Review Article

Primary Care

HYPONATREMIA

HORACIO J. ADROGUÉ, M.D.,
AND NICOLAOS E. MADIAS, M.D.

HYPONATREMIA is defined as a decrease in the serum sodium concentration to a level below 136 mmol per liter. Whereas hypernatremia always denotes hypertonicity, hyponatremia can be associated with low, normal, or high tonicity.[1,2] Effective osmolality or tonicity refers to the contribution to osmolality of solutes, such as sodium and glucose, that cannot move freely across cell membranes, thereby inducing transcellular shifts in water.[3] Dilutional hyponatremia, by far the most common form of the disorder, is caused by water retention. If water intake exceeds the capacity of the kidneys to excrete water, dilution of body solutes results, causing hypo-osmolality and hypotonicity (Fig. 1B, 1E, 1F, and 1G). Hypotonicity, in turn, can lead to cerebral edema, a potentially life-threatening complication.[4] Hypotonic hyponatremia can be associated, however, with normal or even high serum osmolality if sufficient amounts of solutes that can permeate cell membranes (e.g., urea and ethanol) have been retained (Fig. 1C). Importantly, patients who have hypotonic hyponatremia but normal or high serum osmolality are as subject to the risks of hypotonicity as are patients with hypo-osmolar hyponatremia.

The nonhypotonic hyponatremias are hypertonic (or translocational) hyponatremia, isotonic hyponatremia, and pseudohyponatremia.[1,2] Translocational hyponatremia results from a shift of water from cells to the extracellular fluid that is driven by solutes confined in the extracellular compartment (as occurs with hyperglycemia or retention of hypertonic mannitol); serum osmolality is increased, as is tonicity, the latter causing dehydration of cells (Fig. 1D). Retention in the extracellular space of large volumes of isotonic fluids that do not contain sodium (e.g., mannitol) generates iso-osmolar and isotonic hyponatremia but no transcellular shifts of water. Pseudohyponatremia is a spurious form of iso-osmolar and isotonic hyponatremia identified when severe hypertriglyceridemia or paraproteinemia increases substantially the solid phase of plasma and the sodium concentration is measured by means of flame photometry.[1,2] The increasing availability of direct measurement of serum sodium with the ion-specific electrode has all but eliminated this laboratory artifact.[5]

A common clinical problem, hyponatremia frequently develops in hospitalized patients.[6] Although morbidity varies widely in severity, serious complications can arise from the disorder itself as well as from errors in management. In this article, we focus on the treatment of hyponatremia, emphasizing a quantitative approach to its correction.

CAUSES

Hypotonic (dilutional) hyponatremia represents an excess of water in relation to existing sodium stores, which can be decreased, essentially normal, or increased (Fig. 1). Retention of water most commonly reflects the presence of conditions that impair renal excretion of water[1,7,8]; in a minority of cases, it is caused by excessive water intake, with a normal or nearly normal excretory capacity (Table 1).[7]

Conditions of impaired renal excretion of water are categorized according to the characteristics of the extracellular-fluid volume, as determined by clinical assessment (Table 1).[9] With the exception of renal failure, these conditions are characterized by high plasma concentrations of arginine vasopressin despite the presence of hypotonicity.[10,11] Depletion of potassium accompanies many of these disorders and contributes to hyponatremia, since the sodium concentration is determined by the ratio of the "exchangeable" (i.e., osmotically active) portions of the body's sodium and potassium content to total body water (Fig. 1G).[12-14] Patients with hyponatremia induced by thiazides can present with variable hypovolemia or apparent euvolemia, depending on the magnitude of the sodium loss and water retention.[1,15-17]

Excessive water intake can cause hyponatremia by overwhelming normal water excretory capacity (e.g., primary polydipsia) (Table 1). Frequently, however, psychiatric patients with excessive water intake have plasma arginine vasopressin concentrations that are not fully suppressed and urine that is not maximally dilute, thus contributing to water retention.[18,19]

From the Department of Medicine, Baylor College of Medicine and Methodist Hospital, and the Renal Section, Department of Veterans Affairs Medical Center, Houston (H.J.A.); and the Department of Medicine, Tufts University School of Medicine, and the Division of Nephrology and Tupper Research Institute, New England Medical Center, Boston (N.E.M.). Address reprint requests to Dr. Madias at the Division of Nephrology, New England Medical Center, Box 172, 750 Washington St., Boston, MA 02111, or at nmadias@infonet.tufts.edu.

