Chapter 68: Disorders of Sodium and Water Homeostasis

Katherine H. Chessman; Jason S. Haney

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 77, Electrolyte Homeostasis.

KEY CONCEPTS

KEY CONCEPTS

1. Maintenance of normal blood volume and serum osmolality is essential for cellular function and is tightly regulated in the human body. Simply put, water balance determines serum sodium concentration, and sodium balance determines volume status.

2. Total body water (TBW) ranges from 45% to 80% of body weight depending on sex, age, gestational age, and disease states and is distributed primarily into two compartments: the intracellular compartment or intracellular fluid (ICF; two-thirds [67%] of TBW) and the extracellular compartment or extracellular fluid (ECF; one-third [33%] of TBW).

3. Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is synthesized in the hypothalamus and secreted by the posterior pituitary in response to both osmotic (serum sodium greater than 135 mEq/L [mmol/L]) and non-osmotic regulators to maintain water balance.

4. Hyponatremia, defined as a serum sodium concentration less than 135 mEq/L (mmol/L), is the most common electrolyte abnormality encountered in clinical practice in both adults and children and is associated with significant morbidity and mortality.

5. Hyponatremia is predominantly the result of an excess of extracellular water relative to sodium because of impaired water excretion.

6. Hypovolemic hypotonic hyponatremia is common in patients taking thiazide diuretics.

7. Euvolemic (isovolemic) hypotonic hyponatremia is associated with a normal or slightly decreased ECF sodium content and increased TBW and ECF volume and is most often caused by the syndrome of inappropriate ADH secretion (SIADH).

8. Hyponatremia with ECF volume expansion (hypervolemia) occurs in conditions in which sodium and water excretion is impaired such as heart failure, cirrhosis, or nephrotic syndrome.

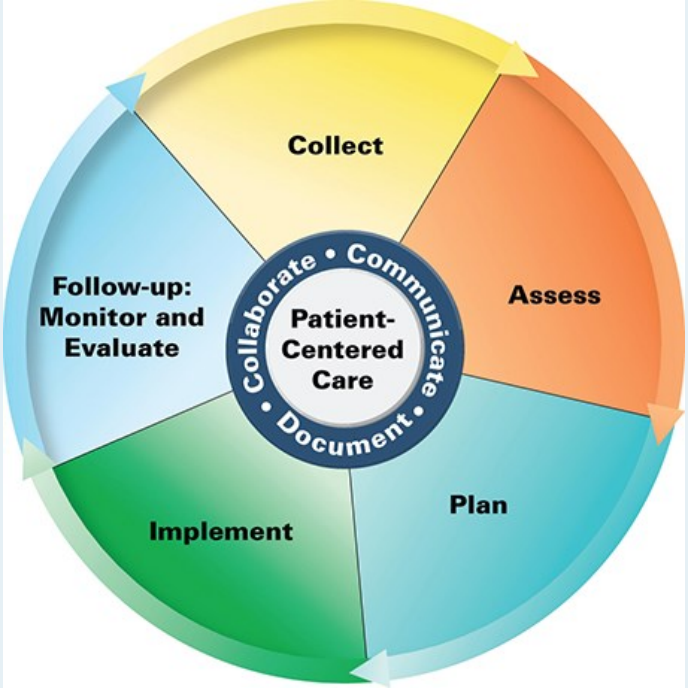
9. The brain's adaptation to chronic serum hypoosmolality or hyperosmolality leads to neurologic symptoms when either hyponatremia (hypoosmolality) or hypernatremia (hyperosmolality) is corrected too rapidly.

10. Hypernatremia, defined as a serum sodium concentration greater than 145 mEq/L (mmol/L), is always associated with hypertonicity and intracellular dehydration, resulting from a water deficit relative to ECF sodium content.

11. Edema, defined as a clinically detectable increase in interstitial fluid volume, is usually due to heart, kidney, or liver failure or a combination of these conditions; although, it can develop with a rapid decrease in serum albumin concentration along with excess fluid intake such as seen in the setting of burns or trauma.

PATIENT CARE PROCESS

Patient Care Process* for the Management of Disorders of Sodium and Water Homeostasis



Collect

- Patient characteristics (eg, age, sex, pregnant)
- Patient history (eg, medical, surgical, diet, recent gastrointestinal [GI] losses; see Tables 68-2 and 68-7)
- Current medications (eg, diuretics, intravenous [IV] fluids, sodium-containing therapies; see Tables 68-3 and 68-8)
- Objective data
  - Body weight (current and historical)
  - Recent intake/output
  - ECF volume status (eg, blood pressure [BP], mucous membranes, skin turgor, cardiopulmonary examination, level of consciousness; see Figs. 68-1 and 68-3)
  - Labs (eg, serum osmolality, electrolytes, glucose, protein, lipids; urine osmolality, sodium, and potassium; thyroid function tests)

Assess

- Chronicity and severity of the disorder
- Potential causative underlying disorders (eg, diarrhea, central nervous system [CNS] disorders, pulmonary disease, cirrhosis, nephrotic syndrome, polydipsia, diabetes insipidus; see Tables 68-2 and 68-7)
- Dysregulated sodium- or fluid-related complications (eg, BP variations, CNS changes, edema; see Clinical Presentation boxes and Tables 68-2 and 68-7)

- Current medications that may affect or worsen the disorder (see Tables 68-2, 68-3, 68-7, and 68-8)
- Goals for sodium and/or volume status and achievement of the goals

Plan*

- Treat the underlying cause of the disorder, if possible
- Develop therapy regimen, including specific medication(s), dose, route, frequency, and duration
- Balance risks of underlying disorder versus risk of too rapid or overcorrection (see Table 68-4)
- Specify continuation and discontinuation of existing therapies
- Tailor dietary modifications (eg, water and solute intake) and weight management
- Establish monitoring parameters, including efficacy (serum sodium, volume status, urine output), safety (rate of serum sodium correction, medication-specific adverse reactions), and time frame
- Provide patient education (purpose of treatment, dietary and lifestyle modification, medications, self-monitoring of weight and volume status)
- Refer to other providers, when appropriate (eg, physician, dietitian)

Implement*

- Provide patient education regarding all elements of treatment plan
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Attainment of sodium and/or volume status goals
- Presence of adverse medication reactions
- Need for long-term management if disorder cannot be corrected
- Patient adherence to treatment plan using multiple sources of information

* **Collaborate with patient, caregivers, and other healthcare professionals.**

BEYOND THE BOOK

BEYOND THE BOOK

Read and evaluate the case presented in Chapter 57 “Syndrome of Inappropriate Antidiuretic Hormone Release: A Sudden Change of Mind Level I. In: Schwinghammer TL, Koehler JM, Borchert JS, Slain D, Park SK. eds. *Pharmacotherapy Casebook: A Patient-Focused Approach, 11e*. McGraw Hill; 2020.” Available at https://accesspharmacy.mhmedical.com/content.aspx?bookid=2868&sectionid=242182677.

This activity is useful to enhance student understanding regarding the COLLECT, ASSESS, PLAN, and IMPLEMENT steps in the patient care process.

INTRODUCTION

Maintenance of normal blood volume and serum osmolality is essential for cellular function and is tightly regulated in the human body. Simply put, water balance determines serum sodium concentration, and sodium balance determines volume status. Adequate blood volume is required for effective tissue perfusion which is required to deliver oxygen and nutrients to and remove metabolic waste products from tissues. Serum osmolality, determined primarily by the serum sodium concentration, is an important determinant of ICF volume. Maintaining normal ICF volume is particularly critical in the brain, which is 80% water, and where alterations, especially rapid changes, can result in significant dysfunction, and even death.

Homeostatic mechanisms for controlling blood volume focus on controlling sodium balance, and, in contrast, homeostatic mechanisms for controlling serum osmolality (serum sodium concentration) focus on controlling water balance. Disorders of sodium and water balance are common, caused by a variety of diseases, conditions, and medications, and potentially serious. This chapter reviews the etiology, pathophysiology, clinical presentation, and treatment options for disorders of sodium and water homeostasis.

SODIUM AND WATER HOMEOSTASIS

The average daily sodium intake of Americans consuming a typical western diet usually exceeds the recommendations for Chronic Disease Risk Reduction (CDRR) levels established by the US Department of Agriculture: adults and children older than 13 years, 2.3 g; 9 to 13 years, 1.8 g; 4 to 8 years, 1.5 g; 1 to 3 years, 1.2 g; and, infants and young children 6 to 11 months, 0.37 g (Adequate Intake, AI).[1] Excessive sodium intake is a major risk factor for hypertension as BP rises with increased sodium intake. Appropriately functioning kidneys excrete excess sodium to maintain the serum sodium concentration and osmolality within a tight range. The kidney can also conserve sodium (urine sodium less than 30 mEq/L [mmol/L]) during periods of low sodium intake or in the presence of excessive losses. Both hypo- and hypernatremia are conditions of altered serum tonicity and cell volume that reflect a change in the ratio of total exchangeable body sodium to TBW.

TBW ranges from 45% to 80% of body weight depending on sex, age, gestational age, and disease states and is distributed primarily into two compartments: the intracellular compartment or intracellular fluid (ICF; two-thirds [67%] of TBW) and the extracellular compartment or extracellular fluid (ECF; one-third [33%] of TBW). The serum (plasma) volume is approximately 17% of the ECF volume. Sodium contributes more than 90% of the ECF osmolality, whereas ICF osmolality is primarily determined by the ICF potassium concentration. The extra- and intracellular sodium and potassium concentrations are maintained by the sodium–potassium–adenosine triphosphatase (Na^+-K^+-ATPase) pump. Because most cell membranes are freely permeable to water, the free flow of water between compartments ensures that the ICF and ECF osmolalities remain equal.

Effective osmoles are solutes that cannot freely cross cell membranes, such as sodium and potassium, which are kept in their respective compartments by the Na^+-K^+-ATPase pump. The ECF concentration of effective osmoles determines its tonicity, which directly affects water distribution between the ECF and ICF. Addition of an isotonic solution (eg, 0.9% NaCl) to the ECF will result in no change in ICF volume because there will be no change in the effective ECF osmolality. However, addition of a hypertonic solution (eg, 3% NaCl) to the ECF will result in a decrease in ICF (cell) volume. Conversely, addition of a hypotonic solution (eg, 0.45% NaCl) to the ECF will result in an increase in ICF (cell) volume. Thus, administration of both hypertonic and hypotonic solutions can result in cell crenation or hemolysis, respectively. Table 68-1 summarizes the composition and osmolality of commonly used IV solutions and their expected distribution into the ICF and ECF compartments following administration.

TABLE 68-1

Composition of Common IV Solutions

								Distribution		
Solution	Dextrose g/dL (kcal/L)	[Na^+] (mEq/L or mmol/L)	[K^+] (mEq/L or mmol/L)	[Cl^-] (mEq/L or mmol/L)	Other (mEq/L)	Osmolality (mOsm/kg or mmol/kg)	Tonicity	% ECF	% ICF	Free water (mL/L)
Dextrose 5% in water	5 (170)	0	0	0	---	253	Hypotonic	33	67	1,000 mL
0.2% NaCl[a]	0	34	0	34	---	68	Hypotonic	50	50	750 mL
0.45% NaCl[b]	0	77	0	77	---	154	Hypotonic	67	33	500 mL
0.9% NaCl[c]	0	154	0	154	---	308	Isotonic	100	0	0 mL
Lactated Ringer's[d]	0	130	4	105	Lactate 28 Ca 4.8	273	Isotonic	97	3	0 mL
Plasma-Lyte A[e] Plasma-Lyte 148[e]	0.44 (21)	140	5	98	Acetate 27 Mg 3 Gluc 23	294	Isotonic	100	0	0 mL
Normosol-R[f] Normosol-R pH 7.4	0	140	5	98	Acetate 27 Mg 3 Gluc 23	294	Isotonic	100	0	0 mL
3% NaCl[g]	0	513	0	513	---	1,026	Hypertonic	100	0	–2,331 mL

Ca, calcium; Cl^-, chloride; ECF, extracellular fluid; ICF, intracellular fluid; IV, intravenous; K^+, potassium; Mg, magnesium; NA, not applicable; Na^+, sodium; NaCl, sodium chloride; For conversion of kcal/L to kJ/L multiply by 4.184).

[a]Also referred to as *quarter normal saline.*

[b]Also referred to as *half normal saline.*

[c]Also referred to as *normal saline.*

[d]Also referred to as LR; also available commercially as Dextrose 5% LR.

[e]Plasma-Lyte A pH 7.4; Plasma-Lyte 148 pH 5.5.

[f]Normosol-R available with pH 6.6 and Normosol-R pH 7.4.

[g]Hypertonic solution; results in osmotic removal of water from the ICF.

Edelman's equation (simplified) defines serum sodium (Na_s) as a function of the total exchangeable sodium and potassium in the body and the TBW:

$$Na_s = Na_{totalbody} + K_{totalbody}/TBW$$ Nas=Natotalbody+Ktotalbody/TBW

where $Na_{total\ body}$ is the total body sodium content; $K_{total\ body}$ is the total body potassium content; and TBW is the total body water (TBW) in liters.[2,3] The usual serum sodium concentration (135-145 mEq/L [mmol/L]) is tightly regulated and thus usually varies by no more than 3%. Serum sodium regulation occurs via mechanisms that control serum osmolality and blood volume. The kidney regulates water excretion through a hypothalamic feedback mechanism, such that the serum osmolality remains relatively constant (275-290 mOsm/kg [mmol/kg]) despite day-to-day variations in water intake. While serum osmolality is primarily determined by the sodium concentration, abnormally high glucose and blood urea nitrogen (BUN) concentrations may contribute significantly. Glucose is an effective osmole, but BUN is not; thus, elevated osmolality due to these two substances will have differing effects. Serum osmolality can be estimated as follows:

$$Osm_s = (2 \times Na_s) + (glucose_s/18) + (BUN/2.8)$$ Osms=(2×Nas)+(glucoses/18)+(BUN/2.8)

where Osm_s is the serum osmolality in mOsm/kg [mmol/kg]; Na_s is the serum sodium concentration in mEq/L; $glucose_s$ is the serum glucose concentration in mg/dL; BUN is the BUN concentration in mg/dL; and 18 and 2.8 are the factors needed to convert from a weight measurement (mg/dL) to a concentration (mmol/L) for glucose and BUN, respectively. Thus, when using SI units, the equation becomes

$$Osm_s = (2 \times Na_s) + glucose_s + BUN$$ Osms=(2×Nas)+glucoses+BUN

where Osm_s is the serum osmolality in mmol/kg; and Na_s, $glucose_s$, and BUN are the respective concentrations in mmol/L.

3 Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is synthesized in the hypothalamus, and secreted by the posterior pituitary in response to both osmotic (serum sodium greater than 135 mEq/L [mmol/L]) and non-osmotic regulators to maintain water balance. When the serum osmolality increases by as little as 1% to 2%, AVP is released and binds to the arginine vasopressin 2 (V_2) receptor, a G protein-coupled receptor, on the basolateral membrane of principal cells lining the renal collecting duct, resulting in the insertion of water channels (aquaporin 2, AQP2) into both the apical cell membrane of the collecting duct principal cells and intracellular vesicles below the apical membrane increasing permeability.[2,4] Water can then pass through the cell into the peritubular capillary space where it is reabsorbed into the systemic circulation. A maximally concentrated urine (1,200 mOsm/L) will be formed when the serum sodium concentration is 145 mEq/L (mmol/L) or above.[2] AVP release also stimulates thirst as an additional means to return serum osmolality toward normal. The combined effect of increased water intake (response to thirst) and decreased water excretion (kidney's response to AVP) results in a decrease in the serum osmolality. Once the serum osmolality is restored to normal, AVP secretion is inhibited, AQP2 water channels are retrieved, water permeability returns to the usual low state, and renal excretion of solute-free water (aquaresis) occurs.

While AVP secretion is regulated primarily by osmolality, non-osmotic AVP release occurs when the brain's osmoreceptors detect as little as a 6% to 10% reduction in the effective circulating volume or arterial BP. The effective circulating volume is the portion of the ECF responsible for organ perfusion. A decrease in the effective circulating volume (more accurately, the arterial BP associated with that volume) activates arterial baroreceptors in the carotid sinus and glomerular afferent arterioles, resulting in stimulation of the renin–angiotensin system and increased angiotensin II synthesis. Angiotensin II stimulates both non-osmotic AVP release and thirst. This non-osmotic volume stimulus can override osmotic AVP inhibition. Water conservation then restores the effective circulating volume and BP at the expense of producing a decreased serum osmolality and hyponatremia.[2] Both hypo- and hypernatremia can be associated with either high, low, or normal ECF sodium or volume. To understand treatment options, differentiating between *dehydration* and *hypovolemia* is important. Dehydration refers to a loss of TBW producing hypertonicity while hypovolemia (volume depletion) is a symptomatic ECF volume deficit. It is important to note that volume depletion and dehydration can exist independently or concurrently.

Often these terms are used interchangeably, but they are different processes requiring different types and rates of fluid replacement.[5]

HYPONATREMIA

Epidemiology and Etiology

4 Hyponatremia, defined as a serum sodium concentration less than 135 mEq/L (mmol/L), is the most common electrolyte abnormality encountered in clinical practice in both adults and children and is associated with significant morbidity and mortality.[4] It affects 3 to 6 million persons and 1 million hospitalized patients yearly.[6,7] Although the prevalence is not well established and varies with the patient population studied, it has been estimated to be 15% to 30% of hospitalized patients.[6,7] In one study, the prevalence of mild hyponatremia (serum sodium concentration less than 136 mEq/L [mmol/L]) in hospitalized patients was 42% (28% on admission, 14% during admission); 6.2% of patients evaluated (2.5% on admission, 3.7% during admission) had values less than 126 mEq/L (mmol/L); and 1.2% (0.5% on admission, 0.7% during admission) had a serum sodium concentration less than 116 mEq/L (mmol/L).[8] The prevalence of hyponatremia in the intensive care unit (ICU) is 30% to 40% with an admission serum sodium less than 130 mEq/L (mmol/L) in approximately 14%.[9] In hospital-based ambulatory care clinics and community clinics, the prevalence of hyponatremia (serum sodium concentration less than 136 mEq/L [mmol/L]) is 21% and 1.7% to 9.2%, respectively.[8,10] Medication-induced hyponatremia, especially that associated with thiazide diuretics[11] and psychotropic medications,[12–14] is common.

Advancing age is a risk factor for hyponatremia, independent of sex.[10,15,16] Residents in nursing homes have a twofold higher incidence of hyponatremia than age-matched, community-dwelling individuals. More than 75% of these hyponatremic episodes in long-term care facilities were precipitated by increased intake of hypotonic fluids either orally or through enteral feedings or IV fluids.[17] Similarly, ingestion of excessive volumes of hypotonic fluids (water, sports drinks) has been identified as a key risk factor in the development of exercise-associated hyponatremia occurring during or up to 24 hours after prolonged physical activity. Men and women are at an equal risk for developing exercise-induced hyponatremia when rates are adjusted based on body mass index (smaller body size) and racing time (longer times).[18] Hyponatremia is also the most common electrolyte abnormality seen in pregnancy, frequently seen in patients with hyperemesis gravidarum and preeclampsia.[19]

Recognition of the high prevalence of hyponatremia is essential because this condition is associated with significant morbidity and mortality.[7,9,19-22] Even in asymptomatic patients, chronic hyponatremia has been associated with decreased cognitive function and increased risk of frailty, falls, fractures, and bone loss, particularly in older adults.[23-26] In patients with hyponatremia, transient or permanent brain dysfunction can result from either acute effects of hypoosmolality or too rapid correction.

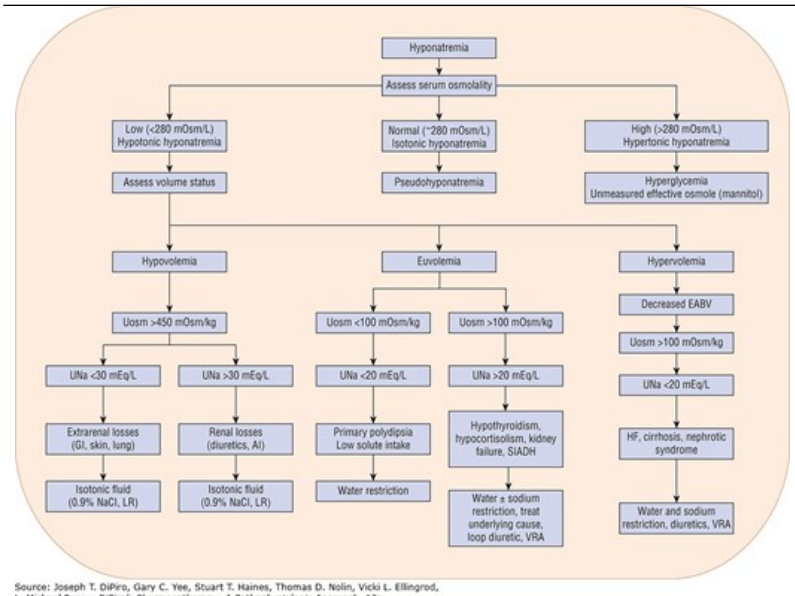
5 Hyponatremia is predominantly the result of an excess of extracellular water relative to sodium because of impaired water excretion. The kidney normally has the capacity to excrete large volumes of dilute urine after ingestion of a water load. Non-osmotic AVP release, however, can lead to water retention and a decrease in the serum sodium concentration, despite a decrease in ECF and ICF osmolality. Causes of non-osmotic AVP release include hypovolemia and a decreased effective circulating volume (eg, chronic heart failure [HF], nephrotic syndrome, cirrhosis). The syndrome of inappropriate antidiuretic hormone secretion (SIADH), a common cause of hyponatremia, is associated with some cancers, CNS damage, certain lung conditions, medications, and primary or psychogenic polydipsia.

Pathophysiology

Hyponatremia can be associated with normal, increased, or decreased serum osmolality, depending on its cause. Figure 68-1 provides an algorithm for the assessment and treatment of patients with non-emergent hyponatremia.[2,4]

FIGURE 68-1

Algorithm for the assessment and treatment of non-emergent hyponatremia. (AI, adrenal insufficiency; EABV, effective arterial blood volume; GI, gastrointestinal; HF, heart failure; LR, lactated Ringers; NaCl, sodium chloride; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; UNa, urine sodium concentration [values in mEq/L are numerically equivalent to mmol/L]; UOsm, urine osmolality [values in mOsm/kg are numerically equivalent to mmol/kg]; VRA, vasopressin receptor antagonist.)



