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INTERNAL MEDICINE BOARD REVIEW MANUAL

Case Studies in Hyponatremia

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Cover Illustration by mb cunney

Preface

During the past decade, internal medicine has become increasingly challenging. The challenge stems from the evolution of managed care and an associated emphasis on cost containment as well as quality. As a result, it is increasingly important to have and maintain board certification. In addition, some health maintenance organizations and other employers of physicians consider board certification essential for employment. The process of certification requires intensive residency training and successful completion of the American Board of Internal Medicine certification examination.

The *Hospital Physician Internal Medicine Board Review Manual* is a study guide intended to help candidates prepare for the written examination. The manual consists of four publications focusing on selected topics. Space will not permit an exhaustive review; however, Volume 10 targets several of the more commonly encountered conditions or topics in internal medicine. Included in this list are:

- Case Studies in Hyponatremia
- Approach to the Diabetic Foot
- Hypernatremia
- Case Studies in Nephrolithiasis
- Malabsorption Syndromes
- Valvular Heart Diseases
- Secondary Causes of Hypertension

Board examination candidates will find this manual to be a concise review of some of the essential and well-recognized aspects of these topics. The case-based format presents the information in a logical fashion, including clinical presentation, history, etiology, diagnosis, and treatment.

This manual has been developed without the involvement of or review by the American Board of Internal Medicine. It is based on the Series Editor's and Contributors' clinical experience, awareness of new developments in the field of internal medicine, and knowledge of basic components of education contained in our residency training program. The Editors wish all candidates success on the examination.

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Case Studies in Hyponatremia

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I. INTRODUCTION

Hyponatremia is an electrolyte abnormality that occurs when serum sodium levels decrease below 135 mEq/L.[1,2] This condition is common in the hospital population,[1,2] and its incidence may be as high as 15% to 20%. Although hyponatremia affects all races and both sexes equally, it is most commonly found in elderly persons because of the increased frequency of comorbidities that can lower serum sodium levels (eg, cardiac, hepatic, or renal failure).[3] In healthy individuals, hyponatremia does not develop unless water intake is greater than renal water excretion. It is essential to diagnose and treat hyponatremia because it can be fatal. Hypotonic hyponatremia is the most common form of hyponatremia. This article will review the presentations, diagnosis, complications, and treatment of hypotonic hyponatremia using 4 case patients.

II. DEFINITIONS

RENAL FUNCTION

Figure 1 illustrates the renal regulation of sodium and water. Because plasma osmolality is primarily determined by plasma sodium concentration, a true decrease in plasma sodium caused by water excess results in hypo-osmolality (< 280 mOsm/kg H_2O). Therefore, it is evident that water content relative to sodium can alter the plasma osmolality.[4] Most cases of hyponatremia are caused by impaired renal water excretion in the presence of continued water intake. Antidiuretic hormone (ADH) plays a very important role in the regulation of the extracellular volume status (**Figure 2**).[5] The important step in assessing patients with hyponatremia is to differentiate this disorder into the 3 major groups using serum osmolality (**Figure 3**).[6]

HYPONATREMIA

Pseudohyponatremia

Occasionally, plasma sodium is artifactually low in patients with severe hyperlipidemia or hyperproteinemia. Plasma is 93% water with 7% proteins and lipids. Reduction in sodium may result from displacement of plasma water by excess lipids or proteins. The measured serum osmolality is normal or elevated, but the calculated osmolality is low because of the artifactually low serum sodium; therefore, the osmolar gap is increased. This condition is called *pseudohyponatremia.* The patient is not symptomatic from the hyponatremia because osmolality is normal. No treatment is required for the low sodium concentration. Clinicians, however, need to be aware of the method used to determine serum sodium levels in their clinical laboratory. Serum sodium may be measured by indirect ion-specific electrodes. These assays are performed after diluting the sample, making the analysis subject to pseudohyponatremia because the sodium is falsely decreased when lipids are increased. This problem does not occur when a sodium electrode is used to measure the sodium concentration in an undiluted sample. Currently, the sodium electrode technique is in wide clinical use, and false-positive studies of pseudohyponatremia are especially rare.[7,8]

Isotonic Hyponatremia

Iso-osmotic or slightly hypo-osmotic hyponatremia can complicate transurethral resection of the prostate or bladder because large volumes of iso-osmotic (mannitol) or hypo-osmotic (sorbitol or glycine) bladder irrigation solution can be absorbed and result in marked dilutional hyponatremia, which can be associated with neurologic symptoms. The metabolism of sorbitol and glycine to carbon dioxide and water may lead to hypo-osmolality if accumulated fluid and solutes are not rapidly excreted.[8]

Hypertonic Hyponatremia

Severe hyperglycemia in uncontrolled diabetic patients also lowers the plasma sodium concentration. The sodium level is low because of transcellular shifting of water, but the measured serum osmolality is very high. Glucose is an effective osmole; the high glucose concentration causes water movement from the intracellular compartment to the extracellular compartment, thus

