic disease.

The vasopressin antagonists specifically correct the mechanism that causes hyponatremia in SIADH. Most of the experience with these agents is in patients with SIADH. Several studies have demonstrated efficacy of these agents at inducing aquaresis and increasing the S_{Na} [45, 46, 52]. In the largest trial reported to date (SALT I and II) more than half of the 223 patients who received Tolvaptan were euvolemic and they increased their S_{Na} consistently [42].

Patients with SIADH often have much lower S_{Na} values than patients with cirrhosis or CHF. The rationale for a treatment that increases the S_{Na} is therefore greater, although the absolute goals of therapy are still not certain. The V2 antagonists are an important emerging option for chronic treatment of patients with SIADH. Those agents with selective activity at the V2 receptor should be used in order to avoid hypotension. As there is not yet much experience with these agents, they should be initiated at the lowest available dose, when they become available. The urine osmolality can be monitored, and the dose can gradually be increased. These drugs should permit easing of the free water restriction, and may increase the achievable S_{Na} . Long-term administration of a V2 antagonist has proven to be safe and effective [53], and ODS has not been reported with these agents. However, with further experience possible adverse effects may emerge as the use of the drug widens.

Hypernatremic States

Hypernatremia results from an increase in total body Na plus K or a decrease in total body water. Because sodium is the main plasma electrolyte, hyperosmolality that is caused by a fall in total body water is marked by an increased plasma sodium concentration. Free water can be lost in urine, in gastrointestinal tract, through respiration, or through insensible losses. Hypernatremia,

or hyperosmolarity, occurs in patients whose intake of free water is insufficient to match these losses. The addition of osmoles that cannot pass freely into cells into the extracellular compartment—such as sodium, glucose, or mannitol—will cause water to shift out of the cells until osmotic balance is established. In the cases of glucose or mannitol this shift of water decreases the S_{Na} even though the net serum osmolality is increased. Patients with severe hyperglycemia, for example, often present with decreased S_{Na} levels, although they have an increased serum osmolality. As insulin is administered and the glucose level falls, the S_{Na} will increase. Furthermore, these patients often also have a net loss in total body water due to osmotic diuresis induced by the hyperglycemia, and after normalization of the serum glucose the S_{Na} is often increased.

Even in patients with severe defects in their ability to concentrate urine, thirst and increased oral intake can usually compensate for free water losses. Therefore, a rise in S_{Na} usually occurs when there is also limited access to free water. For example, if a patient whose maximum U_{Osm} is 200 mOsm/kg eats 800 mOsm/day, he or she only needs to take in 4 L of free water (plus enough to compensate for insensible losses) to stay in balance (Fig. 2.1). If this patient becomes impaired and maintains a near-normal intake of solute but cannot maintain this intake of free water, however, he or she will become hypernatremic.

Mechanisms of Hypernatremia

The addition of sodium or loss of water may cause hypernatremia (2.1). As stated above, however, the maintenance of hyperosmolarity requires impaired access to free water. Awareness of clinical settings in which this commonly occurs aids in its prevention. Predisposing factors include high free water losses, an impaired sense of thirst or impaired sensorium, or lack of access to water.

A decrease of the maximal urine concentration that the kidneys can achieve obligates an increase in the minimal intake of water required

to stay in balance (Fig. 2.1). Concentration of the urine requires (1) release of AVP from the hypothalamus, (2) response of the collecting ducts to the AVP, and (3) a hypertonic renal medulla that favors reabsorption of water from the urine [6]. Failure of the hypothalamus to release AVP sufficiently to maintain the P_{Osm} is referred to as central diabetes insipidus (DI). Failure to concentrate the urine in response to AVP is referred to as nephrogenic DI. The therapeutic importance of this distinction is that administration of vasopressin will reverse the defect and increase the U_{Osm} in patients with central DI, but it will have little effect in patients with nephrogenic DI.

Complications of Hypernatremic States

The complications of hyperosmolar states are primarily caused by the shift of water out of cells. As with hypoosmolar states, the most serious complications occur due to injury to neurons, or traumatic injury to the central nervous system caused by cell shrinkage [54]. Symptoms of hyperosmolarity can include lethargy, seizures, hyperreflexia, nausea, vomiting, seizures, and coma [55]. Mortality may be as high as 70 % in acute hyperosmolar states and long-term sequelae are common [56].