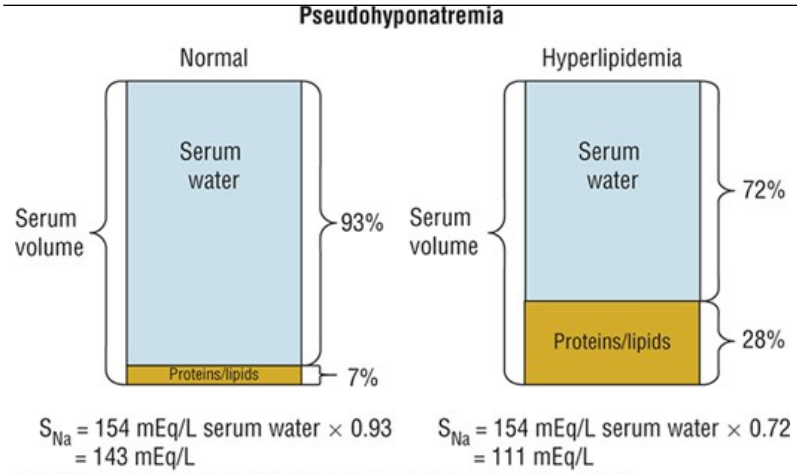
Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Isotonic Hyponatremia

Hyponatremia (expected low osmolality) with a normal measured serum osmolality (*osmol gap*) can be seen in the setting of markedly elevated serum lipids (hyperlipidemia) or proteins (eg, hyperproteinemia, multiple myeloma) when flame photometry or indirect potentiometry is used to measure the sodium concentration (see Fig. 68-2). This *pseudohyponatremia* is an artifact because elevated lipids or proteins account for a larger than usual proportion of the total sample volume, reducing the percentage of water in the serum (Fig. 68-2). Because sodium is distributed in the water component only, the measured serum sodium concentration is falsely decreased, and the calculated osmolality will be low. The measurement of serum osmolality is not affected, leading to a discrepancy between the calculated and measured serum osmolality (*osmolal gap*). Pseudohyponatremia is not seen when the sodium concentration is measured via direct potentiometry using ion-selective electrodes as is most often done in current laboratory practice, including blood gas analyzers, because it does not involve sample dilution. Treatment of *hyponatremia* in a case of pseudohyponatremia can lead to serious consequences.[27]

FIGURE 68-2

Elevated serum lipids or proteins result in a larger discrepancy between the volume of the sample and serum water, which leads to a falsely low measurement of the serum sodium concentration when using flame photometry. (S_{Na}, serum sodium concentration [values in mEq/L are numerically equivalent to mmol/L].)



Hypertonic Hyponatremia

Hypertonic (increased serum osmolality) hyponatremia is due to the presence of excess effective osmoles (other than sodium) in the ECF (Fig. 68-1). Significant hyperglycemia is the most frequent cause. An elevated serum glucose concentration initially causes water diffusion from cells (ICF) into the ECF, thereby decreasing the ICF volume, expanding the ECF volume, and diluting the existing sodium resulting in hyponatremia. The increased ECF volume results in increased urine output (polyuria) which triggers the thirst mechanism (polydipsia). If the hyperglycemia is not corrected and/or extra fluid is not ingested, hypovolemia develops due to excessive urinary losses.

The volume of distribution (V_d) of glucose is a complex function of insulin activity, glucose distribution time, ECF volume, and glucose concentration. Using a clinically relevant glucose V_d of 0.3 to 0.5 L/kg, one would predict a 1.5 to 1.9 mEq/L (mmol/L) decrease in the serum sodium concentration for every 100 mg/dL (5.6 mmol/L) increase in the serum glucose concentration above 100 mg/dL (5.6 mmol/L), and the serum osmolality will increase by 2 mOsm/kg (mmol/kg).[5,28] This correction is only an estimate because of the variability in the V_d of glucose, and clinical practice guidelines recommend simplifying to 1.6 mg/dL as the correction factor using the equation:

$$SNa_{corrected} = SNa_{measured} + (1.6 \times glucose_{measured}/100)$$SNacorrected=SNameasured+(1.6×glucosemeasured/100)

where $SNa_{corrected}$ is the serum sodium (mg/dL) corrected for hyperglycemia; $SNa_{measured}$ is the measure serum sodium (mg/dL); and $glucose_{measured}$ is the measured serum glucose in mg/dL.[20]

Alternatively, one would predict a 0.29 mmol/L decrease in the serum sodium concentration for every 1 mmol/L increase in the serum glucose concentration above 5.6 mmol/L using for glucose and sodium expressed in units of mmol/L the following equation:

$$SNa_{corrected} = SNa_{measured} + 0.29 \times glucose_{measured} - 5.6$$SNacorrected=SNameasured + 0.29 × glucosemeasured − 5.6

where $SNa_{corrected}$ is the serum sodium (mmol/L) corrected for hyperglycemia; $SNa_{measured}$ is the measure serum sodium (mmol/L); and $glucose_{measured}$ is the measured serum glucose in mmol/L.

The presence of other effective osmoles (eg, mannitol) can also cause hypertonic hyponatremia. The presence of an unmeasured osmole should be suspected in patients with a normal glucose concentration and hypertonic hyponatremia when there is a significant osmolal gap.

Hypotonic Hyponatremia

Hypotonic (decreased osmolality) hyponatremia is the most common form of hyponatremia and has many potential causes (see Fig. 68-1 and Table 68-2). Assessment of ECF volume status is important in the evaluation of a patient with hypotonic hyponatremia. Categorization into one of three groups (decreased, increased, or clinically normal ECF volume) is the essential first step in identifying the pathophysiologic mechanism(s) responsible for the hyponatremia and developing an appropriate treatment plan.

TABLE 68-2

Characteristics of Hypotonic Hyponatremic States

Characteristics	Hypovolemic Hyponatremia	Euvolemic (Isovolemic) Hyponatremia	Hypervolemic Hyponatremia
Water and sodium	Sodium loss >> water loss	Water gain only	Water gain > sodium gain
Causes	Renal: thiazide diuretics Nonrenal: diarrhea, cerebral salt wasting	SIADH	Heart failure Liver cirrhosis Kidney failure
Effect on TBW	↓↓	↑	↑↑
Effect on TBNa	↓	↔	↑↑
Additional laboratory findings	Renal: UOsm high, UNa high Nonrenal: UOsm high, UNa low	Renal: UOsm low, UNa variable Nonrenal: UOsm high, UNa variable	UOsm high, UNa high
Clinical presentation	Orthostasis, hypotension, tachycardia, dry mucous membranes, CNS changes	Depends on severity of hyponatremia: seizures, lethargy	Peripheral and pulmonary edema, variable BP
Treatment	0.9% NaCl until vital signs stable; *maintenance* fluids to continue fluid deficit replacement; sodium replacement if cerebral salt wasting; VRA contraindicated	Water restriction, demeclocycline, loop diuretics, VRA, urea	Sodium and water restriction, loop diuretic, VRA, urea

CNS, central nervous system; NaCl, sodium chloride; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TBW, total body weight; UNa, urine sodium; UOsm, urine osmolality; VRA, vasopressin receptor antagonist.

Hypovolemic Hypotonic Hyponatremia

Most patients with ECF volume contraction have lost fluids that are hypotonic relative to the serum and thus may become transiently hypernatremic. This situation includes patients with fluid losses caused by diarrhea, excessive sweating, and diuretics. This transient hypernatremic hyperosmolality results in osmotic AVP release and thirst. If sodium and water losses continue, the resultant hypovolemia results in more AVP release. Patients who then drink water (a hypotonic fluid) or who are given hypotonic IV fluids retain water, and hyponatremia develops. These patients will typically have a concentrated urine (urine osmolality greater than 450 mOsm/kg [mmol/kg]), reflecting AVP action. The urine sodium concentration will be less than 30 mEq/L (mmol/L) when sodium losses are extrarenal (eg, diarrhea, vomiting), and greater than 30 mEq/L (mmol/L) with renal sodium losses (eg, thiazide diuretics, adrenal insufficiency); although, urine sodium concentration is also affected by solute intake.[4,20]

6 Hypovolemic hypotonic hyponatremia is common in patients taking thiazide diuretics.[6,11] Thiazide diuretic-induced hyponatremia is usually mild

and relatively asymptomatic but can be severe. Hyponatremia typically develops within 2 weeks of diuretic initiation but can occur at any time during therapy, particularly after dosage increases or if other causes of hyponatremia are present. Older women are at the greatest risk for thiazide diuretic-induced hyponatremia.[6,11]

Thiazide diuretic-induced hyponatremia is related to a balance of direct and indirect effects. These agents block sodium reabsorption in the distal tubules of the renal cortex, thereby increasing sodium and water removal from the body. The resultant decrease in effective circulating volume stimulates AVP release, resulting in increased free water reabsorption in the collecting duct, as well as increased water intake because of thirst stimulation. Hyponatremia develops when the net result of these effects is the loss of more sodium than water.

Conversely, hyponatremia occurs infrequently with loop diuretics due to their different site of action. Loop diuretics block sodium reabsorption in the ascending limb of the loop of Henle. This action decreases medullary osmolality; thus, when loop diuretic use decreases the effective circulating volume and stimulates AVP release, less water reabsorption occurs in the collecting ducts than would occur with normal medullary osmolality. Thiazide diuretics do not alter medullary osmolality because they act in the renal cortex. Additionally, most loop diuretics have a shorter half-life than thiazides, and patients usually replete the urinary sodium and water losses prior to taking the next dose, thereby minimizing AVP stimulation.[29]

Cerebral (renal) salt wasting syndrome is a condition observed most often in patients with intracranial disorders such as subarachnoid hemorrhage and traumatic brain injury or after neurosurgical procedures, but it can occur in patients without CNS pathology. It results in decreased ECF volume due to a profound natriuresis (urinary sodium loss). A high urine sodium, osmolality, and volume; high serum BUN; orthostatic hypotension; and low central venous pressure suggests cerebral salt wasting.[30] In more severe cases, treatment consists of IV volume repletion with 0.9% NaCl. If serum sodium concentration is less than 120 mEq/L (mmol/L), 3% NaCl may be needed to correct the serum sodium concentration. In some cases, careful titration with 3% NaCl and 0.9% NaCl is required to maintain the serum sodium within an acceptable range.[30] In stable patients, oral administration of a salt supplement and a mineralocorticoid such as fludrocortisone may be used to augment serum sodium and intravascular volume until resolution of this typically transient condition.

Euvolemic Hypotonic Hyponatremia

7 Euvolemic (isovolemic) hypotonic hyponatremia is associated with a normal or slightly decreased ECF sodium content and increased TBW and ECF volume and is most often caused by SIADH. The increase in ECF volume is not sufficient to cause peripheral or pulmonary edema or other signs of volume overload, and thus patients will appear euvolemic upon physical examination.

In SIADH, water intake exceeds the kidney's capacity to excrete a water load, either because of increased AVP release via non-osmotic and/or nonphysiologic processes or enhanced sensitivity of the kidney to AVP. In most patients with SIADH, the urine osmolality and sodium concentrations will be greater than 100 mOsm/kg (mmol/kg) and 20 to 30 mEq/L (mmol/L), respectively, and serum osmolality will be less than 275 mOsm/kg (mmol/kg) due to ECF volume expansion (see **Fig. 68-1** and **Table 68-2**).[4,14]

The most common causes of SIADH are certain cancers (eg, small cell lung, pancreatic, brain), CNS disorders (eg, traumatic brain injury, stroke, meningitis, pituitary surgery), and lung disease (eg, tuberculosis, pneumonia, abscess, acute respiratory distress syndrome). A number of medications can cause SIADH by enhancing AVP release or its action on the kidney or by other mechanisms[13-15,31] (see Table 68-3). Patients with kidney and adrenal insufficiency or hypothyroidism can also present with euvolemic hyponatremia. The evaluation of a patient with suspected SIADH should include consideration of these disorders or medications.

TABLE 68-3

Potential Causes of SIADH

Drug-Induced		Nondrug-Induced
Acetaminophen ACE inhibitors Anti-epileptic agents (barbiturates, carbamazepine, lamotrigine, valproic acid) Anti-infectives (linezolid, moxifloxacin) AVP analogs (desmopressin terlipressin, oxytocin, vasopressin) Bromocriptine Cytotoxic agents (carboplatin, cisplatin, ifosfamide, melphalan, methotrexate, vinca alkaloids)	Chlorpropamide Duloxetine Haloperidol MDMA (ectasy) Monoamine oxidase inhibitors Nicotine NSAIDs Opioids Phenothiazines Proton pump inhibitors Risperidone SSRIs Thioridazine Thiothixene Tolbutamide Tricyclic antidepressants Venlafaxine	Malignancy (lung, pancreatic, duodenal) CNS (trauma, tumor, meningitis, hemorrhage, stroke) Pulmonary (pneumonia, ARDS, TB) Postoperative state Nausea Anxiety

ACE, angiotensin-converting enzyme; ARDS, acute respiratory distress syndrome; AVP, arginine vasopressin; CNS, central nervous system; MDMA, 3,4-methylenedioxymethamphetamin; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SSRIs, selective serotonin receptor inhibitors; TB, tuberculosis.

Euvolemic hypotonic hyponatremia may also be caused by primary or psychogenic polydipsia (water intoxication or compulsive water drinking) where more water (usually more than 20 L/day) is ingested than the kidneys can excrete as solute-free water. Unlike in SIADH, AVP secretion is suppressed, resulting in a urine osmolality less than 100 mOsm/kg (mmol/kg). The urine sodium is typically low (less than 15 mEq/L [mmol/L]) due to dilution.[14] Hyponatremia may develop even with more modest water intakes in individuals who ingest low-solute diets.

Hypervolemic Hypotonic Hyponatremia

8 Hyponatremia with ECF volume expansion (hypervolemia) occurs in conditions in which both sodium and water excretion are impaired such as HF, cirrhosis, or nephrotic syndrome. These patients have an expanded ECF volume and edema but a decreased effective arterial blood volume. The decrease in the effective circulating blood volume results in renal sodium retention and eventual ECF volume expansion and edema. There is concomitant non-osmotic AVP stimulation and water retention in excess of sodium retention, which perpetuates hyponatremia.

Clinical Presentation

Patients with chronic (longer than 48 hours) mild hyponatremia (serum sodium concentration 125-134 mEq/L [mmol/L]) are usually relatively asymptomatic, with hyponatremia often being discovered incidentally when serum electrolytes are measured for other reasons. Mild symptoms of hyponatremia frequently go unnoticed by both clinicians and patients.[32] Chronic, mild hyponatremia, especially in older adults, has been associated with impairment of attention, posture, and gait; all of which contribute to a substantially increased fall risk.[23-26,33] Even *asymptomatic* patients, when formally tested, have impaired attention and gait to a degree that is comparable to symptoms seen with a blood alcohol level of 0.06% (13 mmol/L).[32]

Patients with moderate (serum sodium concentration 115-124 mEq/L [mmol/L]), severe (serum sodium concentration 110-114 mEq/L [mmol/L]), or

rapidly developing hypotonic hyponatremia may present with a range of CNS symptoms resulting from hypoosmolality-induced brain cell swelling. Classic neurologic symptoms include nausea, malaise, headache, lethargy, restlessness, and disorientation. In severe cases, seizures, coma, respiratory arrest, brainstem herniation, and death can occur.

CLINICAL PRESENTATION: Hyponatremia

General

- Severity of symptoms depends on the magnitude and rapidity of onset
- Too rapid correction can lead to severe neurologic symptoms

Symptoms

- Symptoms are primarily neurologic in nature
- Mild: may be asymptomatic; nausea, malaise, gait or cognitive disturbances
- Moderate: headache, lethargy, restlessness, disorientation
- Severe: seizures, coma, respiratory arrest, brainstem herniation, death
- Other symptoms depend on etiology: dry mucous membranes, tachycardia, hypotension, reduced or increased urine output

Laboratory tests

- Serum sodium concentration less than 135 mEq/L (mmol/L)
- Serum osmolality and urine sodium concentration vary depending on etiology
- Altered serum glucose, lipids, proteins, or thyroid function in certain patients

The presence and severity of symptoms depend on both the degree of the hyponatremia and the rate at which it develops. The degree of hyponatremia is important because serum osmolality decreases in direct proportion to the serum sodium concentration, and water movement into cells, including brain cells, increases as serum osmolality decreases. The rate of change of the serum osmolality is important because brain cells are not able to rapidly adjust intracellular osmolality to minimize cellular volume changes.[2,34] When decreased serum osmolality causes water movement into brain cells, inorganic Cl^- and K^+ and organic osmolytes (eg, taurine, glutamate, myoinositol, GABA), move out of the cells to decrease intracellular osmolality and minimize the intracellular water shift. The components of this adaptive mechanism occur and dissipate over different time frames, with Cl^- and K^+ efflux occurring and dissipating within minutes to hours and organic osmolyte efflux occurring and dissipating within hours to days.[3,34] Thus, maximal compensation for decreased serum osmolality typically requires up to 48 hours, and acute changes in serum osmolality are more likely to cause symptoms. Gender and age play a role in the response to severe hyponatremia. Young women (pre-menopausal) have been found to have a higher likelihood of death or permanent brain damage compared to men or older women. Female sex hormones may inhibit the Na^+/K^+-ATPase system. Additionally, interleukin-6 which is found in higher concentrations in women than in men influences vasopressin secretion and reduces the expression of aquaporin-2, impairing free water excretion.[3] Hyponatremia is an important risk factor for morbidity and mortality in patients with HF and cirrhosis.[20,35]

In addition to CNS symptoms, patients with hypovolemic hyponatremia present with signs and symptoms of hypovolemia, including dry mucous membranes, decreased skin turgor, tachycardia, decreased jugular venous pressure, hypotension, and orthostatic hypotension. Lactic acidosis and low mixed venous oxygen saturation, indicating decreased tissue perfusion, may be present with severe hypovolemia.

The brain's adaptation to chronic serum hypoosmolality or hyperosmolality leads to neurologic symptoms when either hyponatremia (hypoosmolality) or hypernatremia (hypertonicity) is corrected too rapidly. The combination of the adaptive decrease in ICF osmolality and a rapid

increase in ECF osmolality results in rapid and excessive water movement out of cells, including brain cells, and ICF volume depletion. Thus, too rapid correction of the serum sodium concentration can lead to an acute decrease in brain cell volume, which contributes to the pathogenesis of *osmotic demyelination syndrome* (ODS) or central pontine myelinolysis.[3] While demyelinated lesions identified on magnetic resonance imaging most often occur in the central pons, ODS can extend to other areas of the brain. Patients with ODS may be asymptomatic or develop mild to severe symptoms including confusion, disorientation, dysarthria, dysphagia, hyperreflexia, obtundation, para- or quadriparesis, parkinsonism, pseudobulbar palsy, *locked-in syndrome* (a condition in which a patient is aware and awake but cannot move or communicate verbally due to complete paralysis of nearly all voluntary muscles except for the eyes), seizures, coma, and/or death in 1 to 7 days after correction of the serum sodium concentration.[3,36] If recovery from ODS occurs, it can take several months for symptoms to improve. Patients with significant cerebral adaptation (eg, chronic serum sodium concentration less than 110 mEq/L [mmol/L]) are at highest risk of developing ODS because these patients have a lower intracellular osmolality at the initiation of therapy, and there is a greater decrease in brain cell volume when the serum osmolality is raised too rapidly.[3] Other conditions that increase the risk of ODS include alcoholism, liver disease including orthotopic liver transplantation, potassium depletion, and malnutrition. Thus, if the duration of hyponatremia is unknown, it is generally safer to treat as if it is chronic when developing an initial therapy plan.

Treatment: Hyponatremia

General guidelines for the treatment of patients with hyponatremia are shown in Table 68-4. Application of these principles to the treatment of various forms of hyponatremia is discussed in the following sections.

TABLE 68-4

General Guidelines for Treatment of Hyponatremia

- For both short- and long-term management, treat the underlying cause of hyponatremia, if possible.
- Appropriate treatment of moderate-to-severe hypotonic hyponatremia requires balancing the risks of hyponatremia vs the risk of ODS.
- Patients who acutely develop moderate-to-severe hyponatremia and/or patients who have severe symptoms are at greatest risk and potentially benefit most from more rapid correction of hyponatremia.
- Correction of hypovolemic hypotonic hyponatremia is usually best accomplished with 0.9% NaCl, as these patients have both sodium and water deficits.
- Active correction of euvolemic and hypervolemic hypotonic hyponatremia in patients who do not require rapid correction is usually best accomplished by water restriction. Demeclocycline, VRA, urea, or a loop diuretic can be used if the initial response to water restriction is not adequate.
- In patients with severe symptoms, 3% NaCl should initially be used to correct the hyponatremia more rapidly. A loop diuretic can be administered concurrently with 3% NaCl to enhance the serum sodium correction by increasing free water excretion.
- Long-term management will be required for patients in whom the underlying cause of hyponatremia cannot be corrected. Depending on the cause, water restriction, increasing sodium intake, and/or a VRA may be used.

NaCl, sodium chloride; ODS, osmotic demyelination syndrome; VRA, vasopressin receptor antagonist.

Desired Outcomes

Regardless of the type or cause of hyponatremia, treatment goals for all patients are to resolve the underlying cause of the sodium and ECF volume imbalance, if possible, and to safely correct the sodium and water derangements. The treatment plan depends on the underlying cause and symptom severity. Patients with acute onset hyponatremia with severe symptoms require more aggressive therapy to correct the hypotonicity. The initial treatment goal is to increase serum tonicity just enough to control severe symptoms which typically requires only a small increase (5%) in the serum sodium concentration. Once severe symptoms have abated, then continued serum sodium correction should be achieved at a slower, more controlled rate. Patients who are asymptomatic or who have only mild to moderate symptoms do not require rapid correction of the serum sodium concentration. While treatment is dictated by the underlying cause, in all cases the goal is to avoid an increase in the serum sodium concentration of more than 6 to 12 mEq/L (mmol/L) in 24 hours (0.5 mEq/L [mmol/L] per hour) or 18 mEq/L (mmol/L) in any 48-hour period.[6,20] When the duration of hyponatremia is unknown, a sodium correction rate of no more than 6 to 8 mEq/L (mmol/L) in 24 hours is prudent to avoid ODS.[3]

ACUTE OR SEVERELY SYMPTOMATIC HYPOTONIC HYPONATREMIA

A patient who has or is at high risk of experiencing severe symptoms caused by hyponatremia (serum sodium less than 110-115 mEq/L [mmol/L]) should receive a small amount of 3% NaCl (513 mEq/L [mmol/L]) until severe symptoms resolve.[2,3] While resolution of severe symptoms generally requires approximately a 5% increase in the serum sodium concentration, some clinicians suggest that the initial safe target should be a serum sodium concentration of approximately 120 mEq/L (mmol/L).