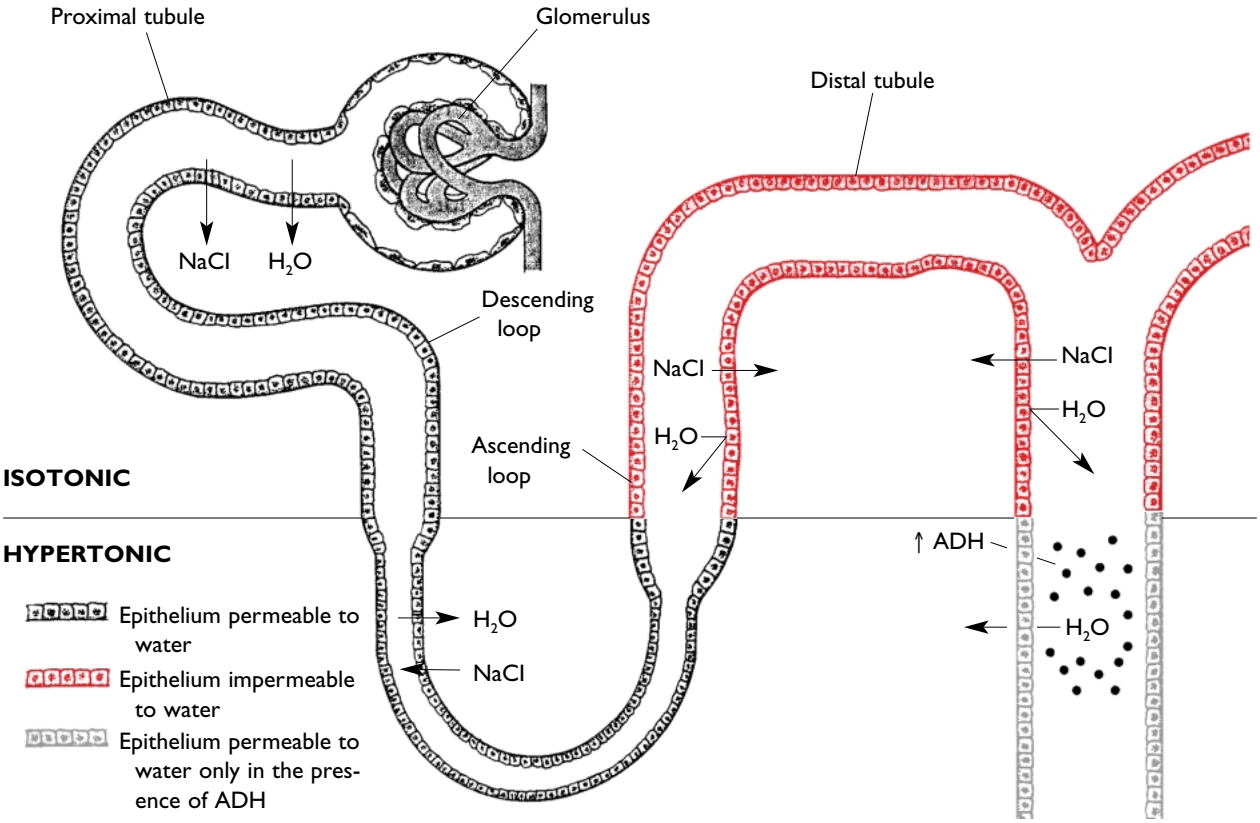

Figure 1. Renal regulation of sodium and water. Inability of the kidney to excrete a water load properly is a basic physiologic element of hyponatremia. Normal excretion depends largely on the kidney's ability to produce urine hypotonic to plasma. The diluting mechanism, which is represented schematically, is governed by osmotic principles and differential epithelial permeabilities. The proximal tubule and descending loop are permeable to water and salt. In the distal tubule, the ascending loop (*red*) is virtually impermeable to water (as is the rest of the distal tubule) except when ADH is present. Normally, approximately 66% of the glomerular filtrate (both salt and water) is reabsorbed isotonically in the proximal tubule. As the remaining fluid passes through the descending limb of Henle's loop, more water is reabsorbed, sodium is added from the interstitium, and tubular fluid becomes hypertonic. In the ascending loop (the diluting region), salt is actively and passively reabsorbed but water is not, which leads to dilution of the urine. When ADH is elevated, the relative impermeability of the distal epithelium is reduced and water is reabsorbed, which leads to concentration rather than dilution of the urine. ADH = antidiuretic hormone. (Adapted with permission from Buckalew VM Jr. Hyponatremia: pathogenesis and management. Hosp Pract [Off Ed] 1986;21:51.)

reducing the extracellular sodium concentration. Plasma sodium decreases by 1.6 mEq/L for each 100 mg/dL of glucose above normal plasma glucose level. Because of hyperglycemia, the plasma osmolality is high. The condition is called *hypertonic hyponatremia*. Administration of hypertonic mannitol also can cause hypertonic hyponatremia. This setting is less common than hyperglycemia, but the mechanism is the same. Mannitol causes movement of water from the cellular compartment with subsequent reduction of the sodium concentration. Measured osmolality increases, although the measured serum sodium concentration and calculated osmolality are low.[4]

Hypotonic Hyponatremia

True hyponatremia, or *hypotonic hyponatremia*, is by far the most common and the most clinically significant form of hyponatremia. Hypotonic hyponatremia always reflects the inability of the kidneys to excrete sufficient free water to match oral intake. It can be divided pathophysiologically according to the effective intravascular volume into the following categories: hypovolemic,

hypervolemic, and euvolemic. Common causes of hypotonic hyponatremia are shown in **Table 1**. These clinically relevant categories aid in determining likely underlying etiology and in guiding treatment.[3]

III. CASE PATIENT 1

PRESENTATION

Patient 1 is a 27-year-old man who has been diagnosed with chronic paranoid schizophrenia. He has been on a home pass for approximately 12 weeks and was doing well until the afternoon of admission, when he began having seizures. After 4 to 5 major motor-type seizures, he is taken to the hospital bleeding from a large tongue laceration and is given 10 mg of diazepam in the emergency department. His current medications are chlorpromazine and imipramine.

On admission, patient 1 has a pulse of 100 bpm, a temperature of 36.8°C, and blood pressure of 108/83 mm Hg. He is semicomatose and responds to painful stimuli. His head is normocephalic without evidence of trauma, and his optic discs are sharp. He has a large laceration on the left margin of his tongue. His neck is supple, his lungs are clear, and he has a regular heart rhythm, with a grade II/VI systolic murmur. His abdomen is soft, with active bowel sounds and no palpable masses or organomegaly. Extremities are free of edema or cyanosis. His deep tendon reflexes are hypoactive but symmetrical; the Babinski's signs are absent on both sides, and he moves all extremities.

Serum electrolyte levels are as follows: sodium, 116 mEq/L; potassium, 4.0 mEq/L; chloride, 88 mEq/L; carbon dioxide, 20 mEq/L; blood urea nitrogen (BUN), 9 mg/dL; creatinine, 1.0 mg/dL; and glucose, 105 mg/dL.

- **What test would be the most helpful in determining the cause of hyponatremia in this patient?**
  - A) Magnetic resonance imaging (MRI) of the brain
  - B) Urine and plasma creatinine
  - C) Serum and urine osmolality
  - D) Serum cortisol level

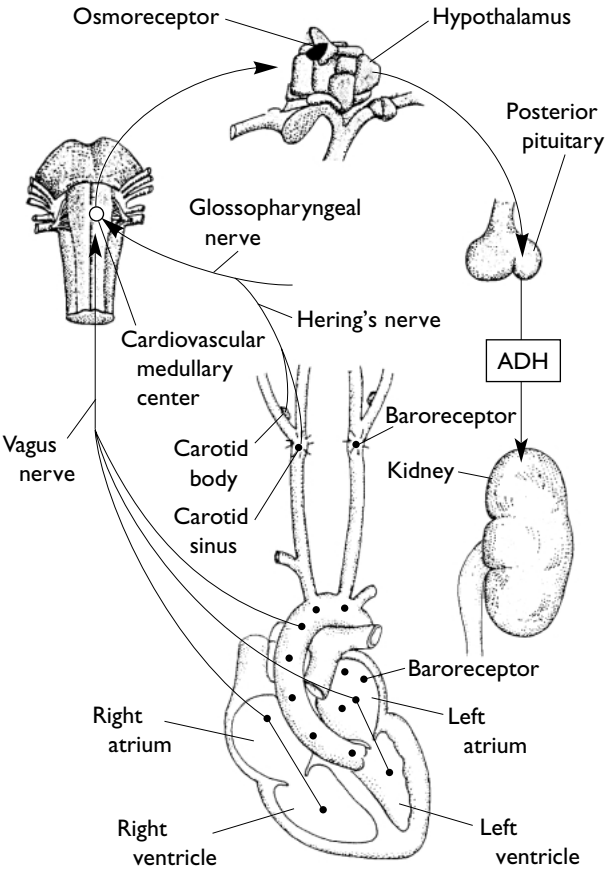

Figure 2. Regulation of extracellular volume. ADH secretion, the major determinant of renal dilution, is controlled by 2 sets of receptors: 1) baroreceptors in the left atrium, aortic arch, and carotid sinus that respond to changes in extracellular fluid volume and arterial BP; and 2) osmoreceptors in the hypothalamus that respond to changes in plasma osmolality. A volume deficit of 5% to 10% promptly simulates ADH release from the posterior pituitary. As a rule, the response to volume loss supersedes the response to changes in osmolality. At plasma osmolality levels below 280 mOsm/kg H_2O, ADH secretion is almost always suppressed, which allows maximum diuresis. When osmolality increases above 280 mOsm/kg H_2O, ADH secretion rapidly increases in direct proportion. ADH = antidiuretic hormone. (Adapted with permission from Buckalew VM Jr. Hyponatremia: pathogenesis and management. Hosp Pract [Off Ed] 1986;21:52.)