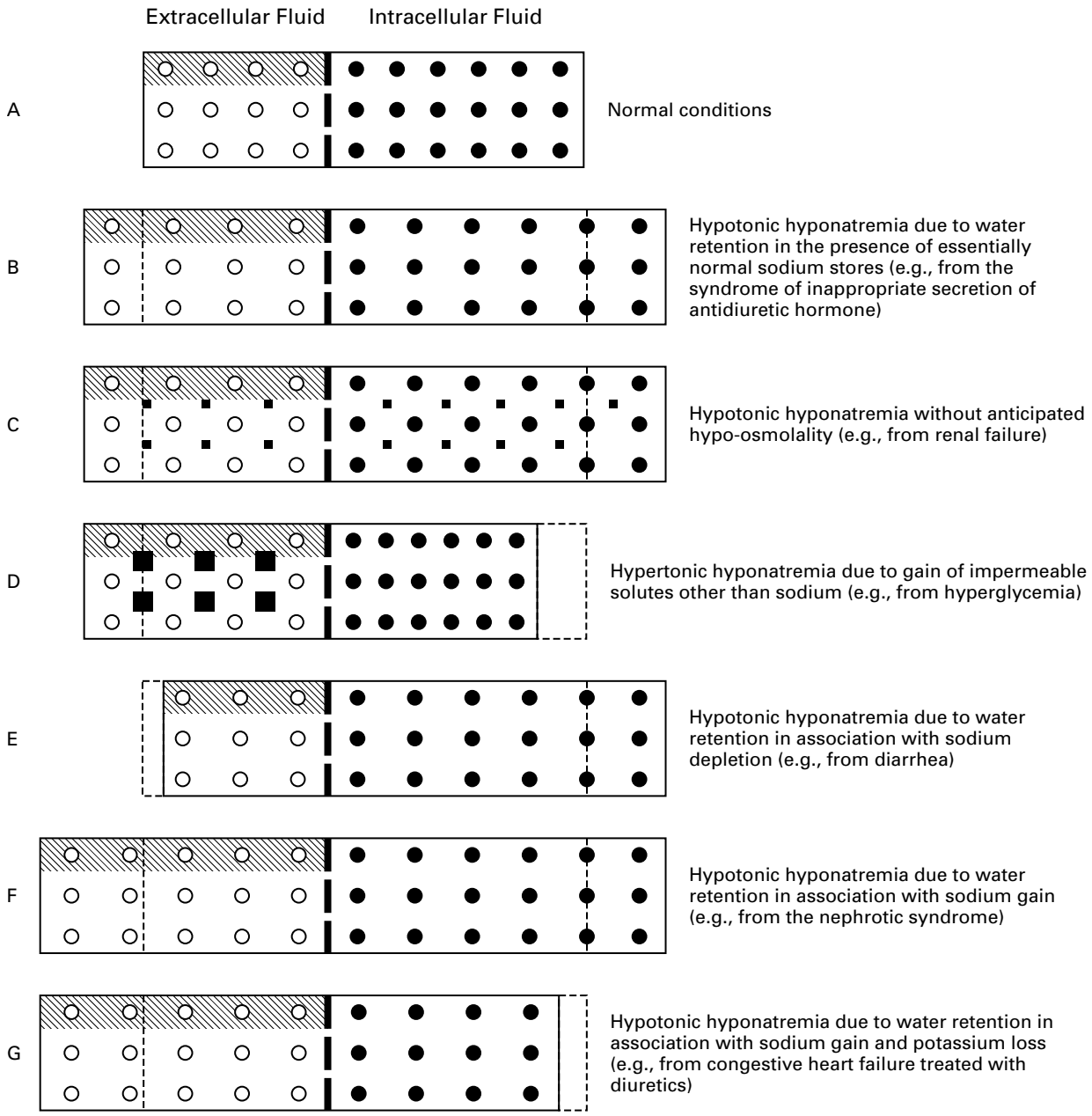

Figure 1. Extracellular-Fluid and Intracellular-Fluid Compartments under Normal Conditions and during States of Hyponatremia.

Normally, the extracellular-fluid and intracellular-fluid compartments make up 40 percent and 60 percent of total body water, respectively (Panel A). With the syndrome of inappropriate secretion of antidiuretic hormone, the volumes of extracellular fluid and intracellular fluid expand (although a small element of sodium and potassium loss, not shown, occurs during inception of the syndrome) (Panel B). Water retention can lead to hypotonic hyponatremia without the anticipated hypo-osmolality in patients who have accumulated ineffective osmoles, such as urea (Panel C). A shift of water from the intracellular-fluid compartment to the extracellular-fluid compartment, driven by solutes confined in the extracellular fluid, results in hypertonic (translocational) hyponatremia (Panel D). Sodium depletion (and secondary water retention) usually contracts the volume of extracellular fluid but expands the intracellular-fluid compartment. At times, water retention can be sufficient to restore the volume of extracellular fluid to normal or even above-normal levels (Panel E). Hypotonic hyponatremia in sodium-retentive states involves expansion of both compartments, but predominantly the extracellular-fluid compartment (Panel F). Gain of sodium and loss of potassium in association with a defect of water excretion, as they occur in congestive heart failure treated with diuretics, lead to expansion of the extracellular-fluid compartment but contraction of the intracellular-fluid compartment (Panel G). In each panel, open circles denote sodium, solid circles potassium, large squares impermeable solutes other than sodium, and small squares permeable solutes; the broken line between the two compartments represents the cell membrane, and the shading indicates the intravascular volume.

TABLE 1. CAUSES OF HYPOTONIC HYPONATREMIA.

IMPAIRED CAPACITY OF RENAL WATER EXCRETION

Decreased volume of extracellular fluid

- Renal sodium loss
  - Diuretic agents
  - Osmotic diuresis (glucose, urea, mannitol)
  - Adrenal insufficiency
  - Salt-wasting nephropathy
  - Bicarbonaturia (renal tubular acidosis, disequilibrium stage of vomiting)
  - Ketonuria
- Extrarenal sodium loss
  - Diarrhea
  - Vomiting
  - Blood loss
  - Excessive sweating (e.g., in marathon runners)
  - Fluid sequestration in "third space"
    - Bowel obstruction
    - Peritonitis
    - Pancreatitis
    - Muscle trauma
    - Burns

Increased volume of extracellular fluid

- Congestive heart failure
- Cirrhosis
- Nephrotic syndrome
- Renal failure (acute or chronic)
- Pregnancy

Essentially normal volume of extracellular fluid

- Thiazide diuretics*
- Hypothyroidism
- Adrenal insufficiency
- Syndrome of inappropriate secretion of antidiuretic hormone
  - Cancer
    - Pulmonary tumors
    - Mediastinal tumors
    - Extrathoracic tumors
  - Central nervous system disorders
    - Acute psychosis
    - Mass lesions
    - Inflammatory and demyelinating diseases
    - Stroke
    - Hemorrhage
    - Trauma
  - Drugs
    - Desmopressin
    - Oxytocin
    - Prostaglandin-synthesis inhibitors
    - Nicotine
    - Phenothiazines
    - Tricyclics
    - Serotonin-reuptake inhibitors
    - Opiate derivatives
    - Chlorpropamide
    - Clofibrate
    - Carbamazepine
    - Cyclophosphamide
    - Vincristine
  - Pulmonary conditions
    - Infections
    - Acute respiratory failure
    - Positive-pressure ventilation
  - Miscellaneous
    - Postoperative state
    - Pain
    - Severe nausea
    - Infection with the human immunodeficiency virus
- Decreased intake of solutes
  - Beer potomania
  - Tea-and-toast diet

EXCESSIVE WATER INTAKE

- Primary polydipsia†
- Dilute infant formula
- Sodium-free irrigant solutions (used in hysteroscopy, laparoscopy, or transurethral resection of the prostate)‡
- Accidental intake of large amounts of water (e.g., during swimming lessons)
- Multiple tap-water enemas

*Sodium depletion, potassium depletion, stimulation of thirst, and impaired urinary dilution are implicated.