The relative concentrations of urine sodium and potassium (osmotically effective urine cations) should be compared with those of the infusate in planning a treatment regimen for patients with hypotonic hyponatremia. For the serum sodium concentration to increase after a NaCl infusion, the sodium concentration of the infusate must exceed the sum of the urinary sodium and potassium concentrations so that an effective net free-water excretion is produced.[6] In SIADH, the urinary concentration of osmotically effective cations often exceeds 154 mEq/L (mmol/L) (sodium concentration of 0.9% NaCl); thus 0.9% NaCl administration could worsen hyponatremia. These patients should be preferentially treated with 3% NaCl.[32,37] The relatively high urinary sodium concentration in patient with SIADH is due to ECF expansion, which minimizes sodium reabsorption along the nephron. When the urine osmolality exceeds 300 mOsm/kg (mmol/kg), it is advisable to administer an IV loop diuretic to increase solute-free water excretion and to prevent volume overload which can result from NaCl administration. Intravenous furosemide 20 to 40 mg given every 6 hours or bumetanide 0.5 to 1 mg given every 2 to 3 hours for several doses is generally sufficient to prevent volume overload and to decrease the urinary concentration of osmotically active cations to less than 150 mEq/L (mmol/L). If intermittent loop diuretic doses are not sufficient to manage volume overload, then either IV furosemide 20 to 40 mg followed by a 10 to 40 mg/hr infusion or IV bumetanide 1 mg followed by a 0.5 to 2 mg/hr infusion can be used.

Patients with hypovolemic hypotonic hyponatremia should be treated initially with 0.9% NaCl. In contrast to SIADH, avid reabsorption of sodium throughout the nephron occurs because the effective circulating blood volume is decreased. Thus, the urine sodium concentration usually will be less than 30 mEq/L (mmol/L), substantially less than the sodium content of 0.9% NaCl. While administration of 3% NaCl will correct hyponatremia, it will not correct the hypovolemia and should be reserved for patients with severe symptoms requiring rapid serum sodium correction.

Acute hypervolemic hypotonic hyponatremia is particularly problematic to manage because the sodium and volume needed to minimize the risk of cerebral edema or seizures can worsen already compromised liver, heart, or kidney function. These patients generally should be treated initially with 3% NaCl and fluid (water) restriction. Loop diuretic or arginine vasopressin receptor antagonist (VRA) therapy is often required to facilitate urinary-free water excretion.

Determination of a NaCl Infusion Regimen

Multiple approaches can be used for determining an empiric NaCl infusion regimen for a patient with hyponatremia.[3,7,20] While several complex equations have been published, improved outcomes have not been demonstrated using these equations. Pragmatically, 150 mL[6] or 1 to 2 mL/kg[2] of 3% NaCl can be infused over 20 minutes. If symptoms do not resolve, then 100 mL or 1 mL/kg of 3% NaCl can be administered over 10 to 20 minutes every 30 minutes until symptoms resolve and/or the target serum sodium concentration is reached (usually 5-8 mEq/L [mmol/L] from baseline). Within the first hour, the serum sodium should not increase by more than 5 mEq/L (mmol/L). After relief of symptoms, 0.9% NaCl can be used to continue the sodium correction.

Another method is to calculate the sodium deficit, then replace one-third of the deficit in the first 6 hours and the remaining two-thirds over the following 24 to 48 hours or longer depending on the acuity of the serum sodium decrease. Sodium deficit can be calculated using the following equation:

$$Na_{deficit}(mEq\ or\ mmol)=[(Na_d\text{-}Na_s)\times TBW]$$ Nadeficit(mEq or mmol)=[(Nad-Nas)×TBW]

where Na_D is the goal or desired serum sodium (usually no higher than 120-125 mEq/L [mmol/L] to avoid too rapid or overcorrection); Na_s is the patient's current serum sodium concentration; and TBW is the patient's current TBW calculated as shown in Table 68-5. The change in serum sodium concentration resulting from the infusion of 1 L of 3% NaCl or 0.9% NaCl can be estimated. An example of this approach is shown in Table 68-5.

TABLE 68-5

Assessment and Treatment of Euvolemic Hyponatremia

Change in serum sodium concentration after an IV fluid bolus

$\Delta Na_S = (Na_{IV} + K_{IV} - Na_S) / (TBW + volume_{IV})$,

ΔNas, change in serum sodium concentration; K_{IV}, potassium concentration of infusate; Na_{IV}, sodium concentration of infusate (eg, 154 mEq/L [mmol/L] for 0.9% NaCl; 513 mEq/L [mmol/L] for 3% NaCl); Na_S, initial serum sodium concentration; TBW, total body water (L); and $volume_{IV}$, volume of infused fluid (L)

TBW can be estimated as:

- Term newborn infants: 0.7 L/kg × wt (kg); higher in premature infants depending on degree of prematurity
- Children and men younger than 70 years: 0.6 L/kg × wt (kg)
- Men older than 70 years and women younger than 70 years: 0.5 L/kg × wt (kg)
- Women older than 70 years: 0.45 L/kg × wt (kg)
- Dehydrated, older patients: 0.4 L/kg × wt (kg)
- (Note: wt is the current body weight)

Clinical example

A 76-year-old man (weight, 70 kg [154 lb]; height, 178 cm [5 ft 10 in]) presents with nausea, headache, and confusion which developed over the past 3 days. Ten days ago, he began taking carbamazepine for trigeminal neuralgia. His serum sodium concentration on admission to the emergency department was 109 mEq/L (mmol/L). He is diagnosed with drug-induced SIADH.

Plan of care

1. Discontinue carbamazepine (the likely etiology of his SIADH).
2. Admit to the hospital for correction of hyponatremia.
3. Increase the serum sodium concentration by no more than 6 to 12 mEq/L (mmol/L) during first 24 hours and no higher than 120 mEq/L (mmol/L); thus, the goal is to increase the sodium concentration by 11 mEq/L (mmol/L).
4. Due to degree of hyponatremia (less than 110 mEq/L [mmol/L]) and the presence of moderate-to-severe symptoms, give 3% NaCl.

Calculate the change in serum sodium after 1 L infusion of 3% NaCl:

ΔNa_S = (513 mEq/L − 109 mEq/L)/[(0.5 L/kg × 70 kg) + 1 L] = 11.2 mEq/L or 1.12 mEq/100 mL

(Note: In SI units, the calculation is the same using mmol/L rather than mEq/L.)

Infusion of 1 L of 3% NaCl will result in a 11.2 mEq/L (mmol/L) rise in the serum sodium concentration. An 11 mEq/L (mmol/L) increase is desired; thus, the appropriate infusion volume is 982 mL [(11 mEq/L/11.2 mEq/L) × 1,000 mL] or [(11 mmol/L/11.2 mmol/L) × 1,000 mL].

(Note: The approach to this calculation would be similar if 0.9% NaCl was used, except that for each 1 L infusion, the expected increase in serum sodium concentration would be only 1.25 mEq/L (mmol/L), and an infusion volume of approximately 8.8 L would be required to achieve the targeted serum sodium concentration.)

5. Moderate-to-severe symptoms: serum sodium concentration should be increased by approximately 1.5 mEq/L/hr (mmol/L/hr) over the first 2 to 4 hours of treatment for a total of 3 to 6 mEq/L [mmol/L] or until the symptoms have resolved. An initial infusion rate of 114 mL/hr for the first 2 to 4 hours is needed.
6. Check serum sodium concentration every 1 to 4 hours depending on rate of rise of serum sodium.
7. Once symptoms subside, continue infusion rate at approximately 23 to 31 mL/hr for the next 20 to 22 hours, to slowly correct hyponatremia. Monitor serum sodium concentration every 4 hours or more often if serum sodium is rapidly changing.

IV, intravenous; SIADH, syndrome of inappropriate antidiuretic hormone secretion; NaCl, sodium chloride.

Clinicians may disagree whether or not to administer 3% NaCl to patients with symptomatic hypotonicity. An advantage of 3% NaCl is more rapid correction of serum sodium concentration with a smaller infusion volume. A disadvantage of 3% NaCl is a higher risk of too rapid correction of serum sodium concentration and ODS. Another disadvantage of 3% NaCl is its high osmolality (1,026 mOsm/L) which can result in phlebitis and significant tissue damage with extravasation when given via a peripheral IV catheter (~7% complication rate with peripheral administration). Central line administration is preferred but short-term peripheral administration is acceptable if the infusion rate is low and a relatively large peripheral IV catheter

is used.[38] The historical use of 5% NaCl has been replaced by 3% NaCl due to these infusion issues. Some clinicians have suggested the use of 2% NaCl to avoid infusion-related issues, but this practice has not been evaluated in clinical trials. Fluid choice depends on the cause and the rapidity of development of the patient's hyponatremia as well as the relative risk of slower correction of the hyponatremia versus the development of ODS.

The appropriate infusion volume for a given patient can be estimated using the amount of fluid needed to provide the calculated sodium deficit or the desired proportion of the estimated change that would result from a 1-L infusion. The final step is to calculate an appropriate infusion rate for the calculated volume that will increase the serum sodium concentration by no more than 6 to 8 mEq/L (mmol/L) in 24 hours in high-risk patients and by 10 to 12 mEq/L (mmol/L) in 24 hours or 18 mEq/L (mmol/L) in 48 hours in others (see Table 68-5).[5] To minimize the risk of too rapid correction of hyponatremia, desmopressin (1-4 mcg) and free water replacement given along with 3% NaCl may be considered in patients with severe hyponatremia until the serum sodium concentration reaches 128 mEq/L (mmol/L).[3,20]

Evaluation of Therapeutic Outcomes

Patients with severely symptomatic hypotonic hyponatremia should be admitted to the ICU or other setting that will allow frequent monitoring of CNS symptoms and volume status. Examination of the heart, lungs, and neurologic status should be performed frequently during the first 12 hours of therapy. The serum sodium concentration should be measured at least every 2 to 4 hours, and the urine sodium, potassium, and osmolality should be measured every 4 to 6 hours during the first 24 to 48 hours of therapy to allow timely infusion rate adjustment to avoid too rapid correction.

NONEMERGENT HYPOVOLEMIC HYPOTONIC HYPONATREMIA

Most patients with hypovolemic hypotonic hyponatremia are either asymptomatic or have only mild-to-moderate symptoms and do not require rapid sodium correction. Many of these patients are at high risk of developing ODS if serum sodium correction occurs too rapidly because they have chronic hyponatremia and maximum compensation by the brain's osmotic adaptive mechanisms. Treatment should include correction of the underlying condition, if possible, and administration of 0.9% NaCl or other isotonic solution (eg, lactated Ringer's, Plasma-Lyte®, Normosol-R®) to correct the hypovolemia. These solutions will replace the existing sodium and water deficits while conveying a lower risk of too rapid sodium correction than 3% NaCl.

The ECF deficit can be estimated based on the patient's sex, age, and change in body weight. One method and an example of its use is shown in Table 68-6. If the patient's previous weight is unknown, the ECF deficit can be roughly estimated based on clinical signs and symptoms. The presence of hyponatremia suggests an ECF deficit of 5% or more, whereas the presence of orthostatic hypotension suggests an ECF deficit of at least 10% to 15%. Administration of an isotonic solution would be optimal to correct the patient's ECF volume deficit because essentially 100% of it will remain in the ECF space (see Table 68-1). The overriding initial treatment goal is to restore effective circulating volume; thus, it may be necessary to administer an IV bolus (500-1,000 mL in adults; 10-20 mL/kg in children) over a period of 1 hour or less or begin an IV infusion of the isotonic solution at 200 to 400 mL/hr (10-20 mL/kg/hr in children) until symptoms of hypovolemia improve. The infusion rate can then be decreased to 100 to 150 mL/hr (4-6 mL/kg/hr in children) so that the serum sodium concentration does not increase too rapidly. Fluids should be given rapidly enough and in sufficient quantity to restore and maintain adequate tissue perfusion without overloading the cardiovascular or pulmonary system.

TABLE 68-6

Assessment and Treatment of Hypotonic Hypovolemic Hyponatremia

Calculating ECF deficit

ECF deficit (mL) = $ECF_{normal} - ECF_{current}$

where ECF volume = 0.33 × TBW

Clinical example

A 75-year-old woman (height, 168 cm [5 ft 6 in]; usual weight, 50 kg [110 lb]) was started on hydrochlorothiazide 25 mg once daily 10 days ago for hypertension. She presents with complaints of mild nausea and dizziness when she stands up. Her current weight is 45 kg (99 lb). Upon physical examination she has dry mucous membranes and orthostatic hypotension. Her serum sodium concentration is 126 mEq/L (mmol/L).

Calculate the ECF deficit

ECF deficit = (50 kg × 0.4 L/kg × 0.33) – (45 kg × 0.4 L/kg × 0.33) = 660 mL

(Note: TBW = 0.4 L/kg used because she is a dehydrated older patient; see Table 68-5.)

Calculate the expected increase in the serum sodium after infusion of 1 L of 0.9% NaCl (see Table 68-1):

ΔNa_S with 1 L of infusate = [154 mEq/L – 126 mEq/L]/[(0.4 L/kg × 45 kg) + 1 L] = 1.47 mEq/L (mmol/L)

The patient's serum sodium concentration will be 127.5 mEq/L (mmol/L) following the infusion of 1 L 0.9% NaCl.

Treatment goals: Restore effective circulating volume and correct serum sodium concentration

Treatment plan:

1. Infuse 0.9% NaCl at 200-250 mL/hr until symptoms of hypovolemia improve; then decrease infusion to 150-200 mL/hr so that the serum sodium concentration increases by no more than 6-12 mEq/L (mmol/L) or 0.5-1 mEq/L/hr (mmol/L/hr) over the initial 24 hours. Rate depends on patient status.
2. Hold thiazide diuretic until volume status is restored.
3. Consider restarting diuretic at lower dose, for example, 12.5 mg once daily, if needed.

ECF, extracellular fluid; NaCl, sodium chloride; TBW, total body water.

It is important to recognize that once hypovolemia is corrected, the serum sodium will increase rapidly if the infusion rate is not adjusted appropriately. When the ECF volume is restored, AVP secretion stops, and a rapid water diuresis can ensue, potentially resulting in a rapid increase in serum sodium. Estimating the patient's ECF deficit at the start of therapy may be helpful. If the serum sodium concentration is increasing at a rate greater than 0.5 mEq/L/hr (mmol/L/hr), the infusate can be changed to 0.45% NaCl, and the infusion rate set to slow the rate of serum sodium increase. In general, 0.45% NaCl should not be infused alone as this hypoosmolar solution (154 mOsm/L) may result in red blood cell hemolysis. Most often, Dextrose 5%/0.45% NaCl is infused to provide a relatively isotonic solution (Dextrose 5% provides 250 mOsm/L to the solution). Potassium depletion or repletion can also affect hyponatremia and its correction. One mEq (mmol) of retained potassium equals 1 mEq (mmol) retained sodium; thus, if hypokalemia is corrected at the same time as hyponatremia, the serum sodium may increase more rapidly.

Evaluation of Therapeutic Outcomes

Patients presenting with hypovolemia should be reexamined frequently during the initial few hours of therapy. Of note, the urine output will often lag behind during fluid resuscitation, so careful monitoring for pulmonary congestion is critical, especially in patients with underlying heart, lung, or kidney dysfunction. The serum sodium concentration should be measured every 2 to 4 hours to allow timely adjustment of the rate and composition of IV fluids to avoid too rapidly increasing the serum sodium concentration. In patients with a history of HF or kidney insufficiency, 0.9% NaCl should be administered judiciously with frequent cardiopulmonary assessments so that the infusion rate can be adjusted at the earliest sign of pulmonary congestion.

NONEMERGENT EUVOLEMIC HYPOTONIC HYPONATREMIA

The fact that neurological performance is restored to normal with correction of even mild hyponatremia provides a rationale for maintaining the serum sodium concentration at 130 mEq/L (mmol/L) or higher, if possible. Long-term management will be required for patients in whom the

underlying cause is not readily correctable.

Treatment of SIADH always involves restricting water and correcting the underlying cause (see Table 68-3). Medications that could be contributing should be identified and discontinued, if possible. The primary treatment goal is to induce a negative water balance by initially restricting water intake to 1,000 to 1,200 mL/day so that insensible water loss (skin and lung, 900 mL/day) plus obligate urine (500 mL/day) and stool (200 mL/day) loss exceed water intake. Because approximately 850 mL of water per day is ingested in food, and an additional 350 mL are generated from oxidative processes, this degree of water restriction should result in a negative water balance of several hundred milliliters per day. Further water restriction may be needed but adherence is difficult. An additional goal is to maintain the serum sodium concentration close to 130 mEq/L (mmol/L) to reduce CNS symptoms and avoid iatrogenic hypovolemia.

Patients with chronic SIADH who are unable to restrict water intake sufficiently to maintain an acceptable serum sodium concentration can be treated by increasing solute intake with NaCl supplementation and/or loop diuretic administration. NaCl supplements increase the obligatory daily solute excretion, which augments the kidney's capacity for water excretion. The goal is to increase the daily solute intake and excretion to approximately 900 mOsm (mmol) per day. Because an average diet contains approximately 600 mOsm (mmol), 9 g of NaCl would be required to increase the osmolar excretion to 900 mOsm/day (mmol/day). Each 1 g NaCl tablet contains 17 mmol of sodium and 17 mmol of chloride. Because ECF volume expansion is an expected adverse effect, a loop diuretic should be administered concurrently to avoid volume overload and edema. Loop diuretics will also enhance water excretion by limiting the formation of the medullary concentration gradient.

Vasopressin Receptor Antagonists

VRAs are high-affinity non-peptide antagonists of arginine vasopressin V_2 and V_{1a} receptors, often referred to as *vaptans*.[39] VRAs have dramatic effects on water excretion and were the first significant breakthrough in hyponatremia treatment since loop diuretics. These agents are additional therapeutic options for both euvolemic and hypervolemic hypotonic hyponatremia but are contraindicated in hypovolemic hyponatremia.

Blockade of AVP binding can occur at any of its three distinct receptors: V_{1a}, predominantly in the liver, CNS, and cardiomyocytes; V_2, in the distal nephron; and V_{1b} (formerly V_3), in the anterior pituitary and pancreas.[39] Selective V_2 receptor antagonism prevents AQP2 water channel transport to the apical surface, thereby decreasing AVP-dependent water reabsorption in the collecting duct. AVP inhibition leads to excretion of large water volumes, decreased urine osmolality, and an increase in the serum sodium concentration. These outcomes are achieved without significantly increasing electrolyte excretion; thus, these agents have been called *aquaretics*.

Only two VRAs are currently marketed in the United States, conivaptan and tolvaptan. Conivaptan (Vaprisol®, Astellas Pharma US, Inc., Northbrook, IL), a mixed vasopressin V_1- and V_2-receptor antagonist, is FDA-labeled for use in the treatment of acute euvolemic and hypervolemic hyponatremia in hospitalized patients. Its utility in chronic hyponatremia is limited because it is only available as an IV formulation, FDA-labeled for up to 4 days of use, a moderate CYP3A4 inhibitor, and not FDA-labeled for use in patients with HF.

Tolvaptan (Samsca®, Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan) is an oral selective VRA with a greater affinity for the V_2 receptor than endogenous AVP. It is FDA-labeled for the treatment of clinically significant (serum sodium concentration less than 125 mEq/L [mmol/L]) euvolemic or hypervolemic hyponatremia or less marked symptomatic hyponatremia that is unresponsive to other therapeutic interventions in patients with HF, cirrhosis, and SIADH. When given alone, tolvaptan promotes aquaresis and modestly raises serum sodium concentrations by 3.6 mEq/L (mmol/L) at 4 days and 4.4 mEq/L (mmol/L) at 30 days, respectively (SALT-1 and SALT-2 studies).[40,41] However, the effect of tolvaptan on serum sodium concentrations may have been limited by the high average fluid intake (~2 L/day) in these studies. In fact, mean increases in serum sodium may be double those found in the SALT studies.[42-44] In SALT-1 and SALT-2, the percentage of patients with a normal serum sodium concentration (greater than 135 mEq/L [mmol/L]) after one month of tolvaptan use was 53% and 58%, respectively, versus 25% (both studies) with placebo.[40,41] When used as monotherapy, tolvaptan is superior to either furosemide or water restriction, and when given in combination with furosemide, there are synergistic effects.[45]

The usual starting tolvaptan dosage is 15 mg given orally once daily based on the SALT studies. A greater risk of overcorrection of serum sodium exists in patients with euvolemic compared to hypervolemic hypotonic hyponatremia.[43,46,47] Thus, a lower starting dosage of 7.5 mg once daily may be considered in patients with euvolemic hypotonic hyponatremia due to its equivalent efficacy and lower risk of overcorrection of serum sodium.[48] This

lower dosage should also be used for patients older than 90 years of age.[49]

In critically ill neurological patients, who often require more aggressive care to prevent long-term morbidity, a single tolvaptan dose (7.5 or 15 mg) can effectively increase serum sodium concentration by 5 to 7.8 mEq/L (mmol/L) with the effect sustained for up to 96 hours. Multiple doses may be required. Overcorrection (increasing serum sodium concentration by more than 6 to 12 mEq/L [mmol/L] in 24 hours) may occur, particularly when a 15-mg dose is given, thus careful monitoring in these high-risk patients is warranted.[50,51] Reducing the starting dosage to less than 15 mg/day may not eliminate the risk of too rapid sodium correction.[52]

The oral bioavailability of tolvaptan is about 56%, and its activity peaks at 2 to 4 hours after a dose. For patients who cannot swallow tablets, the tablets can be crushed, suspended in water, and the slurry administered orally or via a nasogastric tube, but a 25% average decrease in the tolvaptan area under the concentration-time curve may be seen with this administration method.[53] Fluid restriction should be avoided within the first 24 to 48 hours of starting VRA therapy when active sodium correction is occurring.[20] After 24 hours, if a greater increase in serum sodium concentration is needed, the dosage may be increased to 30 mg once daily, and after another 24 hours, to a maximum of 60 mg once daily.