Discussion

The correct answer is C. Three laboratory findings are considered very important in the differential diagnosis of hyponatremia: plasma osmolality, urine osmolality, and urine sodium concentration.[9] Plasma osmolality is decreased in most hyponatremic patients because it is primarily determined by plasma sodium concentration and accompanying anions. In patients with hyponatremia, urine osmolality and plasma osmolality can be used to distinguish between impaired water excretion and *primary polydipsia*, which occurs when water excretion is normal but intake is so high that it

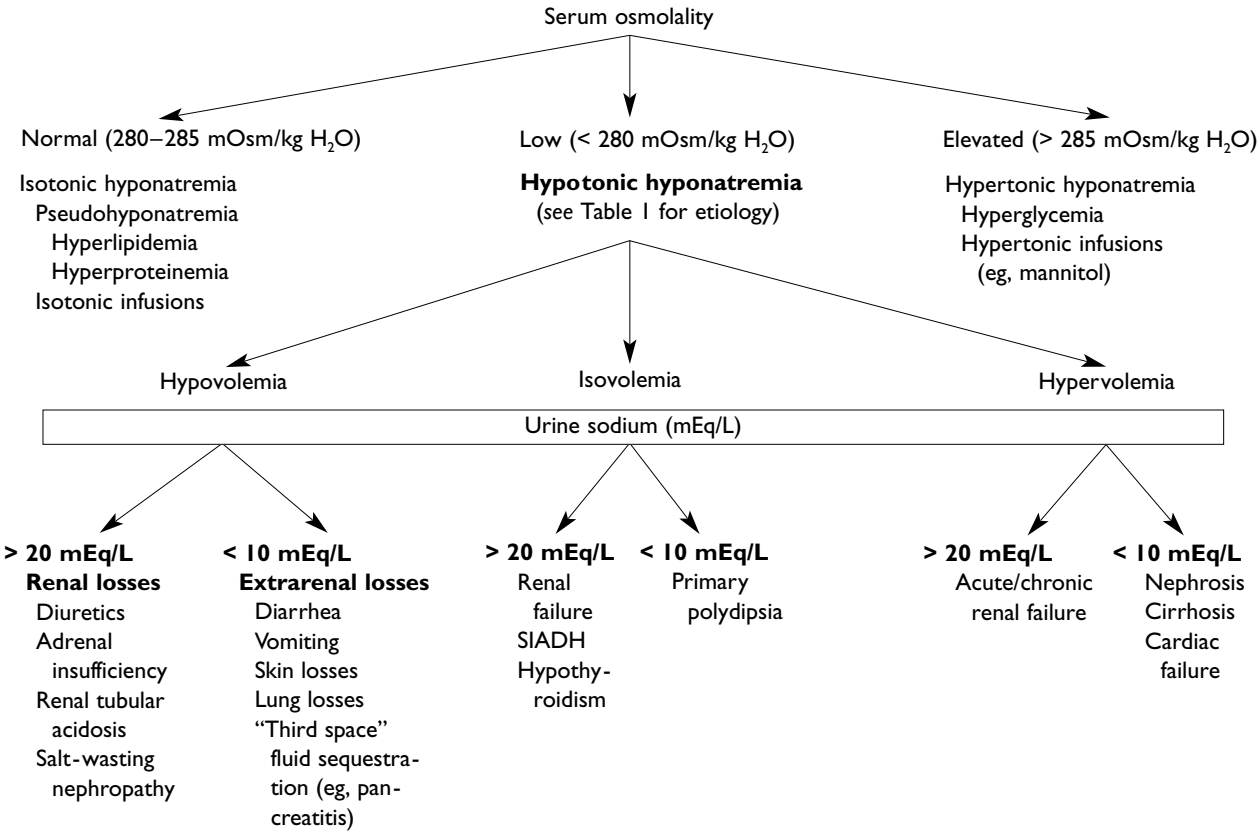

Figure 3. Hypovolemia, isovolemia, and hypervolemia are the 3 major subgroups of hyponatremia. The figure shows how these 3 categories can be differentiated. SIADH = syndrome of inappropriate secretion of antidiuretic hormone. (Adapted from Narins RG, Jones ER, Stom MC, et al. Diagnostic strategies in disorders of fluid, electrolyte and acid-base homeostasis. Am J Med 1982;72:496–520, with permission from Excerpta Medica Inc.)

exceeds excretory capacity. The normal response to hyponatremia (which is maintained in primary polydipsia) is to completely suppress ADH secretion. ADH suppression results in the excretion of maximally dilute urine with osmolality below 100 mOsm/kg H_2O and specific gravity less than 1.003, which is observed in patient 1. Values above this level indicate an inability to normally excrete free water that is generally secondary to continued secretion of ADH. Most patients with hyponatremia have a relatively marked impairment in urinary dilution that is sufficient to maintain the urine osmolality at 300 mOsm/kg H_2O or greater. Normal urine sodium concentration varies greatly, from 20 to 200 mEq/L, depending on fluid intake. Measuring urine sodium concentration can be useful for determining the cause of hyponatremia. For example, a urine sodium concentration less than 20 mEq/L reflects sodium conservation by the kidney and is found in extracellular volume depletion and the edematous states: congestive heart failure (CHF), nephrotic syndrome, and cirrhosis.

DIAGNOSIS

Patient 1's serum osmolality is 231 mOsm/kg H_2O (normal, 280 to 295 mOsm/kg H_2O), urine osmolality is 79 mOsm/kg H_2O, and urine sodium is 24 mEq/L. These laboratory findings are consistent with psychogenic water intoxication.

Psychogenic Water Intoxication

Psychiatric patients, particularly those with schizophrenia, often have abnormalities in water balance.[10,11] The problem of self-induced water intoxication or primary polydipsia in mentally ill patients without other predisposing illness was first reported by Barahal in 1938 and is clearly not a rare phenomenon. Primary polydipsia should be a major consideration in the differential diagnosis of seizure disorders that develop in all mentally ill patients, particularly those in mental institutions.[11] Evaluation of psychotic patients has revealed that various defects in water handling can occur, including altered thirst, the release of ADH, and the renal response to

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, or blood loss
    - Excessive sweating (eg, 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 ADH
    - Cancer
      - Pulmonary, mediastinal, or extrathoracic tumors
    - Central nervous system disorders
      - Acute psychosis
      - Mass lesions
      - Inflammatory and demyelinating diseases
      - Stroke, hemorrhage, or trauma
  - Syndrome of inappropriate secretion of ADH (*cont.*)
    - 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 (eg, during swimming lessons)
- Multiple tap-water enemas

ADH = antidiuretic hormone.

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

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

‡Hyponatremia is not always hypotonic.

ADH. Depending on which abnormality is present, the patient may present with polydipsia, polyuria, and/or hyponatremia. Many chronically psychotic patients have a moderate-to-marked increase in water intake.[12]

It is presumed that a central defect in thirst regulation plays an important role in the pathogenesis of polydipsia. In some cases, the osmotic threshold for thirst is reduced below the threshold for the release of ADH.[13–15] These patients continue to drink until the plasma tonicity is less than the threshold level. (The plasma tonicity refers to that portion of the total plasma osmolality that generates an osmotic pressure; in most cases, tonicity is determined by the concentration of the non-urea solutes.[9])

Some of the drugs used in psychiatric patients also can promote water retention. For example, carbamazepine can produce hyponatremia. The main effect of this drug appears to be an increase in renal responsiveness to ADH rather than a stimulation of ADH release. Primary polydipsia is the most common cause of polyuria in psychotic patients, particularly those with schizophrenia. Polyuria also can occur in patients with bipolar disease who are being treated with lithium, where the major defect is lithium-induced ADH resistance and not central stimulation of the thirst mechanism.[16] Hyponatremia, if not recognized, may contribute to worsening of psychosis despite appropriate pharmacologic treatment.[17] Interestingly, hyponatremia can also significantly alter brain morphology on MRI.[18]

- **What is the next step in managing patient 1?**

A) Administer vasopressin 10 units intravenous (IV)
B) Start IV normal saline
C) Start IV normal saline and fluid restriction
D) Start IV 3% saline

Discussion

The correct answer is C. Many polydipsic schizophrenics have enhanced ADH activity and thus are hyponatremic with life-threatening water intoxication.[19,20]

The recommendation for treatment of hyponatremia relies on the current understanding of how the central nervous system (CNS) adapts to an alteration in serum osmolality (**Figure 4**). In the setting of an acute decrease in the serum osmolality, neuronal cell swelling occurs because the water shifts from the extracellular space to the intracellular space. Severe symptomatic hyponatremia is a dire medical emergency likely to cause brain damage or death unless the serum sodium concentration is raised. However, if the serum sodium concentration is raised too rapidly and increased into the normal range, the patient can develop permanently disabling or fatal central pontine myelinolysis (the osmotic demyelination syndrome).