†Often a mild reduction in the capacity for water excretion is also present.

‡Hyponatremia is not always hypotonic.

Hyperglycemia is the most common cause of translocational hyponatremia (Fig. 1D). An increase of 100 mg per deciliter (5.6 mmol per liter) in the serum glucose concentration decreases serum sodium by approximately 1.7 mmol per liter, with the end result a rise in serum osmolality of approximately 2.0 mOsm per kilogram of water.[1] Retention of hypertonic mannitol, which occurs in patients with renal insufficiency, has the same effect. In both conditions, the resultant hypertonicity can be aggravated by osmotic diuresis; moderation of hyponatremia or frank hypernatremia can develop, since the total of the sodium and potassium concentrations in the urine falls short of that in serum.[20]

Massive absorption of irrigant solutions that do not contain sodium (e.g., those used during transurethral

prostatectomy) can cause severe and symptomatic hyponatremia. Reflecting the composition of the irrigant, the resultant hyponatremia can be either hypotonic (with an irrigant containing 1.5 percent glycine or 3.3 percent sorbitol) or isotonic (with an irrigant containing 5 percent mannitol). Whether the symptoms derive from the presence of retained solutes, the metabolic products of such solutes, hypotonicity, or the low serum sodium concentration itself remains unclear.[21,22]

The most common causes of severe hyponatremia in adults are therapy with thiazides, the postoperative state and other causes of the syndrome of inappropriate secretion of antidiuretic hormone, polydipsia in psychiatric patients, and transurethral prostatectomy.[1,17,23-25] Gastrointestinal fluid loss, ingestion of dilute formula, accidental ingestion of excessive water, and receipt of multiple tap-water enemas are the main causes of severe hyponatremia in infants and children.[17,26]

CLINICAL MANIFESTATIONS

Just as in hypernatremia, the manifestations of hypotonic hyponatremia are largely related to dysfunction of the central nervous system, and they are more conspicuous when the decrease in the serum sodium concentration is large or rapid (i.e., occurring within a period of hours).[27] Headache, nausea, vomiting, mus-

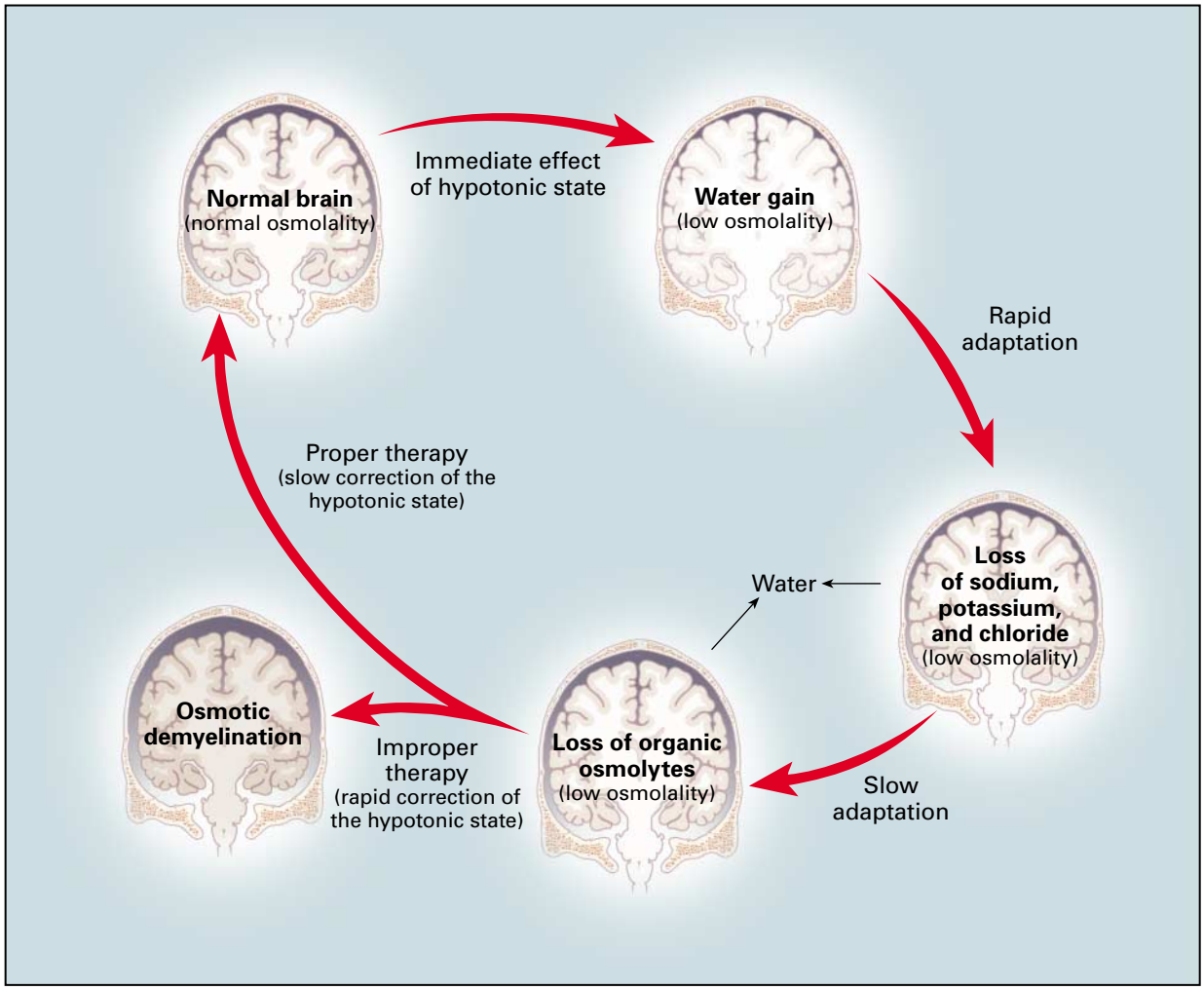

Figure 2. Effects of Hyponatremia on the Brain and Adaptive Responses.