Approximately 10% to 50% of patients do not significantly respond to VRA therapy.[54,55] Therapeutic resistance or failure to respond to VRA therapy could be due to high circulating AVP concentrations, AVP-independent impaired urinary dilution, excessive water intake, or an activating V_2-receptor mutation causing nephrogenic SIADH.[39] There is currently no pharmacogenomic information available for the G protein-coupled receptor family of AVP receptors or the VRAs that can be used to individualize therapy.[56]

Tolvaptan is primarily metabolized to inactive metabolites by CYP3A4 and less than 1% is eliminated unchanged in the urine; thus, its use should be avoided in patient receiving potent CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, itraconazole, ritonavir). Concomitant therapy with P-glycoprotein inhibitors and grapefruit juice results in increased serum tolvaptan concentrations. Tolvaptan inhibits P-glycoprotein and coadministration with P-glycoprotein substrates should be avoided, if possible.[57] Conversely, optimal tolvaptan benefits may not be achieved on usual dosages in patients who are receiving potent CYP3A4 inducers (eg, phenytoin, phenobarbital, St. John's Wort).

Tolvaptan therapy is contraindicated in patients needing rapid serum sodium correction (due to the 2- to 4-hour delayed onset), those unable to sense or respond appropriately to thirst, patients with hypovolemic hyponatremia, patients taking strong CYP3A4 inhibitors, and patients who are anuric. Tolvaptan has not been studied in patients with severe hyponatremia (severe symptoms or serum sodium less than 120 mEq/L [mmol/L]). Patients with more profound hyponatremia are more likely to experience larger increases in serum sodium concentrations. Tolvaptan should be used cautiously in these patients with serum sodium concentration monitoring every 2 to 4 hours. Tolvaptan effectively produces aquaresis and increases serum sodium concentrations in patients with chronic kidney disease (CKD stages 3, 4, 5) who are not receiving renal replacement therapy.[58,59]

VRA use should be avoided with hypertonic saline (eg, 3% NaCl) due to the risk of too rapid and/or overcorrection of the serum sodium concentration. Thirst, dry mouth, weakness, constipation, hyperglycemia, and urinary frequency are the most common adverse medication reactions, and they rarely necessitate therapy discontinuation.[40,41]

Reversible increases in hepatic transaminases have been reported with tolvaptan use; however, concerns for irreversible liver damage arose in the TEMPO 3:4 trial which evaluated tolvaptan in patients with autosomal dominant polycystic kidney disease. Tolvaptan dosages (45-120 mg/day) were much higher than those typically used for hyponatremia, and the duration of therapy was longer than 30 days (up to 3 years in some patients). Increases in hepatic transaminases did not meet Hi's criteria for medication-induced liver injury because the total bilirubin was not elevated to more than twice the upper limit of normal.[60] The FDA issued a warning to avoid tolvaptan use for more than 30 days in anyone with chronic liver disease. Additionally, tolvaptan should be discontinued if any sign of liver injury occurs during therapy. To reduce the ODS risk, tolvaptan therapy should begin or resume only in a hospital where the serum sodium concentration can be closely monitored (boxed warning).

VRAs are more expensive than other treatment options. Multiple economic analyses have determined tolvaptan therapy to be cost-effective for SIADH and HF when compared to fluid restriction or no additional therapy as evidenced by reduced hospital stay, avoidance of ICU admission, and avoidance of hospital readmission.[61-63] However, the cost-effectiveness of VRAs in the management of patients with SIADH is still unclear when considering all therapeutic modalities. Therapy continuation after acute treatment depends on the etiology of SIADH. While many cases are transient, other etiologies require indefinite treatment. The inability to discontinue the offending agent in medication-induced SIADH may also necessitate long-term treatment.

When considering long-term VRA treatment, cost and potential liver toxicity must be weighed against potential benefits.

It is unclear whether normalizing the serum sodium concentration improves the morbidity and/or mortality associated with hyponatremia. Additional research is needed to compare VRA use with traditional therapies after fluid restriction in the acute phase of nonemergent euvolemic hyponatremia. Further investigation is also warranted for long-term VRA use in asymptomatic or minimally symptomatic hyponatremia, particularly in older adults, to reduce morbidity (eg, cognitive deficits, gait disturbance, falls, bone fractures).

Sodium-Glucose Co-Transporter-2 Inhibitors

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are oral hypoglycemic medications with cardiovascular and kidney benefits. Through blockade of SGLT2, a glucose transporter in the proximal renal tubule responsible for 90% of glucose reabsorption, SGLT2 inhibitors lead to excretion of 50% to 60% of filtered glucose, approximately 60 to 100 g/day. The resulting glucosuric effect causes an osmotic diuresis and increases free water excretion.[64] The use of SGLT2 inhibitors in addition to standard fluid restriction of less than 1,000 mL/day in patients with euvolemic hypotonic hyponatremia results in an increased median plasma sodium concentration compared to placebo (10 vs 7 mEq/L [mmol/L]), but this difference may not be clinically significant.[65] Further studies are needed before SGLT2 inhibitors can be routinely recommended for treatment of euvolemic hypotonic hyponatremia.

Demeclocycline

Demeclocycline, a semisynthetic tetracycline antibiotic, is a treatment option for some patients with SIADH whose serum sodium concentration is not adequately controlled by water restriction alone. Demeclocycline use in SIADH is largely based on clinical experience rather than data from clinical trials and it is ineffective in a significant proportion of patients.[4,66] Demeclocycline essentially causes nephrogenic diabetes insipidus (DI) by unpredictably inhibiting tubular AVP activity, which increases free water excretion. Some patients may even develop polyuria and hypernatremia due to this mechanism. The demeclocycline dosage is 300 mg given orally two to four times daily. Because of the delayed onset of action (2-6 days), this agent has no role in the acute management of severe hyponatremia, and dosage adjustments should be made no more frequently than every 3 to 4 days. Demeclocycline should not be used in patients with cirrhosis or compromised fluid intake, who are at high risk for demeclocycline-induced renal tubular toxicity and acute kidney failure,[4] who are pregnant, or who are younger than 8 years unless no other options are available because long-term use may interfere with tooth and bone development. Photosensitivity with skin rash may occur; thus, patients receiving demeclocycline should be counselled to use appropriate UV protection during sun exposure.

Urea

Urea is an osmotic agent that increases urinary-free water excretion and decreases urinary sodium excretion. Urea has been used as an alternative oral treatment for SIADH and other hyponatremic disorders. The administration of urea at a dose ranging from 7.5 to 90 g/day for a median of 4.5 days in the inpatient setting[67] and 15 to 30 g/day for up to 1 year in the outpatient setting[68] is safe and effective for treatment of hyponatremia. Adherence to therapy is a concern due to the bitter taste of urea. The FDA considers urea to be a medical food, thus a prescription is not required. An over-the-counter product, ure-Na™ (Nephcentric LLC, Phoenix, AZ) is available in a pouch that provides 15 g powder that can be dissolved in water or juice (juice usually preferred due to taste). While there is little quality evidence for the efficacy of urea in the treatment of SIADH or other hyponatremic disorders, it is recommended as a second-line agent in the European guidelines.[6]

Evaluation of Therapeutic Outcomes

The serum sodium concentration should be monitored at least every 4 to 6 hours during the active sodium correction phase with treatment other than fluid restriction until reaching a stable value greater than 125 mEq/L (mmol/L). The serum sodium concentration should be measured every 24 to 48 hours when water restriction is initiated until it stabilizes at a concentration at or above 125 mEq/L (mmol/L).[20] Continued decline in the serum sodium concentration would indicate either nonadherence to the prescribed water restriction or the need for more aggressive restriction. If tolvaptan is initiated, the serum sodium concentration should be monitored every 4 to 8 hours for the first 24 to 48 hours.[20]

When the serum sodium has increased by 6 to 8 mEq/L (mmol/L), oral water or IV Dextrose 5% in water (D_5W) should be given to replace urine output to minimize the risk of overcorrecting the serum sodium concentration and ODS. Variable reported rates of sodium overcorrection may be due to differences in baseline serum sodium and definitions of excessive correction. In the SALT trials, only 1.8% of patients exceeded the daily limit for

changes in serum sodium; however, most had serum sodium concentrations greater than 130 mEq/L (mmol/L) at the start of treatment and were protected from overcorrection by thirst, so the risk of sodium overcorrection in clinical practice may be greater.[40,41] In a Cochrane review, VRA therapy increased the risk of a rapid increase in serum sodium (greater than 8 mEq/L [mmol/L] in 24 hours) by 67%, with an additional three patients per 100 treated with a VRA experiencing a rapid sodium increase versus placebo.[69] Other studies have shown a ~25% incidence among patients with euvolemic hypotonic hyponatremia. In these studies, patients with profound hyponatremia (baseline serum sodium 121 mEq/L [mmol/L] or less) experienced significantly greater rates of increase; although none developed neurological symptoms or ODS.[42,47] Since 2010, 38 cases of ODS including five deaths have been reported through the FDA Adverse Events Reporting System (FAERS; fis.fda.gov). Once the serum sodium concentration is stable at 125 mEq/L (mmol/L) or higher, the patient should be evaluated every 2 to 4 weeks to assess neurologic status and to obtain serum and urine sodium, potassium, and osmolality values. Volume status (eg, BP, mucous membranes, skin turgor, heart, and lung examination) should also be assessed, particularly in patients who are being treated with NaCl supplements and/or loop diuretics.

NONEMERGENT HYPERVOLEMIC HYPOTONIC HYPONATREMIA

The initial treatment goals for patients with asymptomatic or minimally symptomatic hypervolemic (expanded ECF volume) hypotonic hyponatremia include achieving a negative water balance and minimizing rapid changes in brain cell volume until the serum sodium concentration is 125 mEq/L (mmol/L) or higher. Management involves correction of the underlying cause, when possible, as well as water restriction of 1,000 to 1,500 mL/day.[35] To be effective, the combined daily losses (insensible water, urine, and stool) must exceed fluid intake. Additionally, dietary sodium intake should be restricted to 1,000 to 2,000 mg/day, depending on the degree of ECF volume expansion. On average, only modest changes in serum sodium concentration are seen over the first 5 days of treatment with fluid restriction (2 mEq/L [mmol/L; IQR 0-4] at 24 hours[70,71]; 0.7 ± 2.1 mEq/L [mmol/L] on day 5.[72] This small change may be due to poor adherence to fluid restriction and the frequent patient practice of sucking on ice chips to quench thirst. In moderately severe cases, other options should be considered if serum sodium does not improve in the first 24 to 48 hours.

In patients with HF, the severity of hypervolemic hypotonic hyponatremia is directly related to HF severity and is associated with a poorer short- and long-term prognosis once the serum sodium concentration falls below 137 mEq/L (mmol/L).[73,74] Patients with hypervolemic hypotonic hyponatremia caused by HF should be treated with measures that can potentially improve cardiac contractility and effective circulating volume, thereby limiting non-osmotic AVP release. Therapeutic options include digitalis or afterload reduction with angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI) SGLT2 inhibitors, or other vasodilators. Of these, only ACEI have proven benefit in partially correcting hyponatremia in patients with HF[75]; however, sodium correction with ACEI does not improve outcomes.[76] No specific ACEI offers any particular advantage for this indication, and the dosage should be titrated in accordance with HF guidelines. Dose-limiting adverse medication reactions of ACEI include hyperkalemia (serum potassium concentration greater than 5.5 mEq/L [mmol/L]) and impaired kidney function. The benefits and risks of continuing ACEI use must be weighed carefully in each case, but a decrease in glomerular filtration rate (GFR) of less than 30% that stabilizes within 2 months of beginning ACEI therapy generally does not require dosage reduction or discontinuation.[73]

Other potentially treatable causes of asymptomatic hypervolemic hyponatremia include nephrotic syndrome and cirrhosis. An ACEI can be used to decrease proteinuria in patients with nephrotic syndrome, leading to partial correction of hypoalbuminemia and to a decrease in non-osmotic AVP release. Management of asymptomatic cases of hyponatremia in patients with cirrhosis includes temporary discontinuation of diuretics and cautious correction of hypokalemia in addition to fluid restriction.[35] Exogenously administered potassium will enter the cells as intracellular sodium is exchanged in the opposite direction. This increase in extracellular sodium must be accounted for to avoid rapid overcorrection of hyponatremia. If hyponatremia persists in patients with cirrhosis, short-term hyper-oncotic albumin solutions (20%-25%) may be administered at dosages of at least 40 g/day.[77,78] Efficacy is likely due to increased urinary-free water clearance following intravascular volume expansion.[35]

VRAs have also been used for the treatment of hypervolemic hypotonic hyponatremia in patients with HF or cirrhosis.[79-84] Conivaptan is not an ideal choice for patients with cirrhosis due to its mixed antagonism of the V_1 and V_2 receptors. V_1 receptor blockade in these patients may worsen hypotension, increase bleeding risk, and compromise kidney function.[80] As previously mentioned, the FDA issued a warning regarding tolvaptan use in patients with impaired liver function due to the potential for further liver injury. However, 25% and 31% of patients in the tolvaptan groups of the SALT-1 and SALT-2 trials, respectively, had underlying liver cirrhosis, and there were no cases of further liver injury.[40,41] Subsequent studies have supported these findings.[81,82] The optimal tolvaptan starting dosage in patients with cirrhosis is unknown. Given the concern for hepatotoxicity, a dose of 3.75 or

7.5 mg may be appropriate; however, usual starting dosages may be recommended based on the SALTWATER study.[35,83,85]

Patients with cirrhosis who receive tolvaptan generally have a more modest increase in serum sodium concentrations compared to patients with euvolemic hyponatremia, and the increase may be more dependent on baseline GFR.[82-85] Patients with advanced cirrhosis may benefit from placement of a transjugular intrahepatic portosystemic shunt, which can increase the effective circulating volume and thus reduce non-osmotic AVP release.[86] This procedure can potentially exacerbate or precipitate hepatic encephalopathy and is not recommended in patients with a history of encephalopathy. Additionally, tolvaptan may be considered in patients with end-stage liver disease awaiting liver transplantation to normalize serum sodium concentrations.[35,87] The benefit of avoiding the need for rapid perioperative sodium correction outweighs the likely negligible effect of tolvaptan-related liver damage in these patients. It is also reasonable to continue treatment until liver transplantation even if the duration is longer than 30 days.

In general, VRA treatment in hyponatremic patients with HF is reserved for refractory patients whose hyponatremia does not adequately respond to other medical management strategies. Tolvaptan dosing for HF-associated hypervolemic hyponatremia is the same as for euvolemic hypotonic hyponatremia. In the short-term management of patients with HF with hypervolemic hyponatremia, tolvaptan use decreases body weight, increases urine output, decreases left ventricular filling pressures, and decreases urine osmolality; however, evidence for clinical benefits such as improved dyspnea is lacking.[88-94] Long-term beneficial effects, reduction in hospitalization or death, or slowed HF progression have not been observed in several pivotal trials. A post-hoc analysis of the EVEREST trial, however, showed patients with severe hyponatremia (less than 130 mEq/L [mmol/L]), who presumably had greater activation of the arginine-vasopressin axis, had reduced cardiovascular morbidity and mortality after discharge.[94] Prolonged tolvaptan use leads to an increased endogenous AVP concentration, and this overstimulation of V_{1a} receptors can lead to increased afterload and HF progression.[95] However, no worsening of left ventricular dilatation was observed after 52 weeks of tolvaptan therapy (30 mg/day).[96] In contrast to European guidelines, an American expert panel on hyponatremia recommended a VRA in non-severe hyponatremia when fluid restriction is unsuccessful.[20] The 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommend short-term use of a VRA in hospitalized patients who have volume overload and persistent severe hyponatremia and who are at risk for or having cognitive symptoms despite fluid restriction and optimization of guideline-directed medical therapy.[97] It is still unknown whether VRAs decrease length of hospitalization, rehospitalization rates, or morbidity or increase quality of life when compared to other treatments.

Various biological markers, such as copeptin, the c-terminal segment of the precursor of provasopressin; apelin; and midregional proatrial natriuretic peptide (MR-proANP), may have diagnostic utility for hyponatremia in HF and improve the overall management.[98] The association between copeptin concentrations and tolvaptan response was investigated in patients with HF and may help determine the most appropriate patients for VRA use.[99] Given the potential vascular and cardiac effects of V_{1a} receptor stimulation and V_{1a} receptor dose-dependent activity (as opposed to maximal V_2 signaling at low AVP activity levels), an oral V_{1a} or nonselective VRA likely would provide greater benefits in patients with HF.[100]

Evaluation of Therapeutic Outcomes

Patients being treated for hypervolemic hyponatremia should initially be evaluated on a daily basis for lung congestion, ascites, peripheral edema, and signs or symptoms of hyponatremia. If water restriction is started, the serum sodium concentration should be measured daily until it stabilizes at 125 mEq/L (mmol/L) or higher. If VRA therapy is initiated, serum sodium concentrations should be monitored every 4 hours to minimize the risk of overcorrection and ODS. Patients should be assessed 1 week following discharge, and then every 2 to 4 weeks to assess adherence to water restriction and other therapies, volume status, and symptoms.

HYPERNATREMIA

Epidemiology and Etiology

10 Hypernatremia, defined as a serum sodium concentration greater than 145 mEq/L (mmol/L), is always associated with hypertonicity and intracellular dehydration, resulting from a water deficit relative to ECF sodium content. This hypertonic state is a potent stimulus for AVP secretion and thirst. Therefore, hypernatremia is most commonly observed in patients with an impaired thirst response or in those who cannot access water. Young infants and children, mechanically ventilated or comatose patients, older adults, and patients with an impaired sensorium or functional status are at

highest risk for this disorder.[101] Hypernatremia generally occurs in sicker patients and has a higher mortality.[102] The incidence of hypernatremia in general medical–surgical hospitalized patients and patients in ICUs has been estimated to be at least 1% and as high as 26% to 59%, respectively.[103-107] A marked increase in the incidence of hypernatremia compared to hyponatremia has occurred in ICUs in the past two decades. In critically ill patients, the majority of cases of hypernatremia are iatrogenic, the result of too little free water and too much hypertonic solution along with increased renal water loss.[108] Focusing only on overall fluid balance and not considering the sodium intake from all sources, including excessive isotonic fluids, and evaluating urine sodium excretion leads to hypernatremia, and more free water is needed in most cases.[106,109]

Clinical outcomes in patients with hypernatremia, as in hyponatremia, depend on the severity of the increase and the rapidity with which it develops. In children, mortality from acute hypernatremia developing in less than 72 hours ranges from 10% to 70%; while chronic hypernatremia which develops over 3 or more days has a mortality rate of only 10%.[110] In adults, an acute increase in serum sodium concentration to greater than 160 mEq/L (mmol/L) is associated with a 75% mortality rate, and hypernatremia that develops at a slower rate also has a high mortality rate of approximately 60%.[111] Hypernatremia is often associated with a serious underlying illness, which likely contributes to the higher mortality rate.

Pathophysiology

Hypernatremia most often results from water loss by either renal or extrarenal mechanisms. Hypernatremia also results from hypertonic or isotonic fluid administration or excess sodium ingestion. Patients can develop hypovolemic, hypervolemic, or euvolemic (isovolemic) hypernatremia depending on the relative magnitude of sodium and water loss or gain caused by the underlying condition (Table 68-7).

TABLE 68-7

Characteristics of Hypernatremic States

Characteristics	Hypovolemic Hypernatremia	Euvolemic (Isovolemic) Hypernatremia	Hypervolemic Hypernatremia
Water and sodium	Water loss >> sodium loss	Water loss only	Sodium gain > water gain
Causes	Renal: osmotic diuresis, diuretic use, postoperative diuresis, high-output acute tubular necrosis	Congenital or acquired DI Nephrogenic DI Primary polydipsia	Sodium overload (eg, 3% NaCl, sodium bicarbonate, NaCl tablets, concentrated tube feedings, hypertonic dialysate, sodium-containing medications)
Effect on TBW	↓↓	↓	↑
Effect on TBNa	↓	↔	↑↑
Additional laboratory findings	Renal: UOsm high, UNa high Non-renal: UOsm high, UNa low	Renal: UOsm low, UNa variable Non-renal: UOsm high, UNa variable	UOsm high, UNa high
Clinical presentation	Orthostasis, hypotension, tachycardia, dry mucous membranes	Depends on severity of hypernatremia; seizures, lethargy	Peripheral and pulmonary edema, variable BP
Treatment	0.9% NaCl until vital signs stable, then free water replacement	Free water replacement, AVP, or AVP analogue	Free water replacement with loop diuretic, may require hemodialysis to remove volume

AVP, arginine vasopressin; DI, diabetes insipidus; NaCl, sodium chloride; TBNa, total body sodium; TBW, total body weight; UNa, urine sodium concentration; UOsm, urine osmolality.

Water loss commonly occurs as a result of insensible losses (evaporative water loss through the skin and lungs) in patients deprived of water. Hospitalized patients who are febrile or being mechanically ventilated are often treated with isotonic IV fluids which contain insufficient free water to replace insensible losses. Hypernatremia can develop in patients with hypotonic GI losses (eg, diarrhea, vomiting, gastric suctioning) or in patients who have been exposed to high temperatures who suffer large water losses from both sweat and insensible losses.

