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Common Electrolyte Disorders: Hyponatremia

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A 75-year-old man with a past medical history significant for hypertension, diabetes mellitus, dyslipidemia, and depression presented with headache, severe nausea, and confusion. His medications included amlodipine, metformin, atorvastatin, and duloxetine. On physical examination, he appeared euvolemic and was alert and oriented only to person. Laboratory studies revealed a plasma sodium level of 120 mEq/L, plasma glucose level of 240 mg/dL, plasma osmolality of 270 mOsm/kg, urine sodium level of 45 mEq/L, urine osmolality of 350 mOsm/kg, and a thyroid-stimulating hormone level within normal limits. The patient was diagnosed with the syndrome of inappropriate antidiuresis, likely secondary to recent initiation of the selective serotonin reuptake inhibitor duloxetine, which was discontinued during his hospital stay. The patient was treated with hypertonic saline, followed by loop diuretics, and then isotonic saline. He was maintained on free water restriction throughout treatment. His mental status returned to baseline by day 3. He was subsequently discharged with instructions to discontinue duloxetine and follow-up with his psychiatrist to consider an alternative medication.

Hyponatremia represents an abnormal ratio of total body sodium to water and is commonly defined as a plasma sodium concentration less than 135 mEq/L (1 mEq/L = 1 mmol/L).[1–7] Hyponatremia is the most common electrolyte abnormality in hospitalized patients, with mild hyponatremia (plasma sodium < 135 mEq/L) present in approximately 15% to 22% of patients, moderate hyponatremia (< 130 mEq/L) present in 1% to 7% of patients, and severe hyponatremia (< 120 mEq/L) present in less than 1% of patients.[8,9] Several populations are at increased risk of developing hyponatremia, including intensive care unit, postoperative, psychiatric, elderly, and nursing home patients.[10–14] This article reviews the diagnostic and management approach to hyponatremia.

ETIOLOGY AND PATHOGENESIS

The kidney has the unique ability to eliminate free water and dilute urine to maintain homeostasis. Rarely does ingestion of excess water cause hyponatremia, as individuals with normal kidney function can eliminate up to 20 to 30 L of free water daily.[15] Hyponatremia typically develops in the context of an underlying disruption of free water elimination, usually as a result of arginine vasopressin (AVP) release or renal failure. AVP, also known as antidiuretic hormone, is a peptide hormone produced by the hypothalamus and transported via axons to the posterior pituitary, from which it is released. AVP is primarily responsible for regulating osmotic homeostasis of body fluids, but it also plays a minor role in volume homeostasis, acting mostly through vasopressin type 1A (V_{1A}) and type 2 (V_2) receptors (activity through $V_2 >> V_{1A}$).[16–18] AVP receptor activation causes a decrease in excretion of free water. Most total body sodium is extracellular and thus is a primary determinant of plasma tonicity. An increase in plasma tonicity stimulates the thirst center to increase fluid consumption and causes release of AVP. Dysregulation of AVP can be caused by both osmotic and nonosmotic mechanisms. Four major types of AVP release have been described in response to hypertonic saline infusion (**Table 1**).[19,20]

AVP release is normally regulated by osmoreceptors

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TAKE HOME POINTS

- Hyponatremia is a disorder of the balance between total body water and sodium.
- Factitious hyponatremia is an effective decrease in plasma sodium concentration that is most commonly caused by hyperglycemia; correct by adding 2.4 mEq/L to measured plasma sodium for each 100 mg/dL increase in plasma glucose over 150 mg/dL.
- Pseudohyponatremia is an artifact due to excess plasma protein and/or lipid with a gap of at least 10 mOsm/kg between calculated [(2Na) + (Blood urea nitrogen/2.8) + (Glucose/18)] and measured plasma osmolality.
- Determination of volume status is key in evaluation of hypotonic hyponatremia.
- Symptomatic hypotonic hyponatremia can be treated with hypertonic saline (severe cases) or isotonic saline (mild to moderate cases) with expert consultation.
- Asymptomatic hypervolemic and euvolemic hypotonic hyponatremia are often treated with free water restriction with or without diuretics; asymptomatic hypovolemic hypotonic hyponatremia is often treated with isotonic saline.