Within minutes after the development of hypotonicity, water gain causes swelling of the brain and a decrease in osmolality of the brain. Partial restoration of brain volume occurs within a few hours as a result of cellular loss of electrolytes (rapid adaptation). The normalization of brain volume is completed within several days through loss of organic osmolytes from brain cells (slow adaptation). Low osmolality in the brain persists despite the normalization of brain volume. Proper correction of hypotonicity reestablishes normal osmolality without risking damage to the brain. Overly aggressive correction of hyponatremia can lead to irreversible brain damage.

cle cramps, lethargy, restlessness, disorientation, and depressed reflexes can be observed. Whereas most patients with a serum sodium concentration exceeding 125 mmol per liter are asymptomatic, those with lower values may have symptoms, especially if the disorder has developed rapidly.[4] Complications of severe and rapidly evolving hyponatremia include seizures, coma, permanent brain damage, respiratory arrest, brain-stem herniation, and death. These complications often occur with excessive water retention in patients who are essentially euvolemic (e.g., those recovering from surgery or those with primary polydipsia); menstruating women appear to be at particular risk.[23,28]

Hypotonic hyponatremia causes entry of water into the brain, resulting in cerebral edema (Fig. 2). Because the surrounding cranium limits expansion of the brain, intracranial hypertension develops, with a risk of brain injury. Fortunately, solutes leave brain tissues within hours, thereby inducing water loss and ameliorating brain swelling.[29,30] This process of adaptation by the brain accounts for the relatively asymptomatic nature of even severe hyponatremia if it develops slowly. Nevertheless, brain adaptation is also the source of the risk of osmotic demyelination.[31-33] Although rare, osmotic demyelination is serious and can develop one to several days after aggressive treatment of hyponatremia by any method, including water restriction alone.[34-36] Shrinkage of the brain triggers demyelination of pontine and extrapontine neurons that can cause neurologic dysfunction, including quadriplegia, pseudobulbar palsy, seizures, coma, and even death. Hepatic failure, potassium depletion, and malnutrition increase the risk of this complication.[1,37]

MANAGEMENT

The optimal treatment of hypotonic hyponatremia requires balancing the risks of hypotonicity against those of therapy.[28] The presence of symptoms and their severity largely determine the pace of correction.

Symptomatic Hypotonic Hyponatremia

Patients who have symptomatic hyponatremia with concentrated urine (osmolality, ≥200 mOsm per kilogram of water) and clinical euvolemia or hypervolemia require infusion of hypertonic saline (Table 2). This treatment can provide rapid but controlled correction of hyponatremia. Hypertonic saline is usually combined with furosemide to limit treatment-induced expansion of the extracellular-fluid volume. Because furosemide-induced diuresis is equivalent to a one-half isotonic saline solution, it aids in the correction of hyponatremia, as do ongoing dermal and respiratory fluid losses; anticipation of these losses should temper the pace of infusion of hypertonic saline. Obviously, electrolyte-free water intake must be withheld. In addition to hypertonic saline, hormone-

TABLE 2. FORMULAS FOR USE IN MANAGING HYPONATREMIA AND CHARACTERISTICS OF INFUSATES.

FORMULA*	CLINICAL USE
1. Change in serum $Na^+ = \frac{\text{infusate } Na^+ - \text{serum } Na^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate on serum Na^+
2. Change in serum $Na^+ = \frac{(\text{infusate } Na^+ + \text{infusate } K^+) - \text{serum } Na^+}{\text{total body water} + 1}$	Estimate the effect of 1 liter of any infusate containing Na^+ and K^+ on serum Na^+

INFUSATE	INFUSATE Na^+	EXTRACELLULAR-FLUID DISTRIBUTION
	mmol per liter	%
5% Sodium chloride in water	855	100†
3% Sodium chloride in water	513	100†
0.9% Sodium chloride in water	154	100
Ringer's lactate solution	130	97
0.45% Sodium chloride in water	77	73
0.2% Sodium chloride in 5% dextrose in water	34	55
5% Dextrose in water	0	40

*The numerator in formula 1 is a simplification of the expression (infusate Na^+ − serum Na^+) × 1 liter, with the value yielded by the equation in millimoles per liter.[38] The estimated total body water (in liters) is calculated as a fraction of body weight. The fraction is 0.6 in children; 0.6 and 0.5 in nonelderly men and women, respectively; and 0.5 and 0.45 in elderly men and women, respectively.[39] Normally, extracellular and intracellular fluids account for 40 and 60 percent of total body water, respectively.[39]

†In addition to its complete distribution in the extracellular compartment, this infusate induces osmotic removal of water from the intracellular compartment.

replacement therapy should be given to patients with suspected hypothyroidism or adrenal insufficiency after blood samples are obtained for diagnostic testing.[7,17] On the other hand, most patients with hypovolemia can be treated successfully with isotonic saline. Patients with seizures also require immediate anticonvulsant-drug therapy and adequate ventilation.[40]

Patients with symptomatic hyponatremia and dilute urine (osmolality, <200 mOsm per kilogram of water) but with less serious symptoms usually require only water restriction and close observation. Severe symptoms (e.g., seizures or coma) call for infusion of hypertonic saline.