A water diuresis can be caused by DI, which can be classified as either central DI (decreased AVP secretion) or nephrogenic DI (decreased kidney response to AVP). Patients with untreated DI excrete large volumes (3-20 L/day) of dilute urine, resulting in hypernatremia. Various causes of DI are listed in Table 68-8. Lithium, which impairs AVP-mediated water transport, is the most common cause of acquired nephrogenic DI.[112]

TABLE 68-8

Causes of DI

Central	Nephrogenic	Other
Familial[a]	Familial	Gestational
Unreplaced insensible losses	Inherited aquaporin-2 defect	Primary polydipsia (dipsogenic DI)
Skin	Inherited vasopressin V2 receptor defect	
Lung	Hypercalcemia (chronic)	
Hypodipsia	Hypokalemia	
Neurogenic	Kidney disease	
Neurosurgery	Medication-induced	
Tuberculosis	**Most common**	
Head trauma	Lithium—most common	
CNS malignancy/cyst	Foscarnet	
Ethanol ingestion (transient)	Clozapine	
Hypoxic encephalopathy	**Less common**	
Lung tumor	Amphotericin B	
Sarcoidosis	Cidofovir	
Sheehan syndrome[b]	Didanosine	
	Ifosfamide	
	Orlistat	
	Vasopressin receptor antagonists	

AVP, arginine vasopressin; CNS, central nervous system; DI, diabetes insipidus.

[a]At least 60 mutations in the AVP gene cause neurohypophyseal DI.

[b]Postpartum hypopituitarism caused by severe bleeding during childbirth.

Hypertonic NaCl administration can result in hypervolemic (expanded ECF volume) hypernatremia. This type of hypernatremia is typically iatrogenic following excess sodium bicarbonate administration, hypertonic NaCl enemas, or intrauterine injection of hypertonic NaCl. Excessive isotonic infusions (0.9% NaCl, lactated Ringers; see Table 68-1) may lead to sodium accumulation, particularly when dilute urine is excreted. A common cause of hypernatremia in the ICU is sodium intake from IV and enteral fluids and medications.[102,105-113] Sodium balance should be monitored carefully in critically ill patients to avoid iatrogenic hypernatremia. Patients with hyperaldosteronism also may present with an expanded ECF and mild hypernatremia.

Clinical Presentation

Hypernatremia results in water movement from the ICF to the ECF. Patients with central DI often present with sudden onset of polyuria, whereas patients with nephrogenic DI develop polyuria more gradually. Symptoms are like those seen with hyponatremia and are primarily neurological due to decreased brain cell volume. Symptoms of mild-to-moderate hypernatremia (hypertonicity) include weakness, lethargy, restlessness, irritability, twitching, and confusion. More severe or rapidly developing hypernatremia can lead to seizures, coma, and death. As discussed in the hyponatremia section, brain cells adapt to ECF tonicity changes by decreasing or increasing the concentration of inorganic (K^+, Cl^-) and organic (glutamate, taurine, and myoinositol) osmolytes.[2,34] ECF hypertonicity results in intracellular organic osmolyte generation within 24 hours of onset leading to an increase in ICF tonicity that then draws water into brain cells, limiting the decrease in cell volume. Thus, patients with chronic hypernatremia are less likely to be symptomatic than patients with acute hypernatremia.

CLINICAL PRESENTATION: Hypernatremia

General

- Increased serum sodium concentration and osmolality causes acute water movement from the ICF to the ECF.
- Decreased brain cell volume can cause cerebral vein rupture, leading to focal intracerebral and subarachnoid hemorrhages and irreversible CNS damage.

Symptoms

- Mild: lethargy, weakness, confusion, restlessness, irritability
- Moderate: twitching
- Severe: seizures, coma, death; usually requires acute increase in serum sodium to ≥160 mEq/L (mmol/L)
- Serum sodium ≥180 mEq/L (mmol/L) is associated with high mortality
- Other symptoms (depend on etiology of hypernatremia): postural hypotension, tachycardia, dry mucous membranes, diminished skin turgor, reduced or increased urine output
- Signs and symptoms are difficult to detect in patients with underlying neurologic dysfunction.

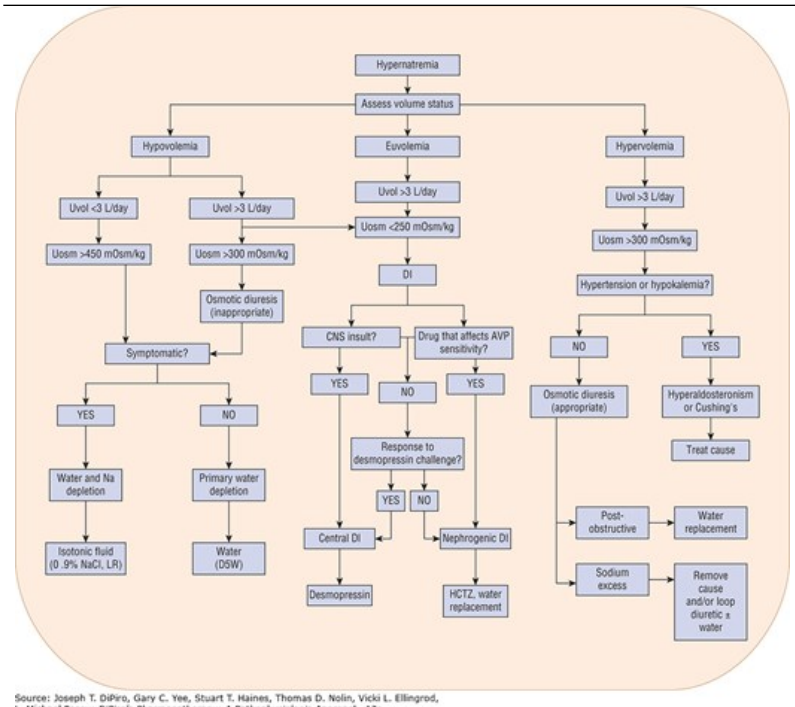
Laboratory tests

- Serum sodium concentration greater than 145 mEq/L (mmol/L)
- Serum osmolality is always high.
- Urine osmolality may be helpful in diagnosing the cause.

Hypernatremia is often associated with serious underlying illness, and signs and symptoms related to the illness are often present. Patients with a history of severe diarrhea or vomiting can present with ECF volume depletion. Older patients deprived of water after sustaining a stroke or hip fracture often present with mental status changes and other signs of ECF volume depletion. Clinically detectable ECF volume depletion, however, may not be evident until the serum sodium concentration exceeds 160 mEq/L (mmol/L) because these patients primarily have water loss, two-thirds of which is derived from the ICF. The urine will be concentrated, often exceeding 450 mOsm/kg (mmol/kg), because of osmotic and non-osmotic AVP release. The first step in the evaluation and treatment of hypernatremia is assessment of the ECF and urine volume and the serum and urine osmolality (Fig. 68-3).

FIGURE 68-3

Algorithm for the assessment and treatment of hypernatremia. (AVP, arginine vasopressin; CNS, central nervous system; D_5W, Dextrose 5% in water; DI, diabetes insipidus; ECF, extracellular fluid; HCTZ, hydrochlorothiazide; LR, lactated Ringers; Na, sodium; NaCl, sodium chloride; Uosm, urine osmolality [values in mOsm/kg are numerically equivalent to mmol/kg]; Uvol, daily urine volume.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Patients with a contracted ECF volume and low urine output include those who have sustained insensible water losses that exceed intake, as well as those with extrarenal losses of hypotonic fluids. On physical examination, the patient will have postural hypotension, diminished skin turgor, and delayed capillary refill. Lactic acidosis and low mixed venous oxygen saturation, indicating decreased tissue perfusion, may be present. The daily urine output is typically less than 1 L.

In older adults, hypotension, tachycardia, dry oral mucosa, decreased skin turgor, and recent changes in consciousness are all more common in patients with hypernatremia. The presence of signs of dehydration are variable, with orthostatic hypotension and decreased subclavicular and forearm skin turgor present in at least 60% of patients.[114]

Osmotic Diuresis

In the presence of an ongoing osmotic diuresis, patients will have a urine volume greater than 3 L/day. Excessive urinary excretion of glucose, sodium, urea, or an exogenously administered solute (eg, mannitol) can be identified either by history or by direct measurement of serum and urinary concentrations of the suspected solute, if possible. Patients with post-obstructive diuresis, such as those with bladder outlet obstruction caused by prostatic hypertrophy, are usually ECF volume expanded because of retained solute because of a reduction in GFR. The osmotic diuresis that follows resolution of the obstruction is appropriate in that it promotes excretion of the excess solute.

Patients with severe hyperglycemia may have a low measured serum sodium concentration (hyponatremia) but a high *corrected* sodium concentration (hypernatremia). Patients with severe hyperglycemia present with signs of hypovolemia, and the diuresis is inappropriate as it further exacerbates the ECF volume contraction associated with hyperglycemia. As previously discussed, the estimated (or corrected) serum sodium concentration can be calculated by adding 1.6 mEq/L (mmol/L) for every 100 mg/dL (5.6 mmol/L) increase in the serum glucose concentration before estimating the water deficit.[5,28]

Diabetes Insipidus

Patients with DI tend to maintain a normal ECF volume if they are conscious, can drink, and have access to water. While hypernatremia can occur with DI, patients typically have serum sodium concentrations of 141-145 mEq/L [mmol/L]) and daily urine volumes greater than 3 L.

A water deprivation test has been recommended to aid in the differential diagnosis. This diagnostic test consists of depriving a patient with marked polyuria of water for 8 to 12 hours in a supervised setting to avoid severe hypernatremia and volume depletion. Body weight and urine osmolality and

volume are measured before and after administration of desmopressin acetate (4 mcg subcutaneously or intravenously or 10 mcg intranasally). After desmopressin administration, patients with central DI will have a prompt increase in urine osmolality to approximately 600 mOsm/kg (mmol/kg) and decreased urine volume. In patients with nephrogenic DI, the urine osmolality will not increase above 300 mOsm/kg (mmol/kg).[115]

The value of a water deprivation test in patients with polyuria and hypernatremia has been questioned. Because hypernatremia provides a maximal stimulus for AVP secretion, discriminating between nephrogenic and central DI can be based on the serum AVP concentration and urinary response to desmopressin without the need for a water deprivation test. The water deprivation test is likely to be of diagnostic value only in patients with polyuria and a normal serum sodium concentration.[116]

Sodium Overload

Patients who have ingested a large amount of sodium (more than four tablespoons table salt [1,400 mEq or mmol sodium]) or who have received more than 5 L of hypertonic fluids are volume expanded; although, this volume may not always be clinically evident as edema. Volume expansion results in an osmotic diuresis, polyuria, and a urine osmolality greater than 300 mOsm/kg (mmol/kg). In patients with normal perfusion and kidney function, the excess sodium will be excreted in the urine; with organ dysfunction, sodium excretion is compromised, and volume expansion occurs.

Treatment

Desired Outcomes

Treatment goals for patients with hypernatremia include correcting the serum sodium concentration to between 145 and 150 mEq/L (mmol/L) at a rate that restores and maintains brain cell volume as close to normal as possible while normalizing ECF volume, if indicated. Hypernatremia is often undertreated; adequate treatment should result in symptom resolution. Although inadvertent overcorrection is more common with hyponatremia, careful titration of fluids and medications should minimize the adverse effects associated with too rapid correction of hypernatremia, including cerebral edema, seizures, neurologic damage, and death. These complications occur almost exclusively in young children with chronic hypernatremia (at least 48 hours duration) and serum sodium concentrations greater than 150 mEq/L (mmol/L).[2] Water replacement and dietary sodium restriction can be necessary to prevent recurrence of hypernatremia.

Physical examination with attention to volume status and laboratory measurement of serum and urine sodium and osmolality should be completed every 2 to 3 months during chronic therapy. A 24-hour urine collection to measure urine volume and sodium excretion may help guide diuretic therapy and determine adherence to sodium restriction.

Hypovolemic Hypernatremia

Patients with symptomatic hypovolemic hypernatremia should be treated similarly to those with hypovolemic hyponatremia with 0.9% NaCl or another isotonic fluid until hemodynamic stability is restored (Fig. 68-3). An initial infusion rate of 200 to 300 mL/hr or higher will likely be appropriate for most adults; children generally receive 10 to 20 mL/kg/hr. Once intravascular volume is restored, 0.45% NaCl, D_5W, or another hypotonic fluid, may be infused to correct the water deficit. In patients with hypernatremia from water loss, the ECF volume deficit can be estimated as follows:

$$\text{ECF(water)deficit} = \text{TBW}_{\text{current}} \times [\,1 - (140/\text{Na}_s)]$$ ECF(water)deficit=TBWcurrent×[1- (140/Nas)]

where Na_S is the initial serum sodium concentration (in mEq/L [mmol/L]), and 140 is the normal or goal serum sodium concentration in mEq/L (mmol/L). Although this formula provides an estimate of the water deficit caused by pure free water loss, it underestimates the deficit in patients with hypotonic fluid loss.[2]

The appropriate rate for correcting the water deficit depends on the rapidity with which the hypernatremia developed. Hypernatremia developing in less than 48 hours can be initially corrected at a rate of approximately 1 mEq/L (mmol/L) per hour, whereas a rate of 0.5 mEq/L (mmol/L) per hour or less should be used when hypernatremia has developed more slowly.[2,112] The sodium should be lowered no more than 10 to 12 mEq/L (mmol/L) per day.[2] Renal replacement therapy may be needed for patients with kidney failure; NaCl will be added to the replacement fluid/dialysate to achieve the same sodium content as the goal serum sodium concentration to avoid too rapid overcorrection and cerebral edema.[102]

The serum sodium concentration and volume status should be monitored every 2 to 3 hours during the first 24 hours of treatment in patients with

symptomatic hypernatremia to permit appropriate adjustment of the rate of the hypotonic fluid administration. Once symptoms resolve and the serum sodium concentration is less than 148 mEq/L (mmol/L), measuring serum sodium concentrations every 6 to 12 hours and assessing fluid status every 8 to 24 hours is generally adequate.

Recurrent iatrogenic hypernatremia can be prevented by avoiding infusing excessive hypertonic solution, providing adequate *maintenance* fluids, and replacing ongoing abnormal losses. Traditional maintenance fluid for adults and children weighing 40 kg or more is Dextrose 5%/0.45% NaCl with 20 mEq (mmol) KCl/L. Children weighing less than 40 kg typically receive Dextrose 5%/0.2% NaCl with 20 mEq (mmol) KCl/L, except infants younger than 3 months who may receive Dextrose 10%/0.2% NaCl with 20 mEq (mmol) KCl/L. These fluids were chosen to provide a small amount of glucose for CNS function and to replace usual urinary sodium and potassium losses. Estimating daily fluid requirements and calculation of an appropriate maintenance fluid rate is discussed in Chapter 164.

Concerns related to the development of hyponatremia in hospitalized patients have led to the recommendation that an isotonic fluid be used for *maintenance* fluids to reduce the incidence of hyponatremia.[117,118] However, excess administration of 0.9% NaCl can result in ICF dehydration and chloride overload leading to metabolic acidosis. A *balanced* electrolyte solution (eg, lactated Ringer's, Plasma-Lyte®) may be preferred for this reason.[118] Excess sodium administration also carries the risk of hypernatremia and volume overload, especially in vulnerable patients. While isotonic fluids may be appropriate for some hospitalized patients, it is important to remember that *maintenance* fluids are appropriate when used as intended (ie, in patients who are euvolemic with no excess ongoing fluid losses and normal kidney function). Careful attention to the sodium content of IV fluids administered to all hospitalized patients is warranted.

Treatment of hyperglycemia-induced osmotic diuresis consists of correcting the hyperglycemia with insulin, as well as administering 0.9% NaCl until signs of hypovolemia resolve. Once hemodynamic stability is restored, the free water deficit can be corrected as described above.

Hypernatremia in patients undergoing a post-obstructive diuresis should be treated with a hypotonic fluid (eg, 0.45% NaCl [IV], Pedialyte® [oral]) administered at a rate of approximately one-half to two-thirds of the urine output over a similar time point. Oral fluid replacement is preferred, if possible. The common practice of administering IV or oral fluids to replace urine output on a 1:1 volume basis tends to perpetuate the diuresis and generally should be avoided.[119]

Euvolemic (Isovolemic) Hypernatremia

Central Diabetes Insipidus

Patients with central DI should generally receive AVP replacement therapy with desmopressin, an AVP analog (Fig. 68-3). The intranasal formulation, 1-desamino-8-D-arginine vasopressin (DDAVP), is preferred; however, oral tablets are available and may be useful in some patients. Each insufflation of intranasal DDAVP (100 mcg/mL) delivers 10 mcg of desmopressin acetate. A rhinal tube delivery system is preferred in patients requiring doses that are lower than 10 mcg or not in 10-mcg increments. In infants with congenital DI, preparation of a DDAVP dilution may be required to provide the small dosages needed. In adults, the initial intranasal DDAVP dosage is 5 to 10 mcg administered once or twice daily, titrated to a maximum dose of 40 mcg given every 8 hours. The oral starting dosage is 0.05 mg BID titrated to a maximum of 0.4 mg every 8 hours.[115]

Patients may prefer oral tablets due to the ease of administration, but not all patients will adequately respond to the oral formulation as the bioavailability is only about 5%. A 0.1 mg tablet is equivalent to 2.5 to 5 mcg of the intranasal formulation. Sublingual tablets are also available. Re-titration of the dosage is required when transitioning between dosage forms due to the unpredictable absorption. A parenteral formulation of desmopressin (4 mcg/mL) is available for either subcutaneous or IV administration and may be administered in cases when the intranasal and oral routes are not feasible or effective, or in acute settings to initiate therapy in symptomatic patients.

The desmopressin dosage should be adjusted to achieve adequate urinary concentration to control nighttime symptoms during sleep (nocturia), a daily urine volume of approximately 1.5 to 2 L, and a safe serum sodium concentration. The mean duration of action of intranasal DDAVP is 7 to 9 hours. The serum sodium concentration should be measured at 24 hours and every 3 to 4 days during the initial dosage titration period, and then every 2 to 4 months. Desmopressin administration results in non-suppressible AVP activity and presents a risk of water intoxication with excess water intake and retention. Patients must be knowledgeable of the signs and symptoms of both hyponatremia and hypervolemia. Patients who experience water intoxication may minimize the risk of a second episode by delaying one desmopressin dose each week until polyuria and thirst develop, thus

demonstrating the continued need for desmopressin therapy.[120]

When there is an inadequate response to desmopressin, additional therapies may be needed. Carbamazepine increases renal sensitivity to AVP, chlorpropamide potentiates the action of circulating AVP and decreases urine output by 50%, and indapamide increases urinary osmolality and decreases serum osmolality. These medications are associated with significant adverse medication reactions and close monitoring is required if added to the patient's therapy.[115]

Nephrogenic Diabetes Insipidus

In patients with nephrogenic DI, concomitant electrolyte disturbances, if present, should be corrected, and any medications that potentially contribute to the pathogenesis should be discontinued, if possible. The free water deficit must be replaced initially. Mild cases may be managed with sufficient water intake only. Because the ongoing urinary losses are essentially free water, patients should receive hypotonic fluids to avoid excess sodium intake which could worsen hypernatremia (Fig. 68-3). Water or milk can be given enterally or D_5W can be given intravenously at a rate that slightly exceeds the urine output with a goal to normalize the serum sodium concentration at a rate no faster than 0.5 mEq/L per hour (mmol/L per hour).[121] A key goal in treating nephrogenic DI is to induce a mild ECF deficit (1-1.5 L) with a thiazide diuretic and dietary sodium restriction (85 mEq [mmol] Na^+ or 2,000 mg NaCl per day), which can decrease urine volume by as much as 50% (Table 68-9). This ECF deficit will increase proximal tubule water reabsorption, decrease the filtrate volume delivered to the distal nephron, and decrease urine volume. In a patient with a maximally dilute urine osmolality (100 mOsm/kg [mmol/kg]), each gram of salt that is avoided will reduce the obligatory urine output by 360 mL because 1 g of table salt provides an osmolar load of approximately 36 mOsm.[121] Indomethacin, 50 mg given orally three times daily, potentiates AVP activity and can be used as adjunctive therapy in patients able to tolerate the gastrointestinal (GI) adverse medication reactions. The relative benefits of other medications for nephrogenic DI, including thiazide diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs), are not well studied; therefore, the choice of agent is primarily based on clinician preference. It is unclear if there is a significant difference in the risk of a clinically important GFR decrease when these medications are used to produce a mild ECF volume deficit. Lithium-induced nephrogenic DI can usually be treated with increased water intake because thirst is intact. If water intake is inadequate, amiloride 2.5 mg to 10 mg daily can be used as amiloride decreases lithium entry into the principal cells by inhibiting the amiloride-sensitive epithelial sodium channel (ENaC).[115] Several other medications with antidiuretic properties have been used successfully in the management of central and nephrogenic DI (Table 68-9). They may be used as adjunctive therapy or rarely as an alternative to DDAVP.

TABLE 68-9

Medications Used in Central and Nephrogenic DI

Medication	Indication	Dose
Desmopressin acetate	Central and nephrogenic	IN: 5-20 mcg q12-24hr IV/SQ: Initial, 0.25-1 mcg q12-24hr PO: Initial: 0.05-0.2 mg qhs; usual: 0.1-0.8 mg in 2-3 doses, max 1.2 mg daily SL: 60 mcg TID; usual, 120-720 mcg daily in 2-3 doses
Chlorpropamide	Central	125-250 mg orally daily
Carbamazepine	Central	100-300 mg orally twice daily
Hydrochlorothiazide	Central and nephrogenic	25 mg orally q12-24hr
Amiloride	Nephrogenic	5-10 mg orally daily Pediatrics: 0.2 mg/kg/day in 3 doses or 20 mg/1.73 m^2/day
Indomethacin	Central and nephrogenic	50 mg orally q8-12hr

DI, diabetes insipidus; IN, intranasal; IV, intravenous; PO, oral; SL, sublingual; SQ, subcutaneous.

Hypervolemic Hypernatremia (Sodium and Water Overload)

Treatment of hypervolemic hypernatremia consists of administration of D_5W and a loop diuretic to facilitate excretion of the excess sodium while replacing free water to prevent worsening of hypernatremia (Fig. 68-3). The volume needed to correct the water deficit and hypernatremia at an appropriate rate can be estimated as described previously. Furosemide, 20 to 40 mg given orally or intravenously every 6 hours, should also be administered.