The degree of brain edema and consequent neurologic symptoms depend largely on the rate and duration of hypotonicity as much as its magnitude. Clinical manifestations of osmotic demyelination are typically delayed for 2 to 6 days after the correction in the plasma sodium concentration.[21] The symptoms include headache, nausea, vomiting, muscle cramps, restlessness, disorientation, depressed reflexes, dysarthria, dysphagia, paraparesis or quadriparesis, lethargy, and coma. Seizures also may be seen but are less common.[21,22] Some of these symptoms may be irreversible or only partially reversible. 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, as is the case with patient 1. Figure 4 illustrates the mechanism. Patients infused with 5% dextrose in water perioperatively and on unrestricted oral intake of water after surgery can develop severe hyponatremia. In this group of patients, young menstruating women appear to be at particular risk. To avoid these complications, it is important to be cautious with amounts of hypotonic fluids ordered for patients.[22–25] Most patients with a serum sodium concentration exceeding 125 mEq/L are asymptomatic.[25]

Acute hyponatremia (duration < 72 hours) can be safely corrected more quickly than chronic hyponatremia. Treating patients with overtly symptomatic hyponatremia in whom rapid correction of the hyponatremia is warranted is more challenging because it carries a significant risk of inducing neurologic damage.[3] Initial observations suggested that patients at greatest risk are those in whom the plasma sodium concentration is raised more than 20 mEq/L in the first 24 hours or is overcorrected above 140 mEq/L.[21,25,26] With acutely symptomatic patients, the treatment goal is to increase serum sodium by approximately 0.5 to 1 mEq/L per hour.[3] Most reported cases of osmotic demyelination occurred after rates of correction were used that exceeded 12 mEq/L per day, but isolated cases occurred after corrections of only 9 to 10 mEq/L in 24 hours or 19 mEq/L in 48 hours.[22]

No specific therapy has been proven for psychotic patients who have primary polydipsia with or without hyponatremia. In acute hyponatremia, limiting water intake will raise the plasma sodium concentration because the excess water is readily excreted in diluted

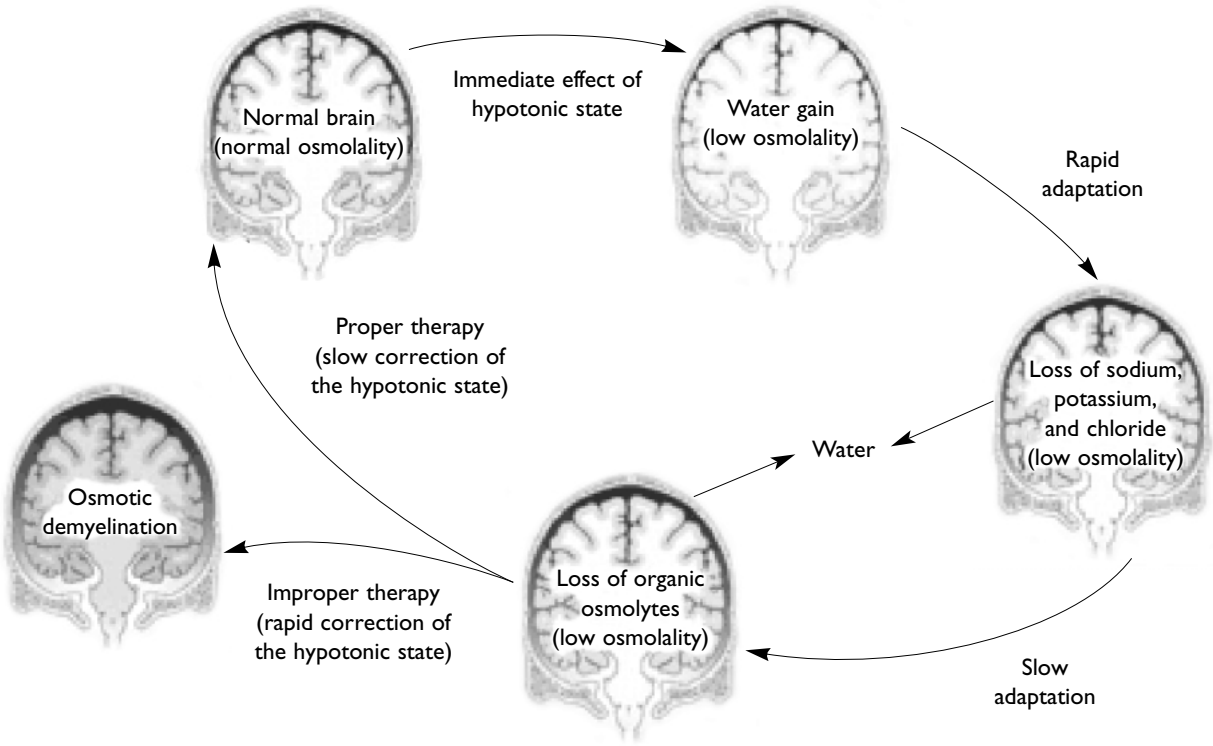

Figure 4. Effects of hyponatremia on the brain and adaptive responses. Within minutes after the development of hypotonicity, water gain causes swelling of the brain and a decrease in osmolality of the brain. Partial restoration of brain volume occurs within a few hours as a result of cellular loss of 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. (Adapted with permission from Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342:1581. Copyright © 2000 Massachusetts Medical Society. All rights reserved.)

urine. The risk of inducing osmotic demyelination in this setting is unclear; it has been suggested that patients with primary polydipsia and repeated episodes of acute hyponatremia are generally resistant to neurologic injury induced by rapid correction.[20] Although such patients may experience repeated episodes of acute hyponatremia, they may be short-lived (because of normal water excretory capacity).

CASE PATIENT 1 TREATMENT

Intravenous normal saline is started and patient 1 is placed on fluid restriction of 500 mL per day. For the next 24 hours, his urine output is 7500 mL. He is alert, communicative, and able to tolerate a normal diet. On the third day of admission, his serum electrolytes are within normal limits. Patient 1's sodium level is 137 mEq/L, potassium is 4.5 mEq/L, chloride is 103 mEq/L, carbon dioxide is 28 mEq/L, and BUN is 9 mg/dL. His serum osmolality is 276 mOsm/kg H_2O. The patient is released on the third day, with instructions to limit his water intake to 1.5 to 2 L per day.

IV. CASE PATIENT 2

PRESENTATION

Patient 2, a 78-year-old man, is a heavy cigarette smoker who presents with increasing cough, hemoptysis, and drowsiness. He is taking no medications. During the last year, he lost approximately 20 lb, and his current weight is 158 lb (72 kg). His mucous membranes are moist, skin turgor is normal, and he does not have an orthostatic fall in blood pressure. Other than nicotine stains on his right index and middle fingers, his physical examination is normal. Chest radiograph

reveals a 4-cm right lung mass. His serum sodium is 123 mEq/L, potassium is 4.3 mEq/L, and creatinine is 1.1 mg/dL. Measured osmolality is 270 mOsm/kg H_2O, uric acid level is 4.2 mg/dL, and urine sodium is 45 mEq/L. Patient 2's thyroid stimulating hormone level is normal.