There is no consensus about the optimal treatment of symptomatic hyponatremia.[28,40-49] Nevertheless, correction should be of a sufficient pace and magnitude to reverse the manifestations of hypotonicity but not be so rapid and large as to pose a risk of the development of osmotic demyelination. Physiologic considerations indicate that a relatively small increase in the serum sodium concentration, on the order of 5 percent, should substantially reduce cerebral edema.[9,50] Even seizures induced by hyponatremia can be stopped by rapid increases in the serum sodium concentration that average only 3 to 7 mmol per liter.[51,52] Most reported cases of osmotic demyelination occurred after rates of correction that exceeded 12 mmol per liter per day were used, but isolated cases occurred after corrections of only 9 to 10 mmol per liter in 24 hours or 19 mmol per liter in 48 hours.[34,35,40,48,53-56] After weighing the available evidence and the all-too-real risk of overshooting the mark, we recommend a targeted rate of correction that does not exceed 8 mmol per liter on any day of treatment. Remaining within this target, the initial rate of correction can still be 1 to 2 mmol per liter per hour for several hours in patients with severe symptoms. Should severe symptoms not respond to correction according to the specified target, we suggest that this limit be cautiously exceeded, since the imminent risks of hypotonicity override the potential risk of osmotic demyelination. Recommended indications for stopping the rapid correction of symptomatic hyponatremia (regardless of the method used) are the cessation of life-threatening manifestations, moderation of other symptoms, or the achievement of a serum sodium concentration of 125 to 130 mmol per liter (or even lower if the base-line serum sodium concentration is below 100 mmol per liter).[28,40] Long-term management of hyponatremia (described below) should then be initiated. Although faster rates of correction can be tolerated safely by most patients with acute symptomatic hyponatremia, there is no evidence that such an approach is beneficial.[40,57] Moreover, ascertaining the duration of hyponatremia is usually difficult.

How can the physician determine what the rate of infusion of the selected solution should be? This rate can be derived expediently by applying formula 1 in Table 2, the same formula used for managing hypernatremia, which projects the change in serum sodium elicited by the retention of 1 liter of any infusate.[38] Dividing the change in serum sodium targeted for a given treatment period by the output of this formula determines the volume of infusate required, and hence the rate of infusion. Table 2 also presents the sodium concentrations of commonly used infusates, their fractional distribution in the extracellular fluid, and clinical estimates of total body water.[39] We do not recommend use of the conventional formula for the correction of hyponatremia, as follows:

$$\text{sodium requirement} = \text{total body water} \times (\text{desired serum sodium concentration} - \text{current sodium concentration}).$$

The conventional formula requires a complicated procedure to convert the amount of sodium required to raise the sodium concentration to an infusion rate for the selected solution.

The cases described below illustrate the various forms of symptomatic hyponatremia and their management.

Hyponatremia in the Postoperative State

A previously healthy 32-year-old woman has three grand mal seizures two days after an appendectomy. She receives 20 mg of diazepam and 250 mg of phenytoin intravenously and undergoes laryngeal intubation with mechanical ventilation. Three liters of 5 percent dextrose in water had been infused during the first day after surgery, and the patient subsequently drank an unknown but substantial amount of water. Clinically, she is euvolemic, and she weighs 46 kg. She is stuporous and responds to pain but not to commands. The serum sodium concentration is 112 mmol per liter, the serum potassium concentration is 4.1 mmol per liter, serum osmolality is 228 mOsm per kilogram of water, and urine osmolality is 510 mOsm per kilogram of water. Hypotonic hyponatremia in this patient is a result of water retention caused by the impaired excretion of water that is associated with the postoperative state. Planned treatment includes the withholding of water, the infusion of 3 percent sodium chloride, and the intravenous administration of 20 mg of furosemide. The estimated volume of total body water is 23 liters (0.5×46).

According to formula 1 of Table 2, it is estimated that the retention of 1 liter of 3 percent sodium chloride will increase the serum sodium concentration by 16.7 mmol per liter ($[513-112] \div [23+1] = 16.7$). Given the seriousness of the patient's symptoms, the initial goal is to raise the serum sodium concentration by 3 mmol per liter over the next three hours; thus, 0.18 liter of hypertonic sodium chloride ($3 \div 16.7$), or 60 ml per hour, is required. Frequent monitoring of the serum sodium concentration, initially every two to three hours, is necessary in order

to make further adjustments in the amount of fluid administered. Although measuring urinary electrolytes can occasionally assist with management, it is generally unnecessary, and we do not recommend the routine use of this procedure.

Three hours later, the patient's serum sodium concentration is 115 mmol per liter. There have been no further seizures, but the level of responsiveness remains unchanged. The new goal is to increase the serum sodium concentration by an additional 3 mmol per liter over a period of six hours with the use of 3 percent sodium chloride; thus, the infusion rate is adjusted to 30 ml per hour. Nine hours after admission, the serum sodium concentration is 119 mmol per liter. There has been no seizure activity, and the patient now responds to simple commands. Hypertonic saline is discontinued, but close monitoring of the patient's clinical status and serum sodium concentration remains in effect. If the rate of correction is estimated to exceed the targeted rate, hypotonic solution should be administered.[58]

Hyponatremia in an Essentially Euvolemic State

A 58-year-old man with small-cell lung carcinoma presents with severe confusion and lethargy. Clinically, he is euvolemic, and he weighs 60 kg. The serum sodium concentration is 108 mmol per liter, the serum potassium concentration is 3.9 mmol per liter, serum osmolality is 220 mOsm per kilogram of water, the serum urea nitrogen concentration is 5 mg per deciliter (1.8 mmol per liter), the serum creatinine concentration is 0.5 mg per deciliter (44.2 μmol per liter), and urine osmolality is 600 mOsm per kilogram of water. The physician makes a provisional diagnosis of the tumor-induced syndrome of inappropriate secretion of antidiuretic hormone on the basis of the presence of hypotonic hyponatremia and concentrated urine in a euvolemic patient, the absence of a history of diuretic use, and the absence of clinical evidence of hypothyroidism or hypoadrenalism. The treatment plan includes water restriction, the infusion of 3 percent sodium chloride, and the intravenous administration of 20 mg of furosemide. The estimated volume of total body water is 36 liters (0.60×60).