The serum sodium concentration should initially be measured at least every 2 to 4 hours, and diuresis continued until signs of ECF volume overload (eg, pulmonary congestion, edema) resolve. The serum sodium concentration can be measured every 6 to 12 hours once the serum sodium concentration is less than 148 mEq/L (mmol/L) and symptoms have resolved.[2]

EDEMA

Edema, defined as a clinically detectable increase in interstitial fluid volume, is usually due to heart, kidney, or liver failure or a combination of these conditions; although, it can develop with a rapid decrease in serum albumin concentration along with excess fluid intake such as seen in the setting of burns or trauma. In an adult, edema formation is indicative of an interstitial volume increase of at least 2.5 to 3 L.

Pathophysiology

Edema develops when excess sodium is retained either as a primary defect in renal sodium excretion or as a response to a decrease in the effective circulating volume (actually the BP resulting from that volume) despite a normal or expanded ECF volume. Under these conditions, the kidneys retain all the water and sodium ingested until the effective circulating volume is restored to near normal. An increase in dietary sodium is accompanied by an

increase in water intake caused by the initial increase in serum osmolality and thirst. The resultant ECF volume increase augments kidney perfusion, resulting in a transient GFR increase, which leads to enhanced sodium filtration and excretion. These homeostatic mechanisms are crucial for maintaining sodium balance, as retention of just a few milliequivalents (millimoles) of sodium per day can eventually lead to an expanded ECF volume and edema formation. An increase in the capillary hydrostatic pressure because of ECF volume expansion or an increase in central venous pressure also can lead to edema formation. Edema may also occur when there is an alteration in Starling forces within the capillary. The Starling equation denotes the relationship between factors affecting fluid movement between the capillary and interstitium. Edema may develop rapidly in patients with an acute decompensation in myocardial contractility, which leads to an elevated pulmonary venous pressure that is transmitted back to the pulmonary capillaries, and ultimately results in acute pulmonary edema.

Patients with nephrotic syndrome may initially present with edema, primarily periorbital, labial/scrotal, and lower extremity which may progress to pulmonary edema, ascites, and anasarca. There are two theories posited to explain edema in nephrotic syndrome: the *underfill* and the *overfill* hypotheses.[122,123] The underfill hypothesis states that high-grade proteinuria leads to decreased oncotic pressure due to hypoalbuminemia (most pronounced with a serum albumin concentration less than 2 g/dL [20 g/L]). Decreased oncotic pressure then leads to excess fluid movement from the intravascular space to the interstitial space (*third spacing*) causing hypovolemia, kidney hypoperfusion, activation of the renin–angiotensin–aldosterone system, and secondary renal sodium retention. The overfill hypothesis is simply that protein loss in the urine leads to primary renal sodium retention causing intravascular volume expansion, leading to fluid overflow into the interstitial space (edema). Edema mechanisms can vary between patients and also vary at different times in an individual patient. Distinguishing the predominant mechanism in individual patients with nephrotic syndrome is often challenging but clinically important, as patients who are primarily underfilled will likely have worsening hypovolemia and an elevated serum creatinine requiring volume repletion after initially tolerating diuresis.

Patients with cirrhosis initially develop ascites because of splanchnic vasodilation resulting in an increase in the pressure in the portal circulation (portal hypertension). This combination of portal hypertension and splanchnic vasodilation increases capillary pressure and permeability and facilitates the accumulation of ascites (fluid in the abdominal cavity). Ascites can cause a decrease in effective circulating volume and activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, leading to secondary hyperaldosteronism. Subsequent renal sodium retention leads to worsened ascites, edema, and hypervolemic hyponatremia.[124]

Clinical Presentation

Edema is usually first detected in the feet or periorbital or pretibial area in ambulatory patients and in the presacral area of bed-bound individuals. Edema is described as “pitting” when a depression created by exerting pressure for several seconds over a bony prominence, such as the tibia, does not rapidly refill. Edema severity is rated on a semi-quantitative scale of 1+ to 4+ depending on the depth of the pit: 1+ = 2 mm; 2+ = 4 mm; 3+ = 6 mm; and 4+ = 8 mm.

The extent of edema should be quantified according to the areas involved. Pretibial edema, for example, should be quantified according to how far it extends up the lower leg (eg, one-third up the lower leg). Pulmonary edema, an increase in lung interstitial and alveolar water, is often evidenced by crackles (rales) upon auscultation. Rales should be quantified according to how far the crackles extend from the dependent portion of the lung(s). For example, edema limited to the ankles and feet would indicate less severe edema than edema that extends halfway up the lower legs, and crackles limited to the base of both lungs in an upright person would indicate less severe pulmonary edema than crackles throughout both lung fields. *Anasarca* is a term used to refer to a massive amount of edema generalized throughout the body.

Treatment

General Approach

Treatment goals for hypervolemic hypernatremia are to minimize edema and to improve organ function, as well as to relieve symptoms (eg, dyspnea, abdominal distention, extremity pain). The presence of edema does not always dictate the need for diuretic therapy; however, severe pulmonary edema is life-threatening and requires immediate pharmacologic treatment. Other forms of edema may be treated less acutely, with a comprehensive approach that includes not only diuretics but also sodium and water restriction and optimal treatment of the underlying disease. Sodium intake should generally be restricted to 1,000 to 2,000 mg/day. A slow judicious approach in non-life-threatening situations will help minimize complications of diuretic therapy, including excessive diuresis, impaired perfusion, azotemia, impaired cardiac output due to decreased left ventricular end-diastolic filling pressure, and electrolyte abnormalities. Fluid should be removed cautiously in patients with cirrhosis and ascites but no peripheral edema. A

goal of 500 mL/day can be safely mobilized in patients with isolated ascites; higher volumes may result in decreased ECF volume and lead to elevated BUN and possibly hepatorenal syndrome.[124]

Diuretic Therapy

Diuretics are the primary pharmacologic therapy for edema when severe or when treatment of the underlying disease and sodium and water restriction are insufficient. Diuretics are categorized according to the site in the nephron where sodium reabsorption is inhibited. Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) inhibit the sodium–potassium–chloride (Na^+–K^+–$2Cl^-$) carrier in the loop of Henle, while thiazide and thiazide-like diuretics (hydrochlorothiazide, chlorothiazide, chlorthalidone, indapamide, metolazone) inhibit the Na^+–Cl^- carrier in the distal tubule. Potassium-sparing diuretics inhibit the sodium channel in the cortical collecting duct either directly (triamterene, amiloride) or by interfering with aldosterone activity (spironolactone, eplerenone). Acetazolamide, a carbonic anhydrase inhibitor, acts in the proximal convoluted tubule and has been used in patients with diuretic resistance. Diuretic efficacy in patients with edema depends on the amount of filtered sodium normally reabsorbed at its site of action, the amount of sodium reabsorbed distal to its site of action, adequate medication delivery to the site of action, and the amount of sodium reaching the site of action.[29]

All diuretics act by inhibiting sodium reabsorption in the renal tubules, increasing the fractional excretion of sodium (FeNa). Loop diuretics are the most potent diuretics, as evidenced by the fact that they increase peak FeNa from normal (1% [0.01] or less) to 20% to 25% (0.20-0.25). Thiazide- and potassium-sparing diuretics are less potent and increase peak FeNa only to 3% to 5% (0.03-0.05) and 1% to 2% (0.01-0.02), respectively.[29] Although a large portion of the filtered sodium is reabsorbed in the proximal nephron, the efficacy of proximal-acting diuretics (acetazolamide) is limited by excess fluid and sodium reabsorption in the loop of Henle. Furthermore, sodium reabsorption by the distal tubule can compensate for reduced reabsorption in the loop of Henle when sodium intake is high.

The pharmacogenomics of diuretic therapy, particularly the thiazides, have been studied extensively in the setting of hypertension therapy.[125] Multiple genetic polymorphisms possibly affecting diuretic activity at the site of action have been identified, but the clinical significance of these genetic variations related to patient outcomes is still being elucidated. It is likely that a complex predictive model utilizing pharmacodynamic, pharmacokinetic, and pharmacogenomic parameters will be necessary to predict significantly different diuretic responses and outcomes due to the potential for compensatory mechanisms in other parts of the nephron. While genetic testing for gene variants is now available, it is not yet a practical option to guide diuretic treatment.

The effectiveness of thiazide and loop diuretics is dependent on the medication concentration in the tubular lumen. These diuretics are delivered to the tubular lumen via active transport by the proximal tubular cells. Osmotic diuretics are freely filtered into the tubular lumen in the proximal tubule, whereas spironolactone reaches mineralocorticoid receptors in the cortical collecting duct via diffusion from the systemic circulation.[29] A threshold concentration of loop or thiazide diuretic must be delivered to the respective site of action to achieve a natriuresis. Once the threshold concentration is achieved, a further diuretic dose increase will not elicit an increased diuretic response. Thus, a *ceiling dose* for these diuretics is recognized. In healthy subjects, administration of IV furosemide 40 mg results in excretion of 200 to 250 mEq (mmol) of sodium in 3 to 4 L of urine over a 3- to 4-hour period.[29]

Loop diuretics, except torsemide, have a rapid onset but short half-life requiring administration every 2 to 3 hours while thiazide diuretics have a longer half-life allowing for less frequent (once daily) dosing (Table 68-10). Table 68-11 lists the maximal effective doses and dosing intervals for loop diuretics in patients with cirrhosis, HF, nephrotic syndrome, and kidney insufficiency.

TABLE 68-10

Characteristics of Thiazide Diuretics

Diuretic	Duration of Action	Initial Daily Dosage	Sequential Nephron Blockade	Maximum Total Daily Dose
Chlorothiazide	6-12 hr	250-500 mg once or twice	500-1,000 mg once plus loop diuretic	1,000 mg
Chlorthalidone	24-72 hr	12.5-25 mg once		100 mg
Hydrochlorothiazide	6-12 hr	25 mg once or twice	25-100 mg once or twice plus loop diuretic	200 mg
Indapamide	36 hr	2.5 mg once		5 mg
Metolazone	12-24 hr	2.5 mg once	2.5-10 mg plus loop diuretic	20 mg

TABLE 68-11

Characteristics of Loop Diuretics

Diuretic	Dosing Interval	Recommended Doses				GFR 10-50 mL/min (0.17-0.83 mL/s)	GFR <10 mL/min (0.17 mL/s)	Maximum Total Daily Dose[a]
		Normal	Cirrhosis	HF	Nephrotic Syndrome			
Furosemide								
IV	6-8 hr	10-40 mg	40 mg	40-80 mg	120 mg	80 mg	200 mg	200 mg
Oral	6-8 hr	20-80 mg	80 mg	80-160 mg	240 mg	160 mg	320-400 mg	600 mg
Bumetanide								
IV/oral	6-8 hr	1 mg	1 mg	2-3 mg	3 mg	2-3 mg	8-10 mg	10 mg
Torsemide								
IV/oral	24 hr	15-20 mg	10-20 mg	20-50 mg	50 mg	20-50 mg	50-100 mg	200 mg
Ethacrynic acid[b]								
IV	8-12 hr[c]	0.5-1 mg/kg (max 100 mg)						
Oral	12-24 hr	25-100 mg	50-100 mg	50-100 mg				400 mg

HF, heart failure; GFR, glomerular filtration rate.

[a]Although these doses are generally accepted maximal doses, higher doses may be required due to insufficient quantities in the renal tubular fluid.

[b]Rarely used because of higher rates of ototoxicity and relative insolubility; may be used in a patient with a sulfa allergy.

[c]Repeat doses not routinely recommended.

Patients with kidney insufficiency often require larger diuretic doses to achieve adequate medication concentrations at the site of action. The natriuretic response is decreased in patients with kidney insufficiency because the filtered sodium load falls proportionately as GFR declines. This effect can be partially overcome by administering diuretics more frequently or by using a continuous infusion, a method commonly employed in critically ill patients. Continuous delivery will limit the effect of the post-diuresis sodium retention in the distal nephron. Table 68-12 lists initial continuous infusion rates based on creatinine clearance and maximum recommended infusion rates.

TABLE 68-12

Continuous Infusion Rates for Loop Diuretics

Medication	Initial Infusion Rate Based on Creatinine Clearance (CrCl)			Maximum Infusion Rate	
	CrCl <25 mL/min (0.42 mL/s)	CrCl 25-75 mL/min (0.42-1.25 mL/s)	CrCL >75 mL/min (1.25 mL/s)	Undiluted bolus	Continuous infusion
Bumetanide	1-2 mg/hr	0.5-1 mg/hr	0.5 mg/hr	5 mg/min	0.17 mg/min
Furosemide	20-40 mg/hr	10-20 mg/hr	10 mg/hr	40 mg/min	4 mg/min
Torsemide	10-20 mg/hr	5-10 mg/hr	5 mg/hr	100 mg/min	0.05 mg/min[a]

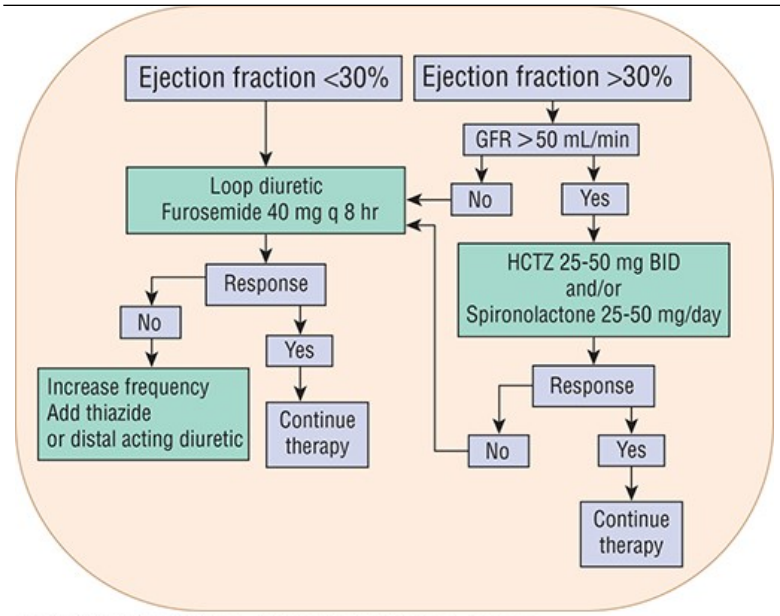
[a]Studies used a 100-mg total daily dose as a 25-mg injection over 2 minutes (25% of total daily dose) followed by an infusion of 3.1 mg/hr over 24 hours (75% of total daily dose).

Loop diuretic resistance can be caused by pronounced sodium reabsorption in the distal nephron when sodium absorption in the loop of Henle is blocked. If sodium intake is not restricted, this distal sodium reabsorption can compensate entirely for loop diuretic-induced sodium loss. Patients with diuretic-resistant edema can be treated with a loop diuretic and metolazone. Metolazone should be given first and allowed sufficient time to start blocking distal sodium reabsorption to maximize loop diuretic efficacy.

Impaired diuretic delivery to the site of action is another mechanism of diuretic resistance. Patients with HF and a normal GFR may have impaired oral furosemide absorption. An adequate diuresis is most readily sustained by increasing the frequency of diuretic administration, but a higher dose may also be effective (Fig. 68-4). Absorption of orally administered loop diuretics can be compromised by GI edema and delayed gastric emptying, conditions often seen in critically ill patients.

FIGURE 68-4

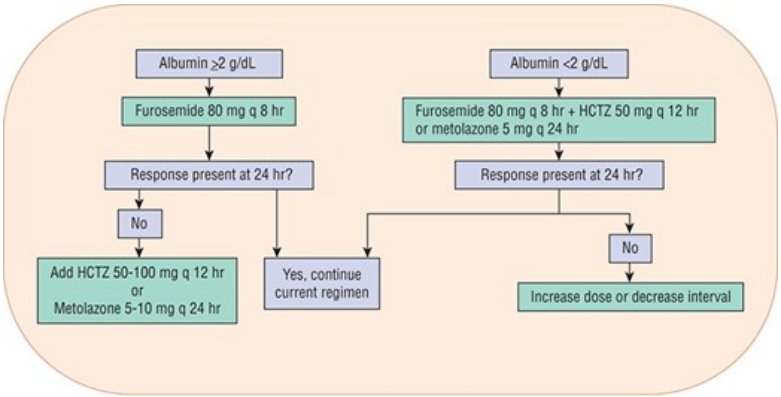
Algorithm for diuretic use in patients with heart failure. (GFR, glomerular filtration rate [50 mL/min is equivalent to 0.83 mL/s]; HCTZ, hydrochlorothiazide.)



Inadequate medication concentration at the site of action also can be caused by decreased perfusion as might be seen in patients with decompensated HF or those with decreased kidney perfusion. Due to extensive albumin binding (more than 95%), little of these agents reach the tubule lumen by filtration, and they are almost exclusively transported into the proximal tubule lumen by active secretion via the organic acid secretory pathway.[29] When albumin binding is inhibited by concurrent sulfasoxazole administration, diuretic resistance persists, suggesting a decrease in intrinsic tubular sensitivity to loop diuretics.[126] This impaired natriuretic response can be overcome by using higher diuretic doses to increase unbound medication delivery to the secretory site in the nephron. Decreased intrinsic diuretic activity with repeated dosing may also play a role in diuretic resistance, the mechanism of which is not well understood. A combination of a loop diuretic with a distally acting diuretic is generally necessary to promote a natriuresis that exceeds distal tubular sodium reabsorption in patients with nephrotic syndrome (Fig. 68-5).[127]

FIGURE 68-5

Algorithm for diuretic therapy in patients with nephrotic syndrome. Albumin concentration of 2 g/dL is equivalent to 20 g/L. (HCTZ, hydrochlorothiazide.)

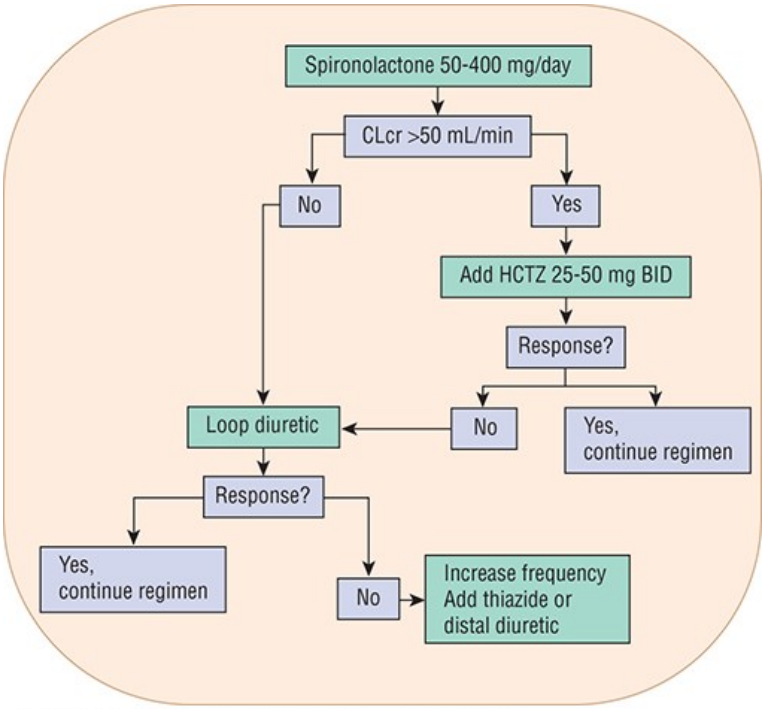


In patients with cirrhosis, secondary hyperaldosteronism from activation of the renin–angiotensin–aldosterone system plays a major role in the pathogenesis of edema. Therefore, these patients should initially be treated with an aldosterone antagonist (eg, spironolactone) in the absence of impaired GFR and hyperkalemia (Fig. 68-6). Thiazides can then be added for patients with a creatinine clearance greater than 50 mL/min (0.83 mL/s).

For those with diuretic-resistant edema, a loop diuretic may be used instead of the thiazide. Patients with impaired GFR (creatinine clearance less than 40 mL/min [0.67 mL/s]) will require a loop diuretic, with addition of a thiazide in those who do not achieve adequate diuresis.[128]

FIGURE 68-6

Algorithm for diuretic use in patients with cirrhosis. (CLcr, creatinine clearance [50 mL/min is equivalent to 0.83 mL/s]; HCTZ, hydrochlorothiazide.)



Adverse medication reactions associated with loop and thiazide diuretics include hypokalemia, excess ECF volume loss (hypovolemia), hypomagnesemia, metabolic alkalosis, and hyperuricemia. Patients with refractory edema treated with high-dose synergistic combinations are at highest risk for developing hypokalemia. As noted earlier, sodium imbalance is a concern with diuretic therapy: hyponatremia with thiazides, hypernatremia with loops. Calcium imbalance also can occur with diuretic use: hypocalcemia with loops, hypercalcemia with thiazides. Thiazide-induced hypercalcemia is more common in patients with mild subclinical hyperparathyroidism. Loop diuretics cause hypercalciuria and can lead to bone disorders (osteopenia, osteoporosis), kidney stones, or nephrocalcinosis when used chronically. Chronic use of potassium-sparing diuretics can cause a mild metabolic acidosis and hyperkalemia. Patients with moderate-to-severe kidney dysfunction or those receiving NSAIDs, ACEIs, or ARBs are at highest risk for hyperkalemia. In addition, spironolactone can cause reversible gynecomastia in about 10% of men receiving it, and in about 50% of men receiving 150 mg/day or more. This adverse medication reaction has not been associated with eplerenone.[129]

Evaluation of Therapeutic Outcomes

In patients with significant edema, volume status must be monitored carefully to ensure adequate tissue perfusion. Patients should be monitored by careful history and intermittent physical examination to detect signs and symptoms of edema as well as adverse effects. Physical examination should include measurement of BP and pulse in either supine or seated positions and after standing for 2 to 3 minutes to assess for orthostasis. ECF volume can be estimated based on the height of the jugular venous pressure, extent of edema, heart and lung auscultation, and skin turgor. Follow-up monitoring 10 to 14 days after therapy initiation should include determinations of serum sodium, potassium, chloride, bicarbonate, magnesium, calcium, BUN, serum creatinine, and uric acid. A new steady-state balance will have developed over that time period and further fluctuations in ECF volume and electrolyte balance generally do not occur in the absence of a change in clinical status, diuretic dosage, or dietary intake. Repeated blood tests generally are not necessary at every visit unless there is a change in the patient's clinical status.