- **What is the cause of patient 2's hyponatremia?**
  - A) Renal failure
  - B) Treatment with thiazides
  - C) Hypothyroidism
  - D) Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Discussion

The correct answer is D. A systematic approach to define the etiology of hyponatremia is helpful. The first step in the evaluation of a patient with true hypotonic hyponatremia is assssment of the patient's volume status. This patient does not have an obvious excess or depletion of extracellular fluid volume. The low serum sodium tells us nothing about the total body sodium status of the patient but rather indicates that there is an excess of water relative to sodium.

Next, the osmolality should be assessed. In patient 2, the osmolality is 270 mOsm/kg H_2O, indicating that he has hyponatremia with hypotonicity. Patient 2's normal creatinine level excludes renal failure. A urine sodium concentration of 45 mEq/L is not consistent with extracellular fluid volume depletion. Patient 2 is not taking thiazide diuretics, and he does not have any evidence of adrenal failure or hypothyroidism. Therefore, SIADH is the most likely cause for patient 2's hyponatremia. A patient with small-cell carcinoma of the lung (which is a neuroendocrine tumor) commonly presents with a persistent cough or hemoptysis. These tumors often secrete ADH. The diagnostic criteria for SIADH are: normal hepatic, renal, and cardiac function; absence of intravascular volume depletion or edema; normal thyroid, adrenal, and pituitary function; hypotonic hyponatremia (plasma osmolality ≤ 270 mOsm/kg H_2O); urine osmolality greater than 100 mOsm/kg H_2O; normal acid-base status; and normal potassium serum level. Thus, patient 2 has SIADH.

The urine sodium concentration is typically greater than 20 mEq/L in SIADH. Serum uric acid levels are generally reduced; this reduced tubular uric acid reabsorption and thus increased uric acid excretion, which parallels the decrease in proximal tubular sodium reabsorption associated with central volume expansion.[3] There are many causes of SIADH, but the major ones can be categorized into 4 major groups: cancer, CNS disorders, medications, and pulmonary conditions (Table 1).

FURTHER PRESENTATION OF CASE PATIENT 2

Patient 2 insists on being treated at home and agrees to restrict his fluid intake to 800 mL each day. The next morning, patient 2's son brings him to the hospital after noticing a significant increase in the patient's lethargy along with restless, disoriented, and unresponsive behavior. Patient 2 is comatose and does not respond to verbal or painful stimuli. His physical examination, apart from mental status changes, is significant for depressed reflexes. The repeat electrolytes are as follows: sodium level is 108 mEq/L, potassium is 4.0 mEq/L, and creatinine is 1.0 mg/dL. Measured serum osmolality is 264 mOsm/kg H_2O. Urine osmolality is 600 mOsm/kg H_2O.

- **How should patient 2 be managed?**
  - A) Begin fluid restriction and administer normal saline infusion
  - B) Start 3% saline infusion and administer vasopressin
  - C) Begin fluid restriction and administer 3% saline infusion
  - D) Administer vasopressin and furosemide

Discussion

The correct answer is C. The approach to the patient with SIADH varies, depending on the level of sodium, clinical symptoms, and etiology. Definitive treatment for SIADH is correction of the underlying cause. If the patient has no symptoms of CNS impairment, therapy is not necessary except for restriction of hypotonic fluids (water). If CNS symptoms are exhibited, more aggressive therapy is urgently required. Treatment needs to be performed in a controlled environment, possibly in the intensive care unit.

The response to normal (isotonic) saline is altered in SIADH. Whereas both the sodium and water are retained in hypovolemia, sodium handling is intact in the SIADH. If normal saline is 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.[27] 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.[24] One accepted therapy that is indicated only for severe symptoms (eg, seizures or

Table 2. Formulas for 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 Na^+	Extracellular Fluid Distribution
Infusate	**mmol/L**	**%**
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 L, with the value yielded by the equation in mmol/L. 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. Normally, extracellular and intracellular fluids account for 40% and 60% of total body water, respectively.

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

coma) is infusion of hypertonic saline, which should be given slowly to minimize the solution's potential for causing transient volume expansion.[5] The rationale for this approach is that hypertonic intake accompanied by a larger volume of isotonic urine yields a net free water loss.[5,27]

- **Choose the rate of 3% saline infusion for the first 12 hours of treatment from the following:**

  A) 5 mL/hr
  B) 15 mL/hr
  C) 38 mL/hr
  D) 70 mL/hr

Discussion

The correct answer is C. According to formula 1 in **Table 2**, the retention of 1 L of 3% sodium chloride is estimated to increase the serum sodium concentration by 10.9 mmol/L ([513 – 108]/[36 + 1] = 10.9). The initial goal is to increase the serum sodium concentration by 5 mmol/L during the next 12 hours. Therefore, 0.46 L of 3% sodium chloride (5/10.9) for 12 hours, or 38 mL per hour, is required. Using the formula in Table 2 gives tremendous advantage compared to the conventional formula for the correction of hyponatremia, which is:

Na^+ requirement + total body water
× ([desired Na^+ concentration]
– [current Na^+ concentration])

It is much more complicated to convert the amount of sodium required to raise the sodium concentration to an infusion rate for selected solution. 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.[24]

In the next 12 hours, patient 2 becomes alert, and he has no complaints. His sodium concentration is 123 mEq/L.

- **What is the next step in the management of patient 2?**
  - A) Continue 3% saline but decrease the rate by 50%
  - B) Continue 3% saline with the same rate
  - C) Change 3% saline to normal saline with the same rate
  - D) Discontinue all IV infusion

Discussion

The correct answer is D. Patient 2's condition has improved. It is very important to realize that close monitoring should continue, but the 3% sodium chloride infusion should be stopped. There is no consensus about the optimal treatment of symptomatic hyponatremia. Nevertheless, correction should be of a sufficient pace and magnitude to reverse the manifestations of hypotonicity but should not be so rapid and large as to pose a risk of developing osmotic demyelination. Physiologic considerations indicate that a relatively small increase in the serum sodium concentration, on the order of 5%, should substantially reduce cerebral edema.[24,28] Even seizures induced by hyponatremia can be stopped by rapid increases in the serum sodium concentrations that average only 3 to 7 mmol/L.[24,29,30]

Most reported cases of osmotic demyelination have occurred after corrections of only 9 to 10 mmol/L in 24 hours or 19 mmol/L in 48 hours.[21,24,31–34] So far, the evidence suggests that the safest rate of correction is the one that does not exceed 8 mmol/L on any day of treatment. Remaining within this target, the initial rate of correction can still be 1 to 2 mmol/L per hour for several hours in patients with severe symptoms. Frequent monitoring of the serum sodium concentration, initially every 2 to 3 hours, is necessary for making further adjustments in the amount of fluid administered.[24] Recommended indications for stopping the rapid correction of symptomatic hyponatremia (regardless of the method used) are cessation of life-threatening manifestations, moderation of other symptoms, or the achievement of a serum sodium concentration of 125 to 130 mmol/L (or even lower if the baseline serum sodium concentration is below 100 mmol/L).[22,24,32] Although faster rates of correction can be tolerated safely by most patients with symptomatic hyponatremia, there is no evidence that such an approach is beneficial.[20,24,33] Accordingly, the best chosen action for patient 2 is to discontinue infusion of 3% sodium chloride and start long-term management, which will include restricting fluid to 800 mL or less each day.