According to formula 1 of Table 2, the retention of 1 liter of 3 percent sodium chloride is estimated to increase the serum sodium concentration by 10.9 mmol per liter ($[513-108] \div [36+1] = 10.9$). The initial goal is to increase the serum sodium concentration by 5 mmol per liter over the next 12 hours. Therefore, 0.46 liter of 3 percent sodium chloride ($5 \div 10.9$), or 38 ml per hour, is required.

Twelve hours after admission, the serum sodium concentration is 114 mmol per liter. The patient is mildly lethargic but easily arousable. Hypertonic saline is stopped, but fluid restriction and close monitoring continue. The new goal is to increase the serum sodium concentration by 2 mmol per liter over the next 12 hours. Twenty-four hours after admission, the serum sodium concentration is 115 mmol per liter and the patient is alert. Long-term management of hyponatremia is instituted.

Hyponatremia in a Hypovolemic State

A 68-year-old woman is brought to the hospital because of progressive drowsiness and syncope. She is being treated with a low-sodium diet and 25 mg of hydrochlorothiazide daily for essential hypertension; she has had diarrhea for the past three days. She is lethargic but has no focal neurologic deficits. She weighs 60 kg. Her blood pressure while in a supine position is 96/56 mm Hg, and the pulse is 110 beats per minute. The jugular veins are flat, and skin turgor is decreased. The serum sodium concentration is 106 mmol per liter, the serum potassium concentration is 2.2 mmol per liter, the serum bicarbonate concentration is 26 mmol per liter, the serum urea nitrogen concentration is 46 mg per deciliter (16.4 mmol per liter), the serum creatinine concentration is 1.4 mg per deciliter (123.8 μmol per liter), serum osmolality is 232 mOsm per kilogram of water, and urine osmolality is 650 mOsm per kilogram of water. Hypotonic hyponatremia caused by thiazide therapy, gastrointestinal losses of sodium, and an associated depletion of potassium are diagnosed. Hydrochlorothiazide and water are withheld, and infusion of a 0.9 percent sodium chloride solution containing 30 mmol of potassium chloride per liter is initiated. The estimated volume of total body water is 27 liters (0.45×60).

According to formula 2 of Table 2 (a simple derivative of formula 1), it is projected that the retention of 1 liter of this infusate will increase the serum sodium concentration by 2.8 mmol per liter ($[154+30] - 106 \div [27+1] = 2.8$). Considering the patient's hemodynamic status, the physician prescribes 1 liter of infusate per hour for the next two hours. At the end of this period, the blood pressure is 128/72 mm Hg, mental status is substantially improved, the serum sodium concentration is 112 mmol per liter, and the serum potassium concentration is 3.0 mmol per liter. The physician recognizes that as soon as the patient's extracellular-fluid volume nears restoration, the nonosmotic stimulus to arginine vasopressin release will cease, thereby fostering rapid excretion of dilute urine and correction of the hyponatremia at an overly rapid pace. Therefore, the prescription is switched to 0.45 percent sodium chloride containing 30 mmol of potassium chloride per liter infused at 100 ml per hour. Despite the estimate that retention of 1 liter of this infusate will have no measurable effect on the serum sodium concentration (i.e., $[77+30] - 112 \div [27+1] = -0.2$), the anticipated production of urine with lower sodium and potassium concentrations than those of the infusate will promote correc-

tion of the hyponatremia. Twelve hours after admission, the patient's condition continues to improve; the serum sodium concentration is 114 mmol per liter, and the serum potassium concentration is 3.2 mmol per liter. To slow down further correction over the next 12 hours, an infusion of 5 percent dextrose in water containing 30 mmol of potassium chloride per liter is started at a rate matching urinary output. Subsequently, long-term management of hyponatremia should be pursued.

Asymptomatic Hypotonic Hyponatremia

For certain patients with asymptomatic hyponatremia, the main risk of complications occurs during the correction phase. This is true of patients who stopped drinking large amounts of water[36] and those who underwent repair of a water-excretion defect (e.g., repletion of extracellular-fluid volume and discontinuation of drugs that cause the condition). If excessive diuresis occurs and the projected rate of spontaneous correction exceeds that recommended for patients with symptomatic hyponatremia, hypotonic fluids or desmopressin can be administered.[44]

By contrast, there is no such risk associated with the asymptomatic hyponatremia that accompanies edematous states or the persistent syndrome of inappropriate secretion of antidiuretic hormone because of the prevailing defect of water excretion. Water restriction (to <800 ml per day) is the mainstay of long-term management, with the goal being induction of negative water balance.[43,44] In severe cardiac failure, optimization of hemodynamics by several measures, including the use of angiotensin-converting–enzyme inhibitors, can increase excretion of electrolyte-free water and moderate hyponatremia. Loop, but not thiazide, diuretics reduce urine concentration and augment excretion of electrolyte-free water, thereby permitting relaxation of fluid restriction. In the syndrome of inappropriate secretion of antidiuretic hormone, but not in edematous disorders, loop diuretics should be combined with plentiful sodium intake (in the form of dietary sodium or salt tablets), a treatment that augments water loss. If these measures fail, 600 to 1200 mg of demeclocycline per day can help by inducing nephrogenic diabetes insipidus.[44] Monitoring of renal function is required, because demeclocycline has nephrotoxic effects, especially in patients with cirrhosis. Moreover, the drug imposes the risk of hypernatremia in patients who do not take in sufficient water. Management of chronic hyponatremia will be helped by the anticipated introduction of promising oral agents that antagonize the effect of arginine vasopressin on the V_2 receptor.[59,60]