and baroreceptors in the central nervous and cardiopulmonary systems. Disorders that affect these systems as well as tumors, drugs, and conditions that increase AVP release or otherwise mimic its activity may result in antidiuresis.[20,21] Endogenous AVP production can be either eutopic (ie, pituitary) or ectopic (eg, tumor). Eutopic pituitary production is stimulated by a number of drugs as well as disease or injured states. Exogenous administration of synthetic AVP (ie, desmopressin) or drugs that mimic its activity (eg, oxytocin) can cause antidiuresis. With respect to AVP release, preservation of intravascular volume outweighs maintenance of normal serum osmolality. This is an important concept when distinguishing between appropriate and inappropriate AVP release in hyponatremia. AVP release would be considered appropriate in the setting of increased effective plasma osmolality and vascular volume contraction, while release in the setting of low effective plasma osmolality would be considered inappropriate.[22] For example, in congestive heart failure (CHF) effective plasma osmolality may be low while extracellular fluid volume is expanded, yet AVP release can be appropriate if effective intravascular volume is sensed by baroreceptors as inadequate.

Table 1. Types of Arginine Vasopressin Release in Response to Hypertonic Saline Infusion

Type A	Random (20% of patients) Abnormal, high, erratic release Release unrelated to increasing plasma osmolality Associated with tumors
Type B	Reset osmostat syndrome (35% of patients) Abnormal, rapid, progressive release Release closely related to increasing plasma osmolality until near normal range
Type C	Leak (35% of patients) Abnormal, low, persistent release at low plasma osmolality Release unrelated to increasing plasma osmolality
Type D	Normal (10% of patients) Normal osmoregulated release

NOTE: Hypertonic saline is 3% saline in water.

DIAGNOSIS

Clinical Manifestations

The clinical manifestations of hyponatremia are largely due to osmotic swelling of brain cells, resulting in neurologic and systemic symptoms.[23–25] With chronic conditions (eg, CHF, hepatic cirrhosis), patients may be asymptomatic because of cellular adaptation via shifting of solutes and organic osmolytes to maintain osmolar gradients and protect from cerebral edema. With more acute manifestations (eg, postoperative, drug-induced), there is a wide range of nonspecific symptoms. Early symptoms are often subtle, such as anorexia, cramping, nausea, vomiting, headache, irritability, disorientation, confusion, weakness, and lethargy, whereas later symptoms can be more profound, such as severe mental status changes, seizure, coma, and respiratory arrest, possibly culminating in death.[23–26] When neurologic manifestations of hyponatremia are profound, they are sometimes referred to collectively as *hyponatremic encephalopathy.*

Clinical Evaluation

Hyponatremia is classified based on plasma osmolality as determined by laboratory evaluation and volume status as determined by physical examination (**Table 2**). A systematic approach to determine the underlying cause and direct therapy is indicated (**Table 3**). Traditional approaches involve measurement of plasma osmolality, assessment of volume status, and measurement of urine sodium concentration and osmolality.[27–29] Plasma osmolality, a measure of plasma tonicity, is first used to rule out

Table 2. Overall Classification of Hyponatremia

Hypertonic hyponatremia (ie, factitious hyponatremia)
Isotonic hyponatremia (ie, pseudohyponatremia)
Hypotonic hyponatremia (ie, "true" hyponatremia)
Hypervolemic hypotonic hyponatremia
Euvolemic hypotonic hyponatremia
Hypovolemic hypotonic hyponatremia

NOTE: Classification is based on plasma osmolality and volume status determined by physical examination.

factitious hyponatremia (ie, hypertonic hyponatremia, > 295 mOsm/kg) and pseudohyponatremia (ie, isotonic hyponatremia, 280–295 mOsm/kg). The remaining patients with decreased plasma osmolality (ie, hypotonic hyponatremia, < 280 mOsm/kg) require accurate clinical assessment of their volume status. However, plasma osmolality measurement may be inaccurate and should not be solely relied upon for treatment decisions.[30] Although the rate of sodium excretion rather than the urine sodium concentration would be most helpful in narrowing the differential diagnosis, the urine sodium concentration is most often used.

Volume status is determined clinically as either hypervolemic, euvolemic, or hypovolemic and is critical for accurate diagnosis and subsequent management.[27–29] Major clinical indicators of hypervolemia include edema, lung crackles, distended neck veins, and a third heart sound. Major clinical indicators of hypovolemia include orthostatic hypotension, tachycardia, and oliguria or anuria. Absence of clinical indicators of hypervolemia or hypovolemia is consistent with a state of euvolemia. Close monitoring and serial reevaluation are also strongly recommended.