V. CASE PATIENT 3

PRESENTATION

Patient 3 is an 86-year-old woman who presents with a 3-week history of memory disturbances. She has a history of hypertension and recently has started a new antihypertensive medication, hydrochlorothiazide tablets. Otherwise, she is healthy and does not take any other medications. She also reports no nausea, vomiting, or diarrhea, and the rest of her systems review is negative. Her heart rate is 100 bpm and her blood pressure is 110/70 mm Hg. When standing, her heart rate increases to 110 bpm and her pressure decreases to 90/60 mm Hg. Respiratory rate is 12 breaths per minute.

The physical examination reveals an elderly woman in no acute distress. She is alert and oriented. The patient has dry mucous membranes and poor skin turgor. The rest of her examination is within normal limits. Laboratory data show that patient 3 has a sodium concentration of 125 mEq/L, a potassium concentration of 3.4 mEq/L, a plasma osmolality of 270 mOsm/kg H_2O, a urine sodium concentration of 23 mEq/L, a BUN level of 48 mg/dL, a creatinine level of 1.2 mg/dL, and a urine osmolality of 400 mOsm/kg H_2O.

- **What is the most likely diagnosis for patient 3?**
  - A) SIADH
  - B) Thiazide-induced hyponatremia
  - C) Hypertonic hypovolemia
  - D) Renal insufficiency

Discussion

The correct answer is B. The physical examination confirms a volume-depleted status. The laboratory data indicate hypovolemia (increased BUN:creatinine ratio), hypotonicity, and hyponatremia with a urine sodium concentration more than 20 mEq/L. These findings are most likely consistent with hypovolemic hypo-osmotic hyponatremia, induced by thiazide diuretic intake.

- **What is the next most important step in managing patient 3?**
  - A) Start IV normal saline
  - B) Start aggressive oral hydration

C) Start 3% sodium chloride infusion to reach 5% increase in sodium concentration for the next 24 hours
D) Discontinue thiazide diuretic and start IV hydration using normal saline

Discussion

The correct answer is D. Hyponatremia is a potentially fatal complication of diuretic therapy. The difference in hyponatremic risk between thiazide-type and loop diuretics is related to differences in their tubular site of action. Loop diuretics inhibit sodium chloride reabsorption in the thick ascending limb of the loop of Henle (Figure 1). Reabsorption of sodium chloride without water into the medullary aspect of this segment is normally the primary step in the generation of the hyperosmotic gradient in the medullary interstitium. In the presence of ADH, the highly concentrated interstitium allows water to be reabsorbed in the medullary collecting tubule down a favorable osmotic gradient between the tubular lumen and the interstitium. Administration of a loop diuretic interferes with this process. Although a loop diuretic can increase ADH levels by inducing volume depletion, the responsiveness to ADH is reduced because the medullary gradient is impaired. As a result, water retention and the development of hyponatremia will be limited, unless distal delivery is very low or water intake is very high.[35,36]

The thiazides, in contrast, act in the cortex of the distal tubule; therefore, they do not interfere with medullary function or with ADH-induced water retention. In some cases, the combination of increased sodium and potassium excretion (resulting from the diuretic) and enhanced water reabsorption (resulting from ADH) can cause urine excretion with a sodium plus potassium concentration higher than that of the plasma.[37] Loss of this fluid can directly promote the development of hyponatremia independent of the degree of water intake. As with other diuretic-induced fluid and electrolyte complications, hyponatremia develops within the first 1 to 2 weeks of therapy if diuretic dose and dietary intake remain relatively constant.[37,38] Older women are at the highest risk for thiazide-induced hyponatremia. The typical scenario is that described for patient 3. In many of these patients, rechallenge with a single dose of a thiazide can lower the plasma sodium concentration by as much as 5 to 6 mEq/L in the first 6 hours and 18 mEq/L in the first 36 hours.[37,39]

Many patients at risk appear to have an underlying tendency for increased water intake (polydipsia), which is partly manifested by a 2 to 3 mEq/L reduction in the pretreatment plasma sodium concentration (138 mEq/L compared with 140 to 141 mEq/L in patients who do not become hyponatremic) and by lower baseline urine osmolality.[46] Elderly patients generally have a reduced ability to excrete a water load, an effect that is most prominent in those who have previously developed thiazide-induced hyponatremia.[40] This defect in water excretion can be worsened by thiazide-induced impairment of urinary dilution because reabsorption of sodium chloride without water at the thiazide-sensitive site in the distal tubule normally lowers the urine osmolality. If water retention is a primary effect, it can explain why many patients with thiazide-induced hyponatremia behave as if they are volume expanded, which is similar to SIADH, as previously described.[35]

TREATMENT OF DIURETIC-INDUCED HYPONATREMIA

The treatment of diuretic-induced hyponatremia consists of discontinuing the diuretic and administering either isotonic saline or hypertonic saline if the hyponatremia is severe or symptomatic. There is, however, a potential risk of correcting the hyponatremia too rapidly with isotonic saline. This isotonic saline solution will minimally raise the plasma sodium concentration and will quickly correct the volume deficit. Once the patient becomes euvolemic, ADH release will be appropriately suppressed, thereby, allowing the formation of dilute urine that can result in very rapid excretion of the excess water. Thus, patients with moderate-to-marked hyponatremia must be monitored carefully to minimize the risk of osmotic demyelination as they receive volume repletion therapy.[35,38] Because of the potential seriousness of thiazide-induced hyponatremia, the clinician should be alert for this condition. It is useful to measure the plasma sodium concentration within 1 week after starting a thiazide diuretic in elderly patients, especially those who habitually ingest large volumes of fluids or who take nonsteroidal anti-inflammatory drugs (NSAIDs), which involve the risk of decreasing intrarenal generation of prostaglandins that could lead to a reduction in water excretion).[35]

OTHER CAUSES OF HYPONATREMIA

Hyponatremia is a common complication of moderate-to-severe hypothyroidism. Thus, thyroid function should be evaluated in any patient with an otherwise unexplained reduction in plasma sodium concentration. The mechanism by which hypothyroidism induces hyponatremia is incompletely understood. The cardiac output and the glomerular filtration rate (GFR) often are reduced in this disorder. Consequently, decreased