Nonhypotonic Hyponatremia

Corrective measures for nonhypotonic hyponatremia are directed at the underlying disorder rather than at the hyponatremia itself. Administration of insulin is the basis of treatment for uncontrolled diabetes, but deficits of water, sodium, and potassium should also be corrected. Furosemide hastens the recovery of patients who absorb irrigant solutions; if renal function is impaired, hemodialysis is the preferred option.[22]

Common Errors in Management

Although water restriction will ameliorate all forms of hyponatremia, it is not the optimal therapy in all cases. Hyponatremias associated with the depletion of extracellular-fluid volume (Table 1) require correction of the prevailing sodium deficit. On the other hand, isotonic saline is unsuitable for correcting the hyponatremia of the syndrome of inappropriate secretion of antidiuretic hormone; if administered, the resulting rise in serum sodium is both small and transient, with the infused salt being excreted in concentrated urine and thereby causing a net retention of water and worsening of the hyponatremia.[38] Although uncertainty about the diagnosis might occasionally justify a limited trial of isotonic saline, attentive follow-up is needed to confirm the diagnosis before substantial deterioration occurs. Great vigilance is required in order to recognize and diagnose hypothyroidism and adrenal insufficiency, since these disorders tend to masquerade as cases of the syndrome of inappropriate secretion of antidiuretic hormone. The presence of hyperkalemia should always alert the physician to the possibility of adrenal insufficiency.

Whereas patients with persistent asymptomatic hyponatremia require slow-paced management, those with symptomatic hyponatremia must receive rapid but controlled correction. Prudent use of hypertonic saline can be lifesaving, but failure to follow the recommendations for treatment can cause devastating and even lethal consequences.

Hyponatremia that is acquired in the hospital is largely preventable.[6] A defect of water excretion can be present on admission, or it can worsen or develop during the course of hospitalization as a result of several antidiuretic influences (e.g., medications, organ failure, and the postoperative state). The presence of such a defect notwithstanding, hyponatremia will not develop as long as the intake of electrolyte-free water does not exceed the capacity for water excretion plus insensible losses. Thus, hypotonic fluids must be supplied carefully to hospitalized patients.

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REFERENCES

1. Gennari FJ. Hypo-hypernatraemia: disorders of water balance. In: Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds. Oxford textbook of clinical nephrology. 2nd ed. Vol. 1. Oxford, England: Oxford University Press, 1998:175-200.