Cells adapt to hyperosmolarity by increasing the intracellular osmolarity, essentially by the reverse process of that used to decrease intracellular osmolarity in response to hypoosmolarity. As with the response to hypoosmolality, adaptation starts within hours but probably continues over several days before approaching normalization of the intracellular water content [11]. The initial response is to increase the cellular content of sodium, potassium, and chloride [57]. With more prolonged hyperosmolarity, the intracellular content of glutamine, glutamate, myoinositol, taurine, and urea increases [57]. Given the lag in adaptation, acute hyperosmolarity causes a greater degree of cellular dehydration and poses a greater risk of neurologic injury. Severe hyperosmolarity is associated with myelinolysis [25, 58].

Correction of hyperosmolarity can cause water to shift back intracellularly, and can cause cerebral edema if performed too rapidly. Patients with chronic hypernatremia are less likely to be symptomatic from the hypernatremia as they will have more fully adapted. However, they are also at greater risk of complications from therapy. Thus, correction of hyperosmolarity should be more gradual in these patients.

Treatment of Hypernatremia

Treatment of hypernatremia and hyperosmolarity must emphasize prevention as there are well-defined groups at risk, and it is commonly iatrogenic [59, 60]. Furthermore, even when the S_{Na} is measured and found to be elevated, treatment is often delayed [59, 60]. Patients at greatest risk of developing hypernatremia include infants and the elderly, hospitalized patients who are receiving hypertonic solutions such as high-protein nutritional supplements, patients receiving loop diuretics, those with altered cognition, and those incapable of drinking ad libitum. Patients who are polyuric or who have urinary

concentrating defects are at risk of developing hypernatremia. Diabetics as a group are also at increased risk of free water depletion since hyperglycemia induces an osmotic diuresis. Patients receiving lactulose frequently have hypotonic stool losses.

The treatment of hypernatremia has two central goals:

- Restoration of water deficit
- Decrease of ongoing water losses

Estimation of Free Water Deficit

Correction of hypernatremia and restoration of water losses involve the administration of free water, and the amount of free water necessary to normalize the S_{Na} can be estimated. In determining how much free water to administer one needs to account for the free water deficit and the ongoing free water losses. If one calculates the free water deficit without accounting for these losses, the therapy will undershoot its target.

From (2.1) and (2.5), one can see that an increase of the S_{Na} above normal by a given percentage indicates a decrease of total body water by the same percentage. The water deficit can therefore be calculated as follows (2.6):

$$\text{Free water deficit} = 0.6 \times \text{weight (kg)} \left[\frac{(S_{Na})}{140} - 1 \right], \quad (2.6)$$

where $0.6 \times \text{weight}$ is taken as the total body water and 140 mEq/L is the normal S_{Na} .

For women the total body water may be approximated as $0.5 \times \text{weight}$. The percentage of body weight that is water may be lower in the elderly. Also, in patients with a large free water deficit the free water comprises a smaller fraction of the body weight. Calculation of the free water deficit in patients who are severely hyperosmolar can therefore be performed using $0.4 \times \text{weight}$ as the estimate of total body water [61].

Ongoing urinary water losses can be estimated using (2.4), the formula for electrolyte free water clearance. If, for example, a patient is excreting 200 mL of urine each hour, and half of it is electrolyte free water, then the patient must receive

100 mL/h of free water just to maintain his or her current S_{Na} . The loss of free water from extrarenal sources must be estimated, but measurement of the change in S_{Na} (either up or down) can be used to estimate the change in total body water (2.6). The change in total body water should roughly equal the amount of free water taken minus that lost in the urine and that lost from extrarenal sources. Thus, extrarenal losses can be deduced.

Rate of Correction

To minimize the risk of cerebral edema hypernatremia should be corrected in a controlled fashion, particularly in those in whom the condition has been present for more than 48 h. In contrast, in patients whose S_{Na} has risen rapidly the correction