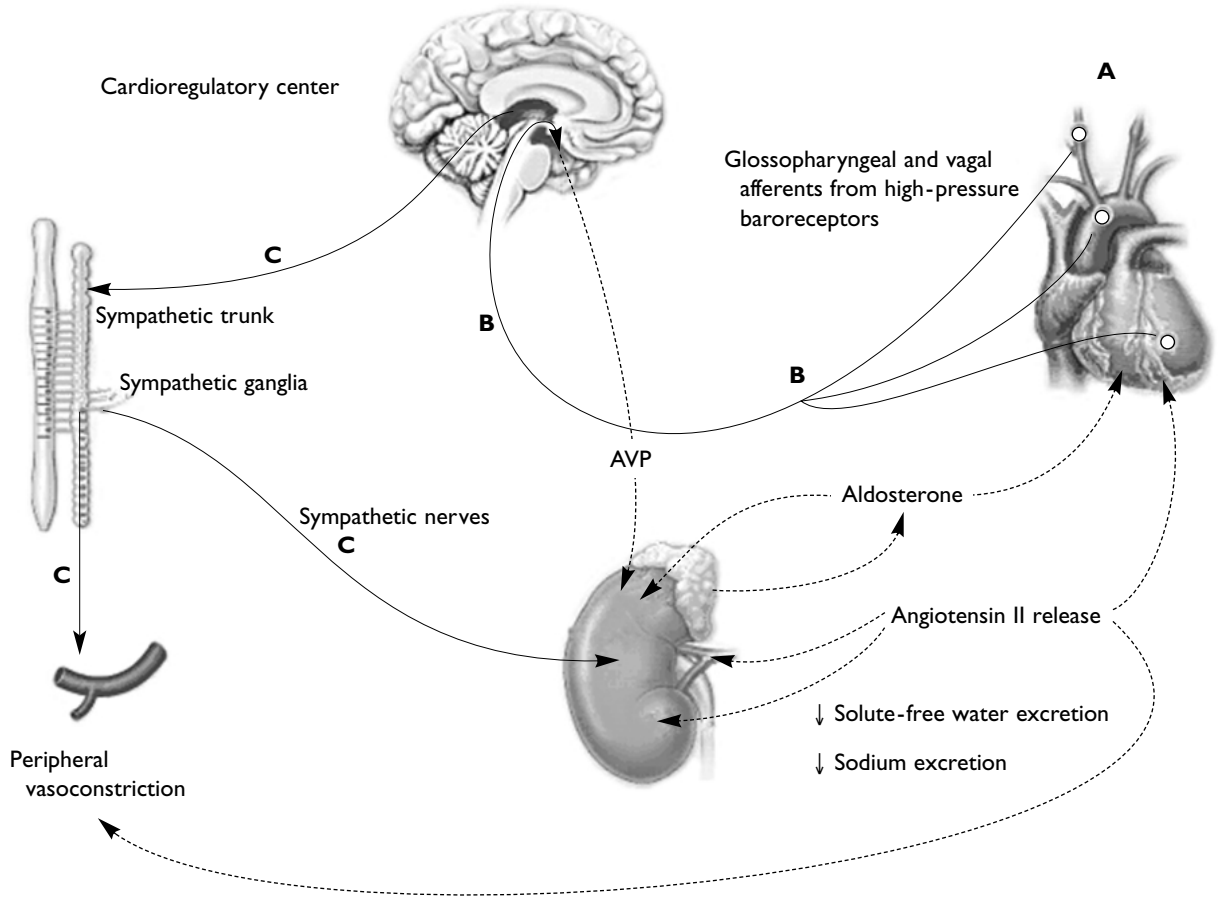

Figure 5. The pathophysiology of heart failure. (**A**) Unloading of high-pressure baroreceptors (*see white circles*) in the left ventricle, carotid sinus, and aortic arch generates afferent signals (**B**) that stimulate cardioregulatory centers in the brain, resulting in the activation of efferent pathways in the sympathetic nervous system (**C**). The sympathetic nervous system appears to be the primary integrator of the neurohumoral vasoconstrictor response to arterial underfilling. Activation of renal sympathetic nerves stimulates the release of renin and angiotensin II, thus activating the renin-angiotensin-aldosterone system. Concomitantly, sympathetic stimulation of the supraoptic and paraventricular nuclei in the hypothalamus results in the nonosmotic release of AVP. Sympathetic activation also causes peripheral and renal vasoconstriction, as does angiotensin II. Angiotensin II constricts blood vessels and stimulates the release of aldosterone from the adrenal gland, and it also increases tubular sodium reabsorption and causes remodeling of cardiac myocytes. Aldosterone may also have direct cardiac effects in addition to increasing the reabsorption of sodium and the secretion of potassium and hydrogen ions in the collecting duct. The *dashed lines* designate circulating hormones. ADH = antidiuretic hormone; AVP = arginine vasopressin. (Adapted with permission from Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999;341:577. Copyright © 1999 Massachusetts Medical Society. All rights reserved.)

cardiac output can cause the release of ADH (via carotid baroreceptors), while the decreased GFR directly diminishes free water excretion by diminishing water delivery to the diluting segments. Decreased water delivery particularly may be important in those cases in which hyponatremia develops despite appropriate suppression of ADH release.[41–47] Regardless of the mechanism, the net effect of the impairment in water excretion is the retention of ingested water and a reduction in the plasma sodium concentration by dilution. Normal water balance and correction of hyponatremia can be achieved rapidly by the administration of thyroid hormone.[47]

Adrenal insufficiency is another common cause of hyponatremia in which a decreased or normal volume of extracellular fluid is present. Hyponatremia associated with adrenal insufficiency is secondary to the diminished secretion of cortisol and aldosterone. Hypoaldosteronism contributes to hyperkalemia and metabolic acidosis.

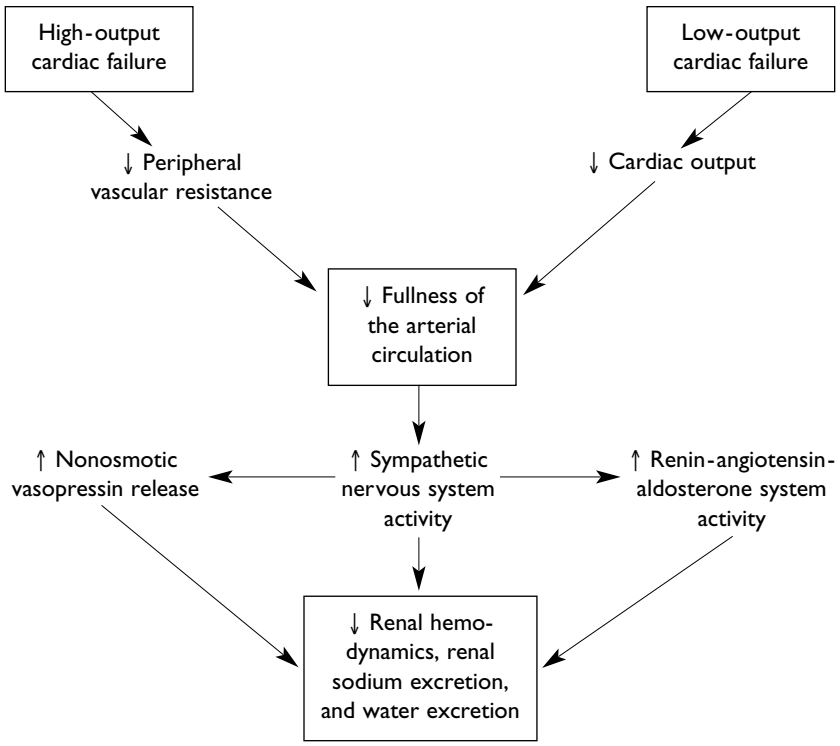

Figure 6. Mechanisms by which high-output or low-output heart failure leads to the activation of neurohormonal vasoconstrictor systems and retention of renal sodium and water. (Adapted with permission from Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999;341:577. Copyright © 1999 Massachusetts Medical Society. All rights reserved.)

Hyponatremia is mediated by increased release of ADH, which results in water retention and a reduction in the plasma sodium concentration. A patient with primary adrenal insufficiency most commonly presents with hyponatremia. Correction of hyponatremia is rapidly achieved by cortisol and volume repletion, which decreases ADH release and allows the excess water to be excreted.[48] Mineralocorticoid replacement also is required in most patients with primary adrenal insufficiency.

As mentioned in Table 1, extrarenal sodium loss in patients with diarrhea, vomiting, blood loss, and fluid sequestration in "third spaces" (eg, patients with pancreatitis) also should be considered in the differential diagnosis of hypovolemic hypo-osmotic hyponatremia. Skin losses (ie, from sweating) also are important to include in this group. For example, in healthy marathon runners, hyponatremia can lead to encephalopathy and can be associated with noncardiogenic pulmonary edema. This condition may be fatal if undiagnosed.[49]

VI. CASE PATIENT 4

PRESENTATION

Patient 4 is a 64-year-old man who presents with increasing shortness of breath, fatigue, paroxysmal nocturnal dyspnea, and marked edema. He has a long history of coronary disease and underwent coronary bypass surgery 6 years ago. The patient's physical examination reveals jugular venous distention, rales, and S_3. His chest radiograph shows bilateral pleural effusions, cardiomegaly, and interstitial pulmonary infiltrates. His serum sodium is 121 mEq/L, his potassium is 3.5 mEq/L, his urine sodium is 5 mEq/L, and his plasma osmolality is 260 mOsm/kg H_2O.