2. Hyponatremia and hypernatremia. In: Adrogué HJ, Wesson DE. Salt & water. Boston: Blackwell Scientific, 1994:205-84.
3. Gennari FJ. Serum osmolality: uses and limitations. N Engl J Med 1984;310:102-5.
4. Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. Medicine (Baltimore) 1976;55:121-9.
5. Maas AHJ, Siggaard-Andersen O, Weisberg HF, Zijlstra WG. Ion-selective electrodes for sodium and potassium: a new problem of what is measured and what should be reported. Clin Chem 1985;31:482-5.
6. Anderson RJ. Hospital-associated hyponatremia. Kidney Int 1986;29: 1237-47.
7. Hypoosmolal states — hyponatremia. In: Rose BD. Clinical physiology of acid-base and electrolyte disorders. 4th ed. New York: McGraw-Hill, 1994:651-94.
8. Frizzell RT, Lang GH, Lowance DC, Lathan SR. Hyponatremia and ultramarathon running. JAMA 1986;255:772-4.
9. Sterns RH, Narins RG. Hypernatremia and hyponatremia: pathophysiology, diagnosis, and therapy. In: Adrogué HJ, ed. Contemporary management in critical care. Vol. 1. No. 2. Acid–base and electrolyte disorders. New York: Churchill Livingstone, 1991:161-91.
10. Anderson RJ, Chung H-M, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. Ann Intern Med 1985;102:164-8.
11. Burrows FA, Shutack JG, Crone RK. Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population. Crit Care Med 1983;11:527-31.
12. Edelman IS, Leibman J, O'Meara MP, Birkenfeld LW. Interrelations between serum sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable potassium and total body water. J Clin Invest 1958;37:1236-56.
13. Fichman MP, Vorherr H, Kleeman CR, Telfer N. Diuretic-induced hyponatremia. Ann Intern Med 1971;75:853-63.
14. Laragh JH. The effect of potassium chloride on hyponatremia. J Clin Invest 1954;33:807-18.
15. Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatremia: review and analysis of 129 reported patients. Chest 1993;103: 601-6.
16. Ashraf N, Locksley R, Arieff AI. Thiazide-induced hyponatremia associated with death or neurologic damage in outpatients. Am J Med 1981; 70:1163-8.
17. Sterns RH, Spital A, Clark EC. Disorders of water balance. In: Kokko JP, Tannen RL, eds. Fluids and electrolytes. 3rd ed. Philadelphia: W.B. Saunders, 1996:63-109.
18. Goldman MB, Luchins DJ, Robertson GL. Mechanisms of altered water metabolism in psychotic patients with polydipsia and hyponatremia. N Engl J Med 1988;318:397-403.
19. Kramer DS, Drake ME Jr. Acute psychosis, polydipsia, and inappropriate secretion of antidiuretic hormone. Am J Med 1983;75:712-4.
20. Gennari FJ, Kassirer JP. Osmotic diuresis. N Engl J Med 1974;291: 714-20.
21. Gonzales R, Brensilver JM, Rovinsky JJ. Posthysteroscopic hyponatremia. Am J Kidney Dis 1994;23:735-8.
22. Agarwal R, Emmett M. The post-transurethral resection of prostate syndrome: therapeutic proposals. Am J Kidney Dis 1994;24:108-11.
23. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. Ann Intern Med 1992;117:891-7.
24. Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. N Engl J Med 1986;314:1529-35.
25. Chung H-M, Kluge R, Schrier RW, Anderson RJ. Postoperative hyponatremia: a prospective study. Arch Intern Med 1986;146:333-6.
26. Adelman RD, Solhung MJ. Sodium. In: Behrman RE, Kliegman RM, Arvin AM, eds. Nelson textbook of pediatrics. 15th ed. Philadelphia: W.B. Saunders, 1996:189-93.
27. Arieff AI, Guisado R. Effects on the central nervous system of hypernatremic and hyponatremic states. Kidney Int 1976;10:104-16.
28. Berl T. Treating hyponatremia: damned if we do and damned if we don't. Kidney Int 1990;37:1006-18.
29. Verbalis JG, Gullans SR. Hyponatremia causes large sustained reductions in brain content of multiple organic osmolytes in rats. Brain Res 1991;567:274-82.
30. Gullans SR, Verbalis JG. Control of brain volume during hyperosmolar and hypoosmolar conditions. Annu Rev Med 1993;44:289-301.
31. Lien YH, Shapiro JI, Chan L. Study of brain electrolytes and organic osmolytes during correction of chronic hyponatremia: implications for the pathogenesis of central pontine myelinolysis. J Clin Invest 1991;88:303-9.
32. Videen JS, Michaelis T, Pinto P, Ross BD. Human cerebral osmolytes during chronic hyponatremia: a proton magnetic resonance spectroscopy study. J Clin Invest 1995;95:788-93.
33. Laureno R, Karp BI. Myelinolysis after correction of hyponatremia. Ann Intern Med 1997;126:57-62.
34. Karp BI, Laureno R. Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. Medicine (Baltimore) 1993;72:359-73.
35. Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med 1986;314: 1535-42.
36. Tanneau RS, Henry A, Rouhart F, et al. High incidence of neurologic complications following rapid correction of severe hyponatremia in polydipsic patients. J Clin Psychiatry 1994;55:349-54.
37. Kumar S, Berl T. Approach to the hyponatremic patient. In: Berl T, ed. Disorders of water, electrolytes, and acid-base. Part 1 of Atlas of diseases of the kidney. Vol. 1. Philadelphia: Blackwell Science, 1999:1.9–1.15.
38. Adrogué HJ, Madias NE. Aiding fluid prescription for the dysnatremias. Intensive Care Med 1997;23:309-16.
39. Oh MS, Carroll HJ. Regulation of intracellular and extracellular volume. In: Arieff AI, DeFronzo RA, eds. Fluid, electrolyte, and acid-base disorders. 2nd ed. New York: Churchill Livingstone, 1995:1-28.
40. Oh MS, Kim HJ, Carroll HJ. Recommendations for treatment of symptomatic hyponatremia. Nephron 1995;70:143-50.
41. Cluitmans FHM, Meinders AE. Management of severe hyponatremia: rapid or slow correction? Am J Med 1990;88:161-6.
42. Lauriat SM, Berl T. The hyponatremic patient: practical focus on therapy. J Am Soc Nephrol 1997;8:1599-607.
43. Gross P, Reimann D, Neidel J, et al. The treatment of severe hyponatremia. Kidney Int Suppl 1998;64:S6-S11.
44. Verbalis JG. Hyponatremia and hypoosmolar disorders. In: Greenberg A, ed. Primer on kidney diseases. 2nd ed. San Diego, Calif.: Academic Press, 1998:57-63.
45. *Idem.* Hyponatremia: epidemiology, pathophysiology, and therapy. Curr Opin Nephrol Hypertens 1993;2:636-52.
46. Soupart A, Decaux G. Therapeutic recommendations for management of severe hyponatremia: current concepts on pathogenesis and prevention of neurologic complications. Clin Nephrol 1996;46:149-69.
47. Sterns RH. Severe symptomatic hyponatremia: treatment and outcome: a study of 64 cases. Ann Intern Med 1987;107:656-64.
48. Sterns RH, Cappuccio JD, Silver SM, Cohen EP. Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. J Am Soc Nephrol 1994;4:1522-30.
49. Fraser CL, Arieff AI. Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. Am J Med 1997;102:67-77.
50. Sterns RH. The treatment of hyponatremia: first, do no harm. Am J Med 1990;88:557-60.
51. Sarnaik AP, Meert K, Hackbarth R, Fleischmann L. Management of hyponatremic seizures in children with hypertonic saline: a safe and effective strategy. Crit Care Med 1991;19:758-62.
52. Worthley LIG, Thomas PD. Treatment of hyponatraemic seizures with intravenous 29.2% saline. BMJ 1986;292:168-70.
53. DeWitt LD, Buonanno FS, Kistler JP, et al. Central pontine myelinolysis: demonstration by nuclear magnetic resonance. Neurology 1984;34: 570-6.
54. Kleinschmidt-DeMasters BK, Norenberg MD. Rapid correction of hyponatremia causes demyelination: relation to central pontine myelinolysis. Science 1981;211:1068-70.
55. Sterns RH, Thomas DJ, Herndon RM. Brain dehydration and neurologic deterioration after rapid correction of hyponatremia. Kidney Int 1989;35:69-75.
56. Brunner JE, Redmond JM, Haggar AM, Kruger DF, Elias S. Central pontine myelinolysis and pontine lesions after rapid correction of hyponatremia: a prospective magnetic resonance imaging study. Ann Neurol 1990; 27:61-6.
57. Cheng JC, Zikos D, Skopicki HA, Peterson DR, Fisher KA. Long-term neurologic outcome in psychogenic water drinkers with severe symptomatic hyponatremia: the effect of rapid correction. Am J Med 1990;88: 561-6.
58. Oh MS, Uribarri J, Barrido D, Landman E, Choi K-C, Carroll HJ. Danger of central pontine myelinolysis in hypotonic dehydration and recommendation for treatment. Am J Med Sci 1989;298:41-3.
59. Serradeil-Le Gal C, Lacour C, Valette G, et al. Characterization of SR 121463A, a highly potent and selective, orally active vasopressin V2 receptor antagonist. J Clin Invest 1996;98:2729-38.
60. Saito T, Ishikawa S, Abe K, et al. Acute aquaresis by the nonpeptide arginine vasopressin (AVP) antagonist OPC-31260 improves hyponatremia in patients with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). J Clin Endocrinol Metab 1997;82:1054-7.