CLASSIFICATION OF HYPONATREMIA

Hypertonic Hyponatremia

Hyponatremia with plasma osmolality exceeding 295 mOsm/kg (ie, hypertonic or hyperosmolar hyponatremia) suggests factitious hyponatremia secondary to hyperglycemia or administration of other osmotically active substances such as mannitol.[31] Factitious hyponatremia represents a true decrease in effective plasma sodium concentration caused by osmotically active extracellular glucose or mannitol drawing water into the plasma from the intracellular space. Hyperglycemia is the most common cause of factitious hyponatremia, generating a 1.6 to 2.4 mEq/L apparent decrease in plasma sodium for each 100 mg/dL increase in plasma glucose above 150 mg/dL.[6] Moreover, evidence suggests that 2.4 mEq/L may represent a more accurate correction factor.[32]

Table 3. Clinical Approach to Diagnosis and Management of Hyponatremia

Step 1. Careful history and physical examination (including assessment of volume status)	
Step 2. Measure plasma osmolality	
Hypertonic	Factitious hyponatremia (P_{Osm} > 295 mOsm/kg)
Isotonic	Pseudohyponatremia (P_{Osm} 280–295 mOsm/kg)
Hypotonic	"True" hyponatremia (P_{Osm} < 280 mOsm/kg)
Step 3. Measure urine sodium and osmolality (then apply volume status information)	
Hypervolemic hypotonic hyponatremia	
U_{Na} > 20 mEq/L or FE_{Na} > 1%	Azotemia (advanced renal failure)
U_{Na} < 20 mEq/L or FE_{Na} < 1%	Edema (CHF, cirrhosis, nephrotic syndrome)
Euvolemic hypotonic hyponatremia	
U_{Osm} < 100 mOsm/kg	Psychogenic (primary) polydipsia Low-solute (beer) potomania
U_{Osm} > 100 mOsm/kg	Increased AVP or mimic Syndrome of inappropriate antidiuresis Endocrinopathies
U_{Osm} variable	Reset osmostat syndrome
Hypovolemic hypotonic hyponatremia	
U_{Na} > 20 mEq/L or FE_{Na} > 1%	Renal sodium losses (primary natriuresis)
U_{Na} < 20 mEq/L or FE_{Na} < 1%	Extrarenal sodium losses (with free water replacement)
Step 4. Initiate treatment	
Hypertonic hyponatremia	Treat underlying hyperglycemia Discontinue osmotically active substances
Isotonic hyponatremia	Laboratory artifact or post-TURP Treat underlying protein or lipid disorder
Hypotonic hyponatremia	Fluids ± diuretics, free water restriction Consider pharmacotherapy (see Table 7)
Step 5. Reassess and adjust treatment	

AVP = arginine vasopressin; CHF = congestive heart failure; FE_{Na} = fractional excretion of sodium; P_{Osm} = plasma osmolality in mOsm/kg; TURP = transurethral resection of the prostate; U_{Na} = urine sodium concentration in mEq/L; U_{Osm} = urine osmolality in mOsm/kg.

Isotonic Hyponatremia

Hyponatremia with normal plasma osmolality of 280 to 295 mOsm/kg (ie, isotonic or isoosmolar hyponatremia) suggests pseudohyponatremia, a laboratory artifact seen in hyperproteinemia and hyperlipidemia whereby lipids (ie, chylomicrons and triglycerides but not cholesterol) and/or protein (> 10 g/dL) occupy plasma volume but do not contribute to plasma osmolality, causing an apparent decrease in the amount of sodium per unit volume when measured by indirect