DIAGNOSIS

- **Which of the following is the appropriate sodium disorder diagnosis for patient 4?**
  - A) Isosmotic hyponatremia
  - B) Isovolemic hypo-osmotic hyponatremia
  - C) Hypovolemic hypo-osmotic hyponatremia
  - D) Hypervolemic hypo-osmotic hyponatremia

Discussion

The correct answer is D. Patient 4 has severe CHF, and he has gross clinical and radiographic evidence of extracellular fluid volume overload. His serum osmolality is low (< 280 mOsm/kg H_2O) and his urine sodium is less than 10 mEq/L, which indicates renal retention of sodium. The renal sodium retention occurs because of decreased renal perfusion secondary to

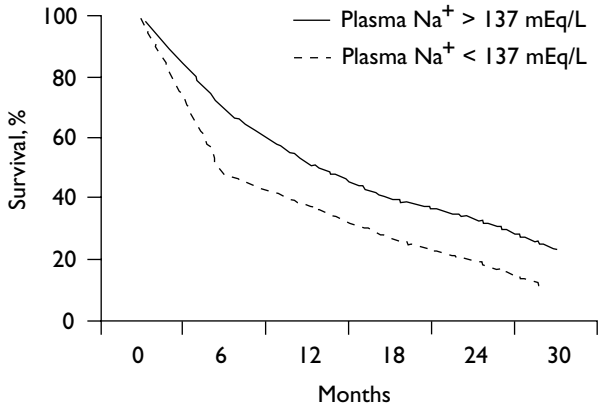

Figure 7. Hyponatremia is associated with reduced survival in congestive heart failure. Survival over time is shown in patients with severe heart failure and normal plasma sodium concentration (*solid line*) or hyponatremia (*dashed line*). Survival was significantly reduced in patients with severe heart failure and hyponatremia. (Data from Lee WH, Packer M. Circulation 1986;73:257.)

poor cardiac output. All of these findings are consistent with a diagnosis of hypervolemic hypo-osmotic hyponatremia.

HYPONATREMIA AND CONGESTIVE HEART FAILURE

- **Why is patient 4's serum sodium concentration low?**
  - A) Impairment of water excretion because of ADH excess
  - B) Increase in water intake
  - C) SIADH
  - D) Adrenal failure

Discussion

The correct answer is A. In patients with CHF, hyponatremia results from an inability to excrete ingested water. This problem is largely related to the associated decrease in cardiac output and systemic blood pressure, which stimulate secretion of the 3 "hypovolemic" hormones: renin (with subsequent increase in angiotensin II formation), ADH, and norepinephrine (**Figures 5** and **6**).[50] Edematous patients with CHF, such as patient 4, have increased plasma and extracellular fluid volumes; however, they are effectively volume depleted because the low cardiac output decreases the pressure perfusing the baroreceptors in the carotid sinus and the renal afferent arteriole. These induced neurohumoral changes effectively limit both sodium and water excretion in an attempt to return perfusion pressure to normal. ADH release directly enhances water reabsorption in the collecting tubules, whereas angiotensin II and norepinephrine limit distal water delivery (and thereby water excretion) by lowering the GFR (because of a marked reduction in renal perfusion) and by increasing proximal sodium and water reabsorption. Both the low cardiac output and high angiotensin levels are potent stimuli to thirst, leading to increased water intake.[51] The net effect is that the severity of the defect in water excretion (resulting from neurohumoral activation) and the associated reduction in the plasma sodium concentration parallel the severity of the heart disease.[52] This relationship has prognostic importance because patient survival is significantly reduced (in comparison with normonatremic patients with CHF) once the plasma sodium concentration falls below 137 mEq/L (**Figure 7**).

A plasma sodium concentration below 125 mEq/L represents near end-stage disease. At this time, hyperkalemia is also a frequent finding; however, hyperkalemia is absent in patient 4. Distal sodium and water delivery are so low in advanced cardiac disease that potassium excretion falls below the level of intake.

TREATMENT OF HYPONATREMIC PATIENTS WITH HEART FAILURE

- **How should patient 4 be treated?**
  - A) Administer IV 3% sodium chloride solution
  - B) Start IV normal saline and loop diuretics
  - C) Implement fluid restriction and start loop diuretics
  - D) Start high doses of β-blockers

Discussion

The correct answer is C. Restricting water intake is the mainstay of therapy in hyponatremic patients with heart failure, although this is often not tolerable because of the intense stimulation of thirst.[52] In patients with severely noncompliant hearts (eg, diastolic dysfunction), restricting water intake may have a secondary benefit because it minimizes acute increases in intravascular volume that can lead to the development of pulmonary congestion. In refractory cases, the combination of an angiotensin converting enzyme (ACE) inhibitor and a loop diuretic can elevate the plasma sodium concentration.[52–55] These agents may act in 2 ways: (1) ACE inhibitors increase cardiac output, which can lower the levels of ADH, angiotensin II, and norepinephrine;[51,55] or (2) ACE inhibitors (via the local generation of prostaglandins) appear to antagonize the

effect of ADH on collecting tubules, thereby decreasing water reabsorption at this site.[51,56] Despite these benefits, ACE inhibitors can present a potential risk for CHF patients. These medications may be poorly tolerated in some patients with advanced CHF, leading to symptomatic hypotension, worsening azotemia, and/or hyperkalemia.[51] Accordingly, careful monitoring is required. CHF patients with hyponatremia also are at increased risk for worsening cardiac and renal function after NSAID administration. In the setting of advanced heart failure and a high level of circulating vasoconstrictors, there is increased renal secretion of vasodilator prostaglandins that act to preserve renal perfusion and to lower systemic vascular resistance. Decreasing prostaglandin synthesis with an NSAID in such a patient is likely to cause renal ischemia, an increase in the plasma creatinine concentration, and a decrease in cardiac output because of increased afterload caused by vasoconstriction.[57] Table 1 lists other common causes of hypervolemic hypotonic hyponatremia (eg, cirrhosis, nephrotic syndrome, renal failure, and pregnancy). Water restriction is the mainstay of therapy for the hyponatremia accompanying these disorders.

VII. SUMMARY POINTS

- Hyponatremia, perhaps the most common of all electrolyte disorders, can be asymptomatic and self-limiting; however, as a marker of abnormal water metabolism, it can quickly transform into a potentially critical disorder.
- It is paramount for the internist to have a firm understanding of the pathogenesis of hyponatremia because appropriate management is determined by establishing the underlying cause.
- The first step in the evaluation of a patient with true hypotonic hyponatremia is assessment of the patient's volume status.
- Although water restriction can help in most cases of hyponatremia, it is not the optimal therapy in all situations. It may not be tolerable in patients with intense stimulation of thirst.
- Hyponatremia associated with a hypovolemic state requires the correction of the prevailing sodium deficit.
- Patients with persistent asymptomatic hyponatremia require slow-paced management. Symptomatic patients must receive a rapid but thoroughly controlled correction of hyponatremia.
- In severe cases of hyponatremia, prudent use of hypertonic saline can be lifesaving; however, failure to follow the recommendations for the treatment can lead to devastating and even lethal consequences.

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