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
AQP2	aquaporin 2
ARB	angiotensin receptor blocker
AVP	arginine vasopressin, also known as vasopressin and antidiuretic hormone (ADH)
ATPase	adenosine triphosphatase
BP	blood pressure
BUN	blood urea nitrogen
CNS	central nervous system
D_5W	dextrose 5% in water
DDAVP	1-desamino-8-D-arginine vasopressin
DI	diabetes insipidus
ECF	extracellular fluid
FeNa	fractional excretion of sodium
GFR	glomerular filtration rate
GI	gastrointestinal
HF	heart failure
ICF	intracellular fluid
ICU	intensive care unit
IV	intravenous
NSAID	nonsteroidal anti-inflammatory drug
ODS	osmotic demyelination syndrome
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SGLT2	sodium-glucose co-transporter-2
TBW	total body water
VRA	vasopressin receptor antagonist

V_d	volume of distribution

REFERENCES

1. U.S. Department of Health and Human Services and U.S. Department of Agriculture. *Dietary Guidelines for Americans*. 9th Edition. December 2020. https://www.dietaryguidelines.gov. Accessed January 17, 2022.

2. Sterns RH. Disorders of plasma sodium—causes, consequences, and correction. *N Engl J Med.* 2015;372:55–65. doi: 10/1056/NEJMc1501342

3. Kheetan M, Ogu I, Shapiro JI, et al. Acute and chronic hyponatremia. *Front Med.* 2021;8:693738. doi: 10.3389/fmed.2021.693738

4. Dineen R, Thompson CJ, Sherlock M. Hyponatremia—presentations and management. *Clin Med (Lond)*. 2017;17:263–269. doi: 10.7861/clinmedicine.17-3-263

5. Bhave G, Neilson EG. Volume depletion versus dehydration: how understanding the difference can guide therapy. *Am J Kidney Dis.* 2011;58:302–309. doi: 10.1053/j.ajkd.2011.02.395

6. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant*. 2014;29(Suppl.2):ii1–ii39. doi: 10.1093/ndt/gfu040

7. Patterson JH. The impact of hyponatremia. *Pharmacotherapy*. 2011;31(5 Pt 2):5S–8S. doi: 10.1592/phco.31.5.55

8. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta.* 2003;337:169–172. doi: 10.1016/j.cccn.2004.08.001

9. Friedman B, Cirulli J. Hyponatremia in critical care patients: frequency, outcome, characteristics, and treatment with the vasopressin V2-receptor antagonist tolvaptan. *J Crit Care*. 2013;28:219.e1-e12. doi: 10.1016/j.jcrc.2012.06.001

10. Rondon-Berrios H, Berl T. Mild chronic hyponatremia in the ambulatory setting: significance and management. *Clin J Am Soc Nephrol.* 2015;10:2268–2278. doi: 10.2215/CJN.00170115

11. Filippone EJ, Ruzieh M, Foy A. Thiazide-associated hyponatremia: clinical manifestations and pathophysiology. *Am J Kidney Dis.* 2020;75:256–264. doi: 10.1053/j.ajkd.2019.07.011

12. Gandhi S, Shariff SZ, Al-Jaishi A, et al. Second-generation antidepressants and hyponatremia risk: a population-based cohort study of older adults. *Am J Kidney Dis.* 2017;69:87–96. doi: 10.1053/j.ajkd.2016.08.020

13. Sahoo S, Grover S. Hyponatremia and psychotropics. *J Geriatr Ment Health*. 2016;3:108–22. doi: 10.4103/2348-9995.195604

14. Pinkhasov A, Xiong G, Bourgeois JA, et al. Management of SIADH-related hyponatremia due to psychotropic medications—an expert consensus from the Association of Medicine and Psychiatry. *J Psychosom Res.* 2021;151:110654. doi: 10.1016/j.jpsychores.2021.110654

15. Cumming K, Hoyle GE, Hutchison JD, et al. Prevalence, incidence and etiology of hyponatremia in elderly patients with fragility fractures. *PLoS ONE*. 2014;9(2):e88272. doi: 10.1371/journal.pone.0088272

16. Correia L, Ferreira R, Correia I, et al. Severe hyponatremia in older patients at admission in an internal medicine department. *Arch Gerontol Geriatr.* 2014;54:642–647. doi: 10.1016/j.archger.2014.08.002

17. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med.* 2006;119(7A):S30–S35. doi:

10.1016/j.amjmed.2006.05.005

18. Bennett BL, Hew-Butler T, Rosner MH, et al. Wilderness Medical Society Clinical Practice Guidelines for the Management of Exercise-Associated Hyponatremia: 2019 Update. *Wilderness Environ Med.* 2020;31:50–62. doi: 10.1016/j.wern.2019.11.003

19. Morton A, Lumchee M, Kumar S, et al. Pregnancy outcomes in women with hyponatraemia and preeclampsia: case series and literature review. *Pregnancy Hypertens*. 2021;26:38–41. doi: 10.1016/j.preghy.2021.08.116

20. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med.* 2013;126:S1–S42. doi: 10.1016/j.amjmed.2013.07.006

21. Koczmara C, Wade AW, Skippen P, et al. Hospital-acquired acute hyponatremia and reports of pediatric deaths. *Dynamics*. 2010;21:21–26. PMID: 20333891 [PubMed: 20333891]

22. Krummel T, Prinz E, Metten M-A, et al. Prognosis of patients with severe hyponatraemia is related not only to hyponatraemia but also to comorbidities and to medical management: results of an observational retrospective study. *BMC Nephrol.* 2016;17:159. doi: 10.1186/s12882-016-0370-z

23. Tachi T, Yokoi T, Goto C, et al. Hyponatremia and hypokalemia as risk factors for falls. *Eur J Clin Nutr.* 2015;69:205–210. doi: 10.1038/ejcn.2014.195

24. Fehlberg EA, Lucero RJ, Weaver MT, et al. Associations between hyponatraemia, volume depletion and the risk of falls in US hospitalised patients: a case–control study. *BMJ Open*. 2017;7:e017045. doi: 10.1136/bmjopen-2017-017045

25. Kuo SCH, Kuo P-J, Rau C-S, et al. Hyponatremia is associated with worse outcomes from fall injuries in the elderly. *Int J Environ Res Public Health*. 2017;14:E460. doi: 10.3390/ijerph14050460

26. Karakousis ND, Kostakoupoulos NA. Hyponatremia in the frail. *J Frailty Sarcopenia Falls*. 2021;6:241–245. doi: 10.22540/JFSF-06-241

27. Igbinedion SO, Pandit S, Mavuram MS, et al. Pseudohyponatraemia secondary to hyperlipidaemia in obstructive jaundice. *BMJ Case Rep.* 2017 Dec 1;2017:bcr2017221984. doi: 10.1136/bcr-2017-221984

28. Palmer BF, Clegg DJ. Electrolyte and acid-base disturbances in patients with diabetes mellitus. *N Engl J Med.* 2015;373:548–559. doi: 10.1056/NEJMra1503102

29. Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part I: mechanisms of action, pharmacological effects and clinical indications of diuretic compounds. *Expert Opin Drug Saf.* 2010;9:243–257. doi: 10.1517/14740330903499240

30. Oh JY, Shin JI. Syndrome of inappropriate antidiuretic hormone secretion and cerebral/renal salt wasting syndrome: similarities and differences. *Front Pediatr.* 2015;2:146. doi: 10.3389/fped.2014.00146

31. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis.* 2008;52:144–153. doi: 10.1053/j.ajkd.2008.03.004

32. Decaux G. Is asymptomatic hyponatremia really asymptomatic? *Am J Med.* 2006;119(7A):S79–S82. doi: 10.1016/j.amjmed.2006.05.013

33. Kinsella S, Moran S, Sullivan MO, et al. Hyponatremia independent of osteoporosis is associated with fracture occurrence. *Clin J Am Soc Nephrol.* 2010;5:275–280. doi: 10.2215/CJN.06120809

34. Fisher SK, Heacock AM, Keep RF, et al. Receptor regulation of osmolyte homeostasis in neural cells. *J Physiol.* 2010;18:3355–3364. doi: 10.1113/jphysiol.2010.190777

35. Alukal JJ, John S, Thuluvath PJ. Hyponatremia in cirrhosis: an update. *Am J Gastroenterol.* 2020;115:1775–1785. doi: 10.14309/ajg/0000000000000786

36. Yuridullah R, Kumar V, Nanavati S, et al. Clinical resolution of osmotic demyelination syndrome following overcorrection of severe hyponatremia. *Case Rep Nephrol.* 2019;1757656. doi: 10.1155/2019/1757656

37. Cuesta M, Thompson CJ. The syndrome of inappropriate antidiuresis (SIAD). *Best Pract Res Clin Endocrinol Metab.* 2016;30:175–187. doi: 10.1016/j.beem.2016.02.009

38. Jones GM, Bode L, Riha H, et al. Safety of continuous peripheral infusion of 3% sodium chloride solution in neurocritical care patients. *Am J Crit Care*. 2016;26:37–42. doi: 10.4037/ajcc2017439

39. Berl T. Vasopressin antagonists. *N Engl J Med.* 2015;372:2207–2216. doi: 10.1056/NEJMra1403672

40. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med.* 2006;355:2099–2112. doi: 10.1056/NEJMoa065181

41. Rozen-Zvi B, Yahav D, Gheorghiade M, et al. Vasopressin receptor antagonists for the treatment of hyponatremia: systematic review and meta-analysis. *Am J Kidney Dis.* 2010;56:325–337. doi: 10.1053/j.ajkd.2010.01.013

42. Tzoulis P, Waung JA, Bagkeris E, et al. Real-life experience of tolvaptan use in the treatment of severe hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion. *Clin Endocrinol (Oxf)*. 2016;84:620–6. doi: 10.1111/cen.12943

43. Li B, Fang D, Qian C, et al. The efficacy and safety of tolvaptan in patients with hyponatremia: a meta-analysis of randomized controlled trials. *Clin Drug Investig.* 2017;37:327–342. doi: 10.1007/s40261-016-0470-3

44. Pose-Reino A, de la Vega IR, de Jong-Laird A, et al. Real-world, non-interventional, retrospective study (SAMPLE) of tolvaptan in patients with hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion. *Adv Ther.* 2021;38:1055–1067. doi: 10.1007/s12325-020-01560-2

45. Shoaf SE, Bramer SL, Bricmont P, et al. Pharmacokinetic and pharmacodynamic interaction between tolvaptan, a non-peptide AVP antagonist, and furosemide or hydrochlorthiazide. *J Cardiovasc Pharmacol.* 2007;50:213–222. doi: 10.1097/FJC.0b013e318074f934

46. Kamgar M, Hanna RM, Hasnain H, et al. Risk of serum sodium overcorrection with V2 antagonists in SIADH and other high risk patients. *J Onco-Nephrol.* 2017;1(3):143–146. doi: 10.5301/jo-n.5000025

47. Morris JH, Bohm NM, Nemecek BD, et al. Rapidity of correction of hyponatremia due to syndrome of inappropriate secretion of antidiuretic hormone following tolvaptan. *Am J Kidney Dis.* 2018;71:772–782. doi: 10.10.1053/j.ajkd.2017.12.002

48. Hanna RM, Velez JC, Rastogi A, et al. Equivalent efficacy and decreased rate of overcorrection in patients with syndrome of inappropriate secretion of antidiuretic hormone given very low-dose tolvaptan. *Kidney Med.* 2019;2:20–28. doi: 10.1016/j.xkme.2019.009.004

49. Liu Y-H, Han X-B, Fei Y-H, et al. Long-term low-dose tolvaptan treatment in hospitalized male patients aged >90 years with hyponatremia: report on safety and effectiveness. *Medicine (Baltimore)*. 2017;96:e9539. doi: 10.1097/MD.0000000000009539

50. Der-Nigoghossian C, Lesch C, Berger K. Effectiveness and tolerability of conivaptan and tolvaptan for the treatment of hyponatremia in neurocritically ill patients. *Pharmacotherapy*. 2017;37:528–534. doi: 10.1002/phar.1926

51. Llompart-Pou JA, Pérez-Bárcena J, Novo M, et al. Effect of single-dose of tolvaptan in neurocritical patients with hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion. *Med Intensiva.* 2017;41:501–503. doi: 10.1016/j.medin.2016.11.007

52. Shoaf SE, Bricmont P, Dandurand A. Low-dose tolvaptan PK/PD: comparison of patients with hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion to healthy adults. *Eur J Clin Pharmacol.* 2017;73:1399–1408. doi: 10.1007/s00228-017-2302

53. McNeely EB, Talameh JA, Adams KF Jr, et al. Relative bioavailability of tolvaptan administered via nasogastric tube and tolvaptan tablets swallowed intact. *Am J Health-Syst Pharm.* 2013;70:1230–1237. doi: 10.2146/ajhp120543

54. Decaux G. V2-antagonists for the treatment of hyponatraemia. *Nephrol Dial Transplant*. 2007;22:1853–1855. doi: 10.1093/ndt/gfm136

55. Pose A, Almenar L, Gavira JJ, et al. Benefit of tolvaptan in the management of hyponatraemia in patients with diuretic-refractory congestive heart failure: the SEMI-SEC project. *ESC Heart Fail.* 2017;4:130–137. doi: 10.1002/ehf2.12124

56. Rosskopf D, Michel MC. Pharmacogenomics of G protein-coupled receptor ligands in cardiovascular medicine. *Pharmacol Rev.* 2008;60:513–535. doi: 10.1124/pr.108.000612

57. Shoaf SE, Ohzone Y, Ninomiya S, et al. In vitro P-glycoprotein interactions and steady-state pharmacokinetic interactions between tolvaptan and digoxin in healthy subjects. *J Clin Pharmacol.* 2011:51:761–769. doi: 10.1177/0091270010376193

58. Shoaf SE, Bricmont P, Mallikaarjun S. Pharmacokinetics and pharmacodynamics of oral tolvaptan in patients with varying degrees of renal function. *Kidney Int.* 2014;85:953–961. doi: 10.1038/ki.2013.350

59. Katsumata M, Hirawa N, Sumida K, et al. Effects of tolvaptan in patients with chronic kidney disease and chronic heart failure. *Clin Exp Nephrol.* 2017;21:858–865. doi: 10.1007/s10157-016-1379-0

60. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med.* 2012;367:2407–2418. doi: 10.1056/NEJMoa1205511

61. Rondon-Berrios H, Berl T. Vasopressin receptor antagonists in hyponatremia: uses and misuses. *Front Med (Lausanne)*. 2017:4:141. doi: 10.3389/fmed.2017.00141

62. Ramamohan V, Mladsi D, Ronquest N, et al. An economic analysis of tolvaptan compared with fluid restriction among hospitalized patients with hyponatremia. *Hosp Pract (1995)*. 2017;45:111–117. doi: 10.1080/21548331.2017.1324227

63. Dasta JF, Sundar S, Chase S, et al. Economic impact of tolvaptan treatment vs. fluid restriction based on real-world data among hospitalized patients with heart failure and hyponatremia. *Hosp Pract (1995)*. 2018:46:197–202. doi: 10.1080/21548331.2018.1505180

64. Sarafidis P, Loutradis C, Ferro CJ, et al. SGLT-2 inhibitors to treat hyponatremia associated with SIADH: a novel indication? *Am J Nephrol.* 2020;51:553–555. doi: 10.1159/000509082

65. Refardt J, Imber C, Sailer CO, et al. A randomized trial of empagliflozin to increase plasma sodium levels in patients with the syndrome of inappropriate antidiuresis. *J Am Soc Nephrol.* 2020;31:615–624. doi: 10.1681/ASN/2019090944

66. Miell J, Dhanjal P, Jamookeeah C. Evidence for the use of demeclocycline in the treatment of hyponatraemia secondary to SIADH: a systematic review. *Int J Clin Pract.* 2015;69:1396–1417. doi: 10.1111/ijcp.12713

67. Rondon-Berrios H, Tandukar S, Mor MK, et al. Urea for the treatment of hyponatremia. *Clin J Am Soc Nephrol.* 2018;13:1627–1632. doi: 10.2215/CJN.04020318

68. Soupart A, Coffernils M, Couturier B, et al. Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin J Am Soc Nephrol.* 2012;7:742–747. doi: 10.2215/CJN.06990711

69. Nagler EV, Haller MC, van Biesen W, et al. Interventions for chronic non-hypovolaemic hypotonic hyponatraemia. *Cochrane Database Syst Rev.*

2018;6:CD010965. doi: 10.1002/14651858.CD010965.pub2

70. Sonawane KB, Hansen RA. PHP92—Serious adverse drug events reported to the Food and Drug Administration (FDA): analysis of the FDA adverse event reporting system (FAERS) 2006-2011 database. *Value in Health*. 2015;18:A86. doi: 10.1016/j.jval.2015.03.502

71. Gheorghiade M, Gottlieb SS, Udelson JE, et al. Vasopressin v(2) receptor blockade with tolvaptan versus fluid restriction in the treatment of hyponatremia. *Am J Cardiol.* 2006;97:1064–1067. doi: 10.1016/j.amjcard.2005.10.050

72. Dunlap ME, Hauptman PJ, Amin AN, et al. Current management of hyponatremia in acute heart failure: a report from the Hyponatremia Registry for Patients with Euvolemic and Hypervolemic Hyponatremia (HN Registry). *J Am Heart Assoc.* 2017;6:e005261. doi: 10.1161/JAHA.116.005261

73. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation*. 1986;73:257–267. doi: 10.1161/01.cir.73.2.257

74. Klein L, O'Connor CM, Leimberger JD, et al; OPTIME-CHF Investigators. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation*. 2005;111:2454–2460. doi: 10.1161/01.CIR.0000165065.82609.3D

75. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevation of creatinine: Is this a cause for concern? *Arch Intern Med.* 2000;160:685–693. doi: 10.1001/archinte.160.5.685

76. Baldasseroni S, Urso R, Orso F, et al. Relation between serum sodium levels and prognosis in outpatients with chronic heart failure: neutral effect of treatment with beta-blockers and angiotensin-converting enzyme inhibitors: data from the Italian network on congestive heart failure (IN-CHF database). *J Cardiovasc Med.* 2011;12:723–731. doi: 10.2459/JCM.0b013e32834ae87e

77. Bajaj JS, Tandon P, O'Leary JG, et al. The impact of albumin use on resolution of hyponatremia in hospitalized patients with cirrhosis. *Am J Gastroenterol.* 2018;113:1339–1344. doi: 10.1038/s41395-018-0119-3

78. Caraceni P, Riggio O, Angeli P, et al for the ANSWER Study Investigators. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. *Lancet*. 2018;391:2417–2429. doi: 10.1016/S0140-6736(18)30840-7

79. Gerbes AL, Gülberg V, Ginès P, et al. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. *Gastroenterology*. 2003;124:933–939. doi: 10.1053/gast.2003.50143

80. Urso C, Brucculeri S, Caimi G. Employment of vasopressin receptor antagonists in management of hyponatraemia and volume overload in some clinical conditions. *J Clin Pharm Ther.* 2015;40:376–385. doi: 10.1111/jcpt.12279

81. Jia J-D, Xie W, Ding H-G, et al. Utility and safety of tolvaptan in cirrhotic patients with hyponatremia: a prospective cohort study. *Ann Hepatol.* 2017;16:123–132. doi: 10.5604/16652681.1226823

82. Tahara T, Mori K, Mochizuki M, et al. Tolvaptan is effective in treating patients with refractory ascites due to cirrhosis. *Biomed Rep.* 2017;7:558–562. doi: 10.3892/br.2017.1005

83. Sakaida I, Terai S, Kurosaki M, et al. Effectiveness and safety of tolvaptan in liver cirrhosis patients with edema: interim results of post-marketing surveillance of tolvaptan in liver cirrhosis (START study). *Hepatol Res.* 2017;47:1137–1146. doi: 10.1111/hepr.12852

84. Pose E, Solà E, Piano S, et al. Limited efficacy of tolvaptan in patients with cirrhosis and severe hyponatremia: real-life experience. *Am J Med.* 2017;130:372–375. doi: 10.1016/j.amjmed.2016.09.011

85. Berl T, Quittnat-Pelletier F, Verbalis JG, et al for the SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol.* 2010;21:705–712. doi: 10.1681/ASN.200908857

86. Jaber BL, Almarzouqi L, Borgi L, et al. Short-term efficacy and safety of vasopressin receptor antagonists for treatment of hyponatremia. *Am J Med.* 2011;124:977.e1-9. doi: 10.1016/j.amjmed.2011.04.028

87. Parekh A, Rajaram P, Patel G, et al. Utility of tolvaptan in the perioperative management of severe hyponatremia during liver transplantation: a case report. *Transplant Proc.* 2017;49:2399–2401. doi: 10.1016/j.transproceed.2017.09.011

88. Felker GM, Mentz RJ, Cole RT, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol.* 2017;69:1399–1406. doi: 10.1016/j.jacc.2016.09.004

89. Konstam MA, Kiernan M, Chandler A, et al. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *J Am Coll Cardiol.* 2017;69:1409–1419. doi: 10.1016/j.jacc.2016.12.035

90. Ikeda S, Ohshima K, Miyazaki S, et al. Impact of chronic kidney disease on the diuretic response of tolvaptan in acute decompensated heart failure. *ESC Heart Fail.* 2017;4:614–622. doi: 10.1002/ehf2.12190

91. Gheorghaide M, Niazi I, Quyang J, et al. Vasopressin V2-receptor blockage with tolvaptan in patients with chronic heart failure: results from a double-blind randomized trial. *Circulation*. 2003;107:2690–2696. doi: 10.1161/01.CIR.0000070422.41439.04

92. Gheorghaide M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA.* 2004;291:1963–1971. doi: 10.1001/jama/291.16.1963

93. Gheorghaide M, Konstam MA, Burnett JC Jr, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA.* 2007;297:1332–1343. doi: 10.1001/jama.297.12.1332

94. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA.* 2007;297:1319–1331. doi: 10.1001/jama.297.12.1319

95. Hauptman PJ, Burnett J, Gheorghiade M, et al. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. *J Card Fail.* 2013;19:390–397. doi: 10.1016/j.cardfail.2013.04.001

96. Udelson JE, McGrew FA, Flores E, et al. Multicenter, randomized, double-blind, placebo-controlled study on the effect of oral tolvaptan on left ventricular dilation and function in patients with heart failure and systolic dysfunction. *J Am Coll Cardiol.* 2005;49:2151–2159. doi: 10.1016/j.jacc.2007.01.091

97. Heidenreich PA, Bozkurt B, Bozkurt D, et al. 2022 AHA/ACC/HFSA Guidelines for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895–e1032. doi: 10.1161?CIR.0000000000001063.