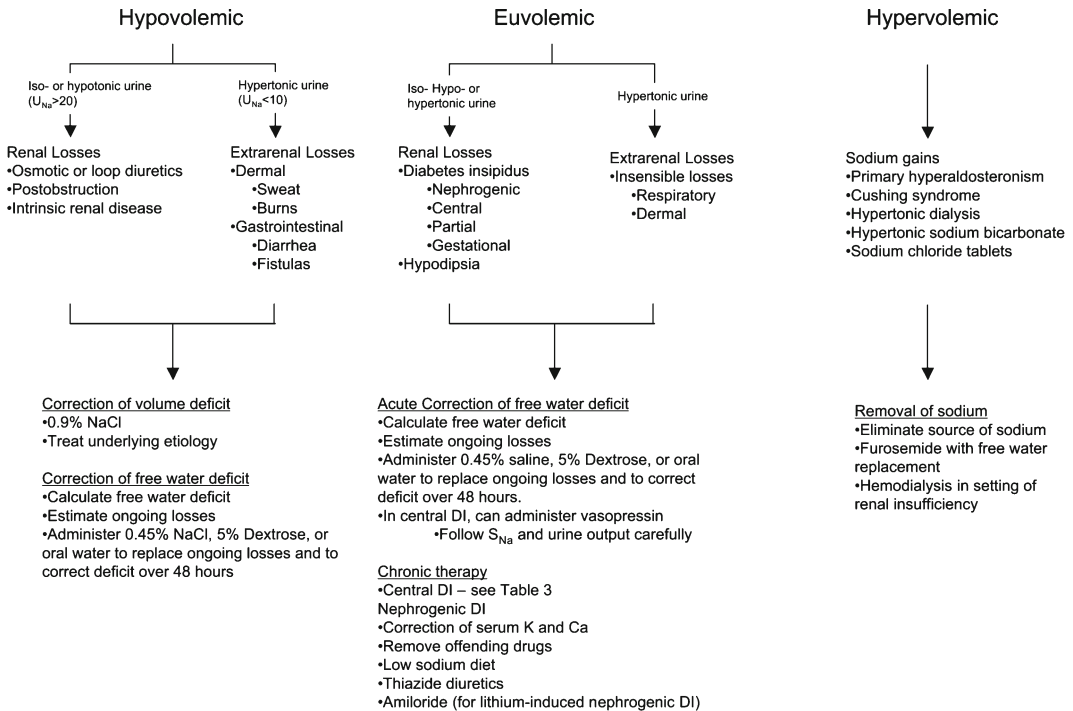


Fig. 2.3 Diagnostic approach to the patient with hyponatremia based upon clinical volume status. Adapted with permission from *Therapy of dysnatremic disorders*,

Joshua M. Thurman, Tomas Berl. In: Wilcox CS, editor. *Therapy in nephrology and hypertension*, 3rd ed. WB Saunders; 2008

can also probably proceed rapidly as cerebral adaptation is less likely to be complete. Correction of the free water deficit should occur over 48 h, with the rate of correction not exceeding 2 mEq/L/h. A slower rate is appropriate, however, if the patient is not symptomatic. For example, two studies in children found that outcomes were better when the rate of correction was ≤ 0.5 mEq/L/h [62, 63], and no complications were seen in patients corrected at this rate.

Volume Status

Assessment of the hyperosmolar patient includes clinical estimation of volume status, and measurement of urine osmolality, sodium, potassium, and urine flow rate. Perturbations in the total body water may also be accompanied by perturbations in the total body osmoles, and treatment is guided by the patient's volume status and urine sodium (Fig. 2.3).

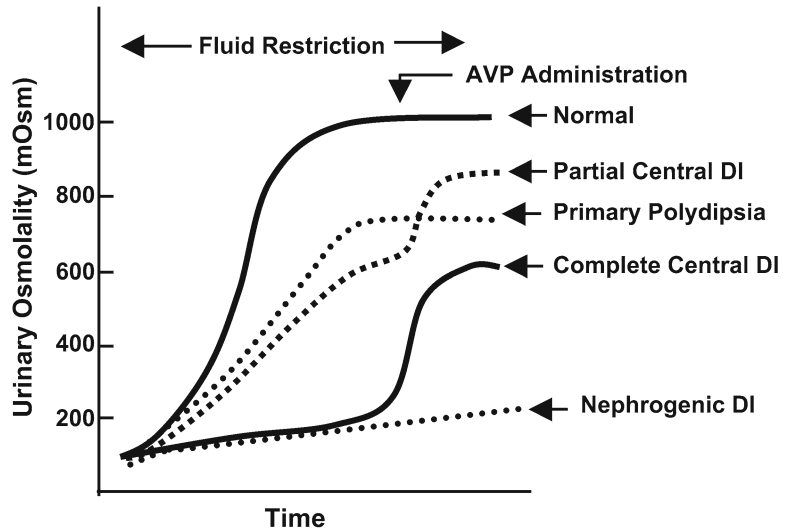
Hypovolemic Hypernatremia

Patients who lose hypotonic fluids and do not adequately replace them can become hypovolemic and hypernatremic. Therapy should usually begin with isotonic fluid such as normal saline. Volume resuscitation with isotonic fluids will restore the extracellular fluid and hemodynamic stability. This fluid will be relatively hypotonic compared to the patient's plasma and will cause a slight decrease in the S_{Na} , although this will be modest. Once the patient is euvolemic, hypotonic fluid (such as 0.45 % saline or D5) can be used to correct the free water deficit.

Euvolemic Hypernatremia

Initial therapy of patients with euvolemic hypernatremia is the repletion of free water—either intravenously or orally. As described above, the amount of water administered should aim to match ongoing losses and correct the free water deficit

Fig. 2.4 Diagnostic approach to patients with diabetes insipidus based upon the response of the urine osmolality to exogenous AVP. Adapted with permission from Robertson G. *Am J Med.* 2006;119(7 Suppl 1): S36–42



over 48 h. It is important, but sometimes difficult, to determine the source of free water losses. Polyuria, a submaximally concentrated urine, or a positive electrolyte free water clearance indicates ongoing urinary losses of free water. In hypernatremic patients with polyuria and/or an inappropriately dilute urine there must be a defect in urinary concentration as the hypernatremic state should induce AVP-mediated concentration of the urine. These patients have effectively failed a water deprivation test. The distinction, then, is whether urinary water losses are caused by central diabetes insipidus, nephrogenic diabetes insipidus, or an osmotic diuresis. This last possibility would be indicated by an elevated U_{Osm} (indicating an intact AVP axis) but a positive electrolyte free water clearance (2.4). Such patients can concentrate their urine, but large quantities of non-electrolyte solute (such as glucose, urea, or mannitol) obligate the loss of water.

In patients with polydipsia and polyuria who present with a normal serum sodium it can be difficult to differentiate whether the polydipsia is causing the polyuria or vice versa. The response of a polyuric patient to exogenous vasopressin helps distinguish primary polydipsia, central DI, and nephrogenic DI (Fig. 2.4). Administration of AVP can be as aqueous vasopressin or dDAVP. Aqueous vasopressin has a shorter half-life and

may be preferential in the acute setting. It is an agonist for the V_1 receptor, however, and is contraindicated in patients with vascular disease. Patients with central DI should respond to the exogenous AVP by decreasing their urine flow and increasing their urine osmolality [64]. An increase in the U_{Osm} of more than 10 % is diagnostic of at least a component of central DI.

Ongoing treatment with exogenous vasopressin reverses the primary defect of central DI and decreases the free water requirement (nn). Aqueous vasopressin has a very short half-life and because of its vasoconstrictive action should not be given intravenously; it is mainly used in transient postoperative DI. dDAVP has a longer half-life (8–12 h) and has less activity at the V_1 receptor. It is less likely, therefore, to cause vasoconstriction. It can also be administered intranasally or orally. The intranasal preparation provides $10 \mu(\text{mu})\text{g}/0.1 \text{ mL}$. The oral preparation is available as 0.1 or 0.2 mg tablets. When prompt anti-diuresis is needed a parenteral route should be considered and is effective at 1–2 $\mu(\text{mu})\text{g}$ every 8–12 h. dDAVP should be started at a low dose and can be titrated to achieve a decreased urine output. The lowest effective dose should be used in order to minimize cost and the risk of hyponatremia. Events such as a CVA can cause transient central DI. Patients should therefore be

periodically reassessed to determine whether they still need the dDAVP (e.g., by reducing the dose and observing for a significant increase in urinary volume) and the S_{Na} should be monitored periodically. Care should also be taken if the patient is receiving large volumes of free water replacement. Continued replacement in addition to dDAVP may cause an overly rapid fall in the S_{Osm} . Vasopressin does not, itself, lower the S_{Osm} , however; it only decreases urinary losses. One hour after administration of vasopressin, the urine volume and urine osmolality should be measured.

Alternative therapies for central DI include chlorpropamide, clofibrate, and carbamazepine. These drugs are not as effective as vasopressin, but they may be useful when vasopressin is unavailable. These agents potentiate the release and/or response to endogenous AVP. Chlorpropamide may also increase water intake. Thiazide diuretics (and amiloride for lithium-induced DI) may also be effective at decreasing free water losses. By inducing volume depletion these drugs enhance proximal sodium and water reabsorption. Thiazides also reduce the absorption of NaCl at the distal tubule without decreasing the osmolality in the medulla, and may also increase expression of aquaporin-2 [65]. Loop diuretics, in contrast, should not be used in patients with DI as they can decrease the medullary tonicity and reduce free water reabsorption in the collecting ducts. Potential future therapies for DI include manipulation of the chaperone proteins that enable insertion of aquaporin-2 in the epithelial cell membrane [66].

Hypervolemic Hyponatremia

Patients who are clinically hypervolemic and also have hyponatremia have an increase in TBW but also a greater proportional increase in total body Na (2.1). Hypervolemic hyponatremia may, in fact, not be uncommon, particularly in intensive care unit settings [67, 68]. Administration of free water will cause a volume expansion, so treatment to increase natriuresis should also be employed. Thiazide diuretics may be useful, but are not as potent as loop diuretics. Loop diuretics, on the other hand, will increase free water losses, likely increasing the need for free water replacement.

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