98. Hoorn EJ, Zietse R. Diagnosis and treatment of hyponatremia: compilation of the guidelines. *J Am Soc Nephrol.* 2017;28:1340–1349. doi: 10.1681/ASN.2016101139

99. Adams KF. Tolvaptan treatment to reverse worsening outpatient heart failure: possible role of copeptin in identifying responders (TROUPER). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000. https://clinicaltrials.gov/ct2/show/NCT02476409, NLM Identifier: NCT02476409. Accessed January 17, 2022.

100. Goldsmith SR. Is there a cardiovascular rationale for the use of combined vasopressin V1a/V2 receptor antagonists? *Am J Med.* 2006;119(7 Suppl 1):S93–S96. doi: 10.1016/j.amjmed.2006.05.015

101. Al-Absi A, Gosmanova EO, Wall BM. A clinical approach to the treatment of chronic hypernatremia. *Am J Kidney Dis.* 2012;60:1032–1038. doi: 10.1053/j.ajkd.2012.06.025

102. Overgaard-Steensen C, Ring T. Clinical review: practical approach to hyponatraemia and hypernatraemia in critically ill patients. *Crit Care*. 2013;17:206. doi: 10.1186/cc11805

103. Waite MD, Fuhrman SA, Badawi O, et al. Intensive care unit-acquired hypernatremia is an independent predictor of increased mortality and length of stay. *J Crit Care*. 2013;28:405–412. doi: 10.1016/j.jcrc.2012.11.013

104. Stelfox HT, Ahmed SB, Khandwala F, et al. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. *Crit Care*. 2008;12:R162. doi: 10.1186/cc7162

105. Mestrom EHJ, van der Stam JA, te Pas ME, et al. Increased sodium intake and decreased sodium excretion in ICU-acquired hypernatremia: a prospective cohort study. *J Crit Care*. 2021;63:68–75. doi: 10.1016/j.jcrc.2021.02.002

106. Rugg C, Schmid S, Kreutiziger J, et al. The lack of free water on ICU: mere fluid-balances are not enough with regard to hypernatremia. *J Crit Care*. 2021;65:232–234. doi: 10.1016/j.jcrc.2021.07.001

107. Lansink-Hartgring AO, Hessels L, Weigel J, et al. Long-term changes in dysnatremia incidence in the ICU: a shift from hyponatremia to hypernatremia. *Ann Intensive Care*. 2016:6:22. doi: 10.1186/s13613-016-0124-x

108. Hoorn EJ, Betjes MG, Weigel J, et al. Hypernatremia in critically ill patients: Too little water and too much salt. *Nephrol Dial Transplant*. 2008;23:1562–1568. doi: 10.1093/ndt/gfm831

109. van Regenmortel N, Moers L, Langer T, et al. Fluid-induced harm in the hospital: look beyond volume and start considering sodium. From physiology towards recommendations for daily practice in hospitalized adults. *Ann Intensive Care*. 2021;11:79. doi: 10.1186/s13613-021-00851-3

110. Moritz ML, Ayus JC. The changing pattern of hypernatremia in hospitalized children. *Pediatrics*. 1999;104:435–439. doi: 10.1542/peds.104.3.435

111. Lindner G, Funk GC. Hypernatremia in critically ill patients. *J Crit Care*. 2013;28:216.e11-20. doi: 10.1016/j.jcrc.2012.05.001

112. Qian Q. Hypernatremia. *Clin J Am Soc Nephrol.* 2019;14:432–444. doi: 10.2215/CJN.12141018

113. Buckley MS, Leblanc JM, Cawley MJ. Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit. *Crit Care Med.* 2010;38(6 Suppl):S253–S264. doi: 10.1097/CCM.0b01333181dda0be

114. Chassagne P, Druesne L, Capet C, et al. Clinical presentation of hypernatremia in elderly patients: a case control study. *J Am Geriatr Soc.* 2006;54:1225–1230. doi: 10.1111/j.1532-5415.2006.00807.x

115. Saifan C, Nasr R, Mehta S, et al. Diabetes insipidus: a challenging diagnosis with new drug therapies. *ISRN Nephrol.* 2013:797620. doi: 10.5402/2013/797620

116. Moritz ML. A water deprivation test is not indicated in the evaluation of hypernatremia [letter]. *Am J Kidney Dis.* 2005;46:1150–1151. doi: 10.1053/j.ajkd.2005.09.018

117. Feld LG, Neuspiel DR, Foster BA, et al. Clinical practice guideline: maintenance intravenous fluids in children. *Pediatrics*. 2018;142:e20183083. doi: 10.1542/peds.2018-3083

118. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med.* 2018;378:829–839. doi: 10.1056/NEJMoa1711584

119. Shah A, Ellis G, Kucheria R. A guide for the assessment and management of post-obstructive diuresis. *Urology News*. 2015; March 1. https://www.urologynews.uk.com/features/features/post/a-guide-for-the-assessment-and-management-of-post-obstructive-diuresis. Accessed January 17, 2022.

120. Reynolds RM, Padfield PL, Seckl JR. Disorders of sodium balance. *BMJ.* 2006;332:702–705. doi: 10.1136/bmj.332.6543.702

121. Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. *Nat Rev Nephrol.* 2015;11:576–588. doi: 10.1038/nrneph.2015.89

122. Downie ML, Gallibois C, Parekh RS, et al. Nephrotic syndrome in infants and children: pathophysiology and management. *Paediatr Int Child Heal.* 2017;37:248–258. doi: 10.1080/20469047.2017.1374003

123. Kallash M, Mahan JD. Mechanisms and management of edema in pediatric nephrotic syndrome. *Pediatr Nephrol.* 2021;36:1719–1730. doi: 10.1007/s00467-020-04779-x

124. Fortune B, Cardenas A. Ascites, refractory ascites and hyponatremia in cirrhosis. *Gastroenterol Report*. 2017;5:104–112. doi: 10.1093/gastro/gox010

125. Rysz J, Franczyk B, Rysz-Górzyńska, et al. Pharmacogenomics of hypertension treatment. *Int J Mol Sci.* 2020;21:4709. doi: 10.3390/ijms21134709

126. Agarwal R, Gorski JC, Sundblad K, et al. Urinary protein binding does not affect response to furosemide in patients with nephrotic syndrome. *J Am Soc Nephrol.* 2000;11:1100–1105. doi: 10.1681/ASN.V1161100

127. Siddall EC, Radhakrishnan J. The pathophysiology of edema formation in the nephrotic syndrome. *Kidney International*. 2012;82:635–642. doi: 10.1038/ki.2012.180

128. Somberg JC, Molnar J. Therapeutic approaches to the treatment of edema and ascites: the use of diuretics. *Am J Ther.* 2009:16:98–101. doi: 10.1097/MJT.0b013e318196082e

129. Nappi JM, Sieg A. Aldosterone receptor antagonists in patients with chronic heart failure. *Vasc Heal Risk Manag.* 2011;7:353–363. doi: 10.2147/VHRM.S13779

SELF-ASSESSMENT QUESTIONS

1. A 76-year-old woman (weight, 65 kg; height, 170 cm) has been hospitalized for a few days. Her laboratory results this morning reveal a serum sodium of 110 mEq/L [mmol/L]. What is this patient's sodium deficit (note: use 120 mEq/L [mmol/L] as the desired safe serum sodium concentration)?

   A. 278 mEq (mmol)

   B. 293 mEq (mmol)

   C. 732 mEq (mmol)

   D. 878 mEq (mmol)

2. Which of the following is the appropriate *initial* treatment for a patient with nephrogenic DI?

   A. Amiloride

   B. Furosemide

   C. Enteral water

   D. 0.9% NaCl

3. An adult patient was initiated on bumetanide approximately 1 week ago. During a follow-up appointment, she is noted to be confused, lethargic, and weak. Vital signs are taken and she is found to be hypotensive, tachycardic, and orthostatic. Laboratory studies are sent, and the serum sodium is reported as 159 mEq/L (mmol/L). Which of the following is the *most appropriate* initial intravenous fluid to administer to this patient?

   A. 0.9% NaCl

   B. Dextrose 5% in water

   C. 3% NaCl

   D. 0.45% NaCl

4. An adult patient with type 1 diabetes mellitus is admitted with a serum glucose concentration of 990 mg/dL (54.9 mmol/L) and a serum sodium concentration of 124 mEq/L (mmol/L). What is the *best* estimate of the patient's serum sodium concentration corrected for hyperglycemia?

   A. 109 mEq/L (mmol/L)

   B. 132 mEq/L (mmol/L)

   C. 139 mEq/L (mmol/L)

   D. 154 mEq/L (mmol/L)

5. An adult patient is admitted with a severe metabolic acidosis secondary to diarrhea. The patient is administered sodium bicarbonate to correct the acidosis. Excessive sodium bicarbonate administration could result in which of the following sodium disorders?

   A. Hypovolemic hypernatremia

   B. Euvolemic hypernatremia

   C. Hypervolemic hypernatremia

   D. Hypervolemic hyponatremia

6. What are the usual determinants of serum osmolality?

   A. Serum sodium, glucose, and blood urea nitrogen concentrations

   B. Serum sodium, potassium, and glucose concentrations

   C. Serum potassium, bicarbonate, and glucose concentrations

   D. Serum sodium, bicarbonate, and blood urea nitrogen concentrations

7. A 75-year-old woman (weight, 60 kg) is hospitalized after suffering a stroke. Her serum sodium concentration has been trending downward since admission (baseline 137 mEq/L [mmol/L]; third hospital day 121 mEq/L [mmol/L]). Upon physical examination, she has good skin turgor, no lower extremity edema, and appears hydrated. The medical team is considering the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or cerebral salt wasting syndrome among their differential diagnoses. Which of the following is *most helpful* in differentiating between these two diagnoses?

   A. Serum sodium concentration

   B. Serum osmolality

   C. Serum antidiuretic hormone concentration

   D. Urine sodium concentration

8. The medical intern asks your assistance in developing a treatment plan for a patient with severe hyponatremia who is seizing. The serum sodium concentration is 110 mEq/L (mmol/L), which is felt to be an acute change from baseline based on laboratory values from the previous day. An order is placed for an initial dose of 3% NaCl. Which sodium concentration below represents the maximum sodium increase recommended in the *first one hour* of treatment in this setting?

   A. 111 mEq/L (mmol/L)

   B. 113 mEq/L (mmol/L)

   C. 115 mEq/L (mmol/L)

   D. 120 mEq/L (mmol/L)

9. A 48-year-old woman with a history of heart failure with reduced ejection fraction (left ventricular ejection fraction 25% [0.25]) presents to clinic for routine follow-up. She has increased lower extremity edema and has experienced an 8-lb (3.6 kg) weight gain over the previous 2 weeks. She reports no dietary indiscretions and is adherent to her guideline-directed medical therapy. Her serum creatinine is at baseline (1.1 mg/dL [97 µmol/L]). She is taking furosemide 120 mg orally three times daily at home. Which of the following is the *most appropriate* outpatient intervention?

   A. Continue the current furosemide dose

   B. Increase furosemide to 240 mg orally three times daily for the next 2 days

   C. Initiate metolazone 5 mg orally before the first furosemide dose each morning

   D. Initiate furosemide 40 mg IV every 4 hours

10. A 24-year-old construction worker (weight, 70 kg; no significant past medical history) experiences a syncopal episode on the roof of a new apartment building on a hot summer day (100°F [37.8°C]). He presents to the emergency department with a BP of 76/30 mm Hg, HR of 138 bpm, and significant orthostasis. His serum sodium is 164 mEq/L (mmol/L). Which of the following is the *most appropriate* initial intervention?

    A. A 500-mL IV bolus of Dextrose 5% in water (D_5W) over 30 minutes

    B. A 750-mL bolus of oral rehydration solution ingested over 4 hours

    C. A 1,000-mL IV bolus of 0.9% NaCl over 30 minutes

    D. A 1,000-mL IV bolus of Dextrose 5%/0.45% NaCl over 30 minutes

11. Spironolactone reaches its site of action in the cortical collecting duct via which of the following processes?

    A. Diffusion from the systemic circulation

    B. Active secretion by proximal tubular cells

    C. Glomerular filtration by proximal tubular cells

    D. Reabsorption by proximal tubular cells

12. Which of the following is the most appropriate *maintenance* fluid for adults to avoid the occurrence of iatrogenic hypernatremia?

    A. Dextrose 5%/0.45% NaCl with 20 mEq (mmol) KCl/L

    B. Dextrose 5%/0.2% NaCl with 20 mEq (mmol) KCl/L

    C. Dextrose 5%/0.9% NaCl with 20 mEq (mmol) KCl/L

    D. Lactated Ringer's solution

13. A 26-year-old (NKDA) who takes lithium 1,200 mg daily presents to clinic with a serum sodium concentration of 145 mEq/L (mmol/L) and complaints of excessive urination over the previous few days. The patient's psychiatrist recommends continuing the lithium due to the patient's treatment-resistant bipolar disorder. Which of the following is the most appropriate recommendation for this patient?

    A. Indomethacin 50 mg by mouth twice daily

    B. Amiloride 5 mg by mouth daily

    C. Sodium restriction to 4,000 mg NaCl per day

    D. Demeclocycline 300 mg by mouth three times daily

14. How will the administration of 1,800-mL of D5/0.45% NaCl change the extracellular fluid (ECF) and intracellular fluid (ICF) compartment volumes?

    A. Increase the ECF by 1,800 mL

    B. Increase the ECF and ICF by 900 mL each

    C. Increase the ECF by 1,200 mL and the ICF by 600 mL

    D. Increase the ECF by 1,500 mL and the ICF by 300 mL

15. A 32-year-old pregnant woman is admitted to the hospital with nausea and disorientation. She is diagnosed with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The patient's serum sodium has decreased from 130 mEq/L (mmol/L) to 118 mEq/L (mmol/L), and she is becoming increasingly confused and somnolent. The patient has a history of anaphylaxis when receiving a sulfa-containing medication. Which of the following is the *most appropriate* treatment to initiate in this patient?

    A. Demeclocycline 300 mg by mouth three times daily

    B. Dietary sodium restriction to 2,000 mg/day

    C. Furosemide 40 mg by mouth twice daily

    D. Tolvaptan 15 mg by mouth daily

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Sodium deficit is calculated using the following equation: Na deficit (mEq or mmol) = $[(Na_D - Na_S) \times TBW]$, where Na_D is the goal or desired serum sodium; Na_S is the patient's current serum sodium concentration; and, TBW is the patient's currently estimated total body water. For a woman older than 70 years, TBW is estimated to be 0.45 L/kg × actual weight (kg) so the Na deficit = (120 – 110) × (65 × 0.45) = 293 mEq (mmol).

2. **C.** Patients with nephrogenic DI produce large amounts of hypotonic urine (essentially free water) due to a decreased kidney response to AVP. Patients should receive hypotonic fluids to avoid excess NaCl intake and worsening hypernatremia. Enteral water or milk is preferred, but intravenous D5W or other hypotonic fluid can be given if necessary depending on the severity of the hypernatremia and water loss. Thiazide diuretics or indomethacin may be given as adjunctive therapy to dietary sodium restriction and hypotonic fluids; however, loop diuretics are not recommended.

3. **A.** Patients with hypovolemic hyponatremia should be treated initially with an isotonic fluid (ie, 0.9% NaCl, lactated Ringer's) which will remain in the ECF until they are hemodynamically stable. Once the intravascular volume is restored, hypotonic fluids (ie, 0.45% NaCl, D_5W) may be administered to restore the ICF volume.

4. **C.** Hyperglycemia can cause hypertonic hypovolemic hyponatremia by increasing the effective osmoles in the ECF. Based on the volume of distribution of glucose, a 1.5 to 1.9 mEq/L (mmol/L; mean, 1.7 mEq/L [mmol/L]) increase in the serum sodium concentration for every 100 mg/dL

(5.6 mmol/L) decrease in the serum glucose concentration to 100 mg/dL (5.6 mmol/L) can be predicted. Thus, the predicted serum sodium concentration would be: (990-100/100 × 1.7) + 124 = 139 mEq/L (mmol/L). Or for results expressed in SI units ((54.9-5.6)× 0.29) + 124 = 138 mmol/L, which is remarkably similar for the two equations.

5. **C.** Hypertonic fluid administration and sodium-containing medications like sodium bicarbonate can result in hypernatremia and an expanded ECF volume. Sodium bicarbonate provides 1 mEq sodium for each 1 mEq bicarbonate infused. The sodium load can be excessive if treating a severe metabolic acidosis. Even slightly hypertonic, sodium-containing solutions (ie, 0.9% NaCl, lactated Ringer's) can lead to sodium accumulation, particularly if a dilute urine is excreted.

6. **A.** The primary determinant of serum osmolality is the sodium concentration; however, glucose and blood urea nitrogen also contribute to serum osmolality and are included in the equation for estimating serum osmolality. Serum osmolality can be estimated as: $Osm_S = (2 \times Na_S) + (glucose_S/18) + (BUN/2.8)$, where Osm_S is the serum osmolality in mOsm/kg; Na_S is the serum sodium concentration in mEq/L; $glucose_S$ is the serum glucose concentration in mg/dL; and BUN is the blood urea nitrogen concentration in mg/dL. Serum osmolality can also be estimated as: $Osm_S = (2 \times Na_S) + (glucose_S) + (BUN)$, where Osm_S is the serum osmolality in mmol/kg; Na_S is the serum sodium concentration in mmol/L; $glucose_S$ is the serum glucose concentration in mmol/L; and BUN is the blood urea nitrogen concentration in mmol/L.

7. **D.** The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt wasting (CSW) syndrome can both occur in patients with intracranial disorders. Both SIADH and CSW result in hypotonic hyponatremia with a low serum osmolality and high urine osmolality and cannot be differentiated by the serum sodium concentration. CSW will result in a significantly high urine output and high urine sodium concentration (>20 mEq/L [mmol/L]); however, patients with SIADH will have a lower urine output and a variable urine sodium concentration depending on the severity. Additionally, patients with SIADH will be euvolemic, whereas those with CSW will be hypovolemic; thus, appropriate volume assessment is important. Serum ADH levels can be primarily high with SIADH or rise secondary to volume depletion with CSW.

8. **C.** In patients with acute severe symptoms (eg, seizures) related to hyponatremia, the serum sodium concentration should be increased with 3% NaCl by no more than 5 mEq/L (mmol/L) in the first hour of treatment. The goal should be to increase the serum sodium concentration by no more than 8 to 12 mEq/L (mmol/L) during the first 24 hours but treatment will need to be continued until acute, life-threatening symptoms resolve.

9. **C.** The patient needs more aggressive diuresis due to her lower extremity edema and significant 2-week weight gain. The patient likely is experiencing diuretic resistance due to chronic dosing; therefore, adding a thiazide-like diuretic like metolazone for sequential nephron blockade is appropriate. While it is possible to increase the furosemide oral dose, 600 mg is the maximum recommended total daily dose. The frequency of furosemide administration could also be increased, but this change would likely lead to adherence issues. Continuing the current regimen would be inappropriate now. Intravenous furosemide is not a reasonable option for outpatient therapy, and there were no symptoms presented worrisome enough to warrant hospitalization now.

10. **C.** In patients with hypovolemic hypernatremia who are severely dehydrated, volume resuscitation with IV lactated Ringer's or 0.9% NaCl at a rate of 1,000 mL or 20 mL/kg given over 30 minutes can be given until the patient is hemodynamically stable and mental status improves. Oral therapy is inappropriate in a hemodynamically unstable patient. Once intravascular volume is restored, 0.45% NaCl, D_5W, or another hypotonic fluid can be infused to correct the water deficit.

11. **A.** Spironolactone gains access to mineralocorticoid receptors in the cortical collecting duct through diffusion from the systemic circulation. Osmotic diuretics are freely filtered into the tubular lumen in the proximal tubule; whereas, thiazide and loop diuretics are delivered to the tubular lumen via active transport by the proximal tubular cells.

12. **A.** Recurrent iatrogenic hypernatremia can be prevented by avoiding infusing too much hypertonic solution, providing adequate amounts of *maintenance* fluids, and replacing ongoing abnormal losses. The standard maintenance fluid for adults is Dextrose 5%/0.45% NaCl with 20 mEq (mmol) KCl/L. Isotonic maintenance fluids may be appropriate for some patients but increase the risk of hypernatremia, volume overload, and metabolic acidosis (due to the chloride load).

13. **B.** Lithium should be discontinued, if possible, in patients with lithium-induced nephrogenic diabetes insipidus. When discontinuation is not possible, the concomitant use of the potassium-sparing diuretic amiloride is recommended. Serum lithium concentrations should be carefully monitored in patients taking amiloride because diuretic-induced volume depletion may increase lithium reabsorption and cause supratherapeutic

levels.

14. **C.** A 0.45% NaCl solution will distribute as follows: 67% within the extracellular fluid (ECF) and 33% within the intracellular fluid (ICF). The fact that it is called “half normal saline” can be misleading if you think that half goes into the ICF and half stays in the ECF. The sodium in 0.45% NaCl (half of that in 0.9% NaCl, 77 mEq/L [mmol/L]) will stay in the ECF compartment keeping 50% of the water with it (900 mL). The remaining 900 mL has no sodium to keep it in the ECF, so it will distribute 33% into the ECF (300 mL) and 67% into the ICF (600 mL). The resulting distribution is 1,200 mL in the ECF and 600 mL within the ICF. Dextrose does not affect the fluid distribution because in low concentrations it freely passes through the cell membranes and is not an effective osmole.

15. **D.** Usual treatment for SIADH includes water restriction with demeclocycline, loop diuretics, and vasopressin receptor antagonists (VRAs) being added in patients whose sodium concentration does not respond adequately to water restriction or in whom adherence with water restriction is challenging. Demeclocycline should not be used during pregnancy or in children younger than 8 years. Furosemide should not be given to this patient due to her history of anaphylaxis with a sulfa-containing medication. In addition to water restriction, a VRA would be an appropriate choice for this patient.