Table 4. Causes of Hypotonic Hyponatremia Differentiated by Volume Status

Hypervolemic	Euvolemic	Hypovolemic
Azotemic state	**More dilute urine**	**Renal sodium losses** (primary natriuresis)
U_{Na} > 20 mEq/L or FE_{Na} > 1%	*U_{Osm} < 100 mOsm/kg*	*U_{Na} > 20 mEq/L or FE_{Na} > 1%*
Advanced renal failure	Psychogenic polydipsia (primary polydipsia)	Diuretics
Edematous states	Low-solute potomania: beer (alcohol) potomania,* tea and toast diet	Osmotic diuresis
U_{Na} < 20 mEq/L or FE_{Na} < 1% (without diuretics)	**Less dilute urine** (increased AVP or mimic)	Metabolic alkalosis
Congestive heart failure	*U_{Osm} > 100 mOsm/kg*	Salt-losing nephropathies: type II RTA, polycystic kidney disease, obstructive uropathy
Hepatic cirrhosis	SIAD:† SIADH, NSIAD	Adrenal insufficiency: hypocortisolism, hypoaldosteronism
Nephrotic syndrome	Endocrinopathies: hypothyroidism, hypocortisolism	Cerebral salt-wasting syndrome
	Variably dilute urine	**Extrarenal sodium losses** (with free water replacement)
	U_{Osm} variable	*U_{Na} < 20 mEq/L or FE_{Na} < 1% (without diuretics)*
	Reset osmostat syndrome	Gastrointestinal: vomiting, diarrhea
		Fluid sequestration: peritonitis, pancreatitis
		Insensible: sweat, burns

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ADH = antidiuretic hormone; AVP = arginine vasopressin; FE_{Na} = fractional excretion of sodium; NSIAD = nephrogenic syndrome of inappropriate antidiuresis; RTA = renal tubular acidosis; SIAD = syndrome of inappropriate antidiuresis; SIADH = syndrome of inappropriate ADH secretion; U_{Na} = urine sodium concentration in mEq/L; U_{Osm} = urine osmolality in mOsm/kg.

*Beer (alcohol) potomania results from increased intake of a low-solute fluid and should be distinguished from alcoholism, which can cause hyponatremia by other mechanisms.

†Elevated levels of ADH (AVP) are not an essential feature of antidiuresis.

methods.[6,33] This condition is further characterized by a gap of 10 mOsm/kg or more between calculated [(2Na) + (Blood urea nitrogen/2.8) + (Glucose/18)] and measured plasma osmolality due to the presence of excess plasma protein and/or lipid detected by laboratory measurement but not included in the calculation of plasma osmolality.[6] Many laboratories now measure plasma sodium directly using ion-specific electrodes, thus eliminating this artifact. A new method has been developed to directly measure sodium activity independent of the fraction of plasma volume occupied by water, representing a significant advancement in laboratory technology.[34]

Isotonic hyponatremia has also been reported after transurethral resection of the prostate (TURP). The *post-TURP syndrome* can produce hyponatremia, coma, blindness, and cardiorespiratory depression and is believed to be caused by absorption of large volumes of osmotically active solutions (eg, isotonic or hypotonic solutions such as sorbitol, mannitol, glycine) used for bladder irrigation, resulting in dilutional hyponatremia.[35]

Hypotonic Hyponatremia

Hyponatremia with plasma osmolality less than 280 mOsm/kg (ie, hypotonic or hypoosmolar hyponatremia) represents "true" hyponatremia, and assessment of volume status is required to further narrow the differential of underlying causes and direct therapy.[1–7,27–29]

Hypervolemic hypotonic hyponatremia. Hypervolemic hypotonic hyponatremia results from an increase in total body water and can be further differentiated based on urine sodium concentration (**Table 4**).[1–7,29,36] Hypervolemic patients with a urine sodium level exceeding 20 mEq/L or fractional excretion of sodium (FE_{Na}) exceeding 1% typically have advanced renal failure. Hypervolemic patients with urine sodium less than 20 mEq/L or FE_{Na} less than 1% typically suffer from edematous states, including CHF, cirrhosis, and nephrotic syndrome.

Hyponatremia in the presence of edema indicates an increase in total body water that is greater than total body sodium. However, it is important to note that CHF and cirrhosis represent states of effective circulating volume depletion.[36,37] Sodium and water retention in edematous disorders are likely due to nonosmotic, baroreceptor-mediated AVP release and activation of the renin-angiotensin-aldosterone system, which are responses aimed at maintaining tissue perfusion.[38]

Patients with nephrotic syndrome have similar reductions in effective intravascular volume.[37,39]

Euvolemic hypotonic hyponatremia. Euvolemic hypotonic hyponatremia is associated with a group of clinical syndromes that may be further differentiated based on urine osmolality, reflecting more, less, or variably dilute urine (Table 4). Euvolemia with urine osmolality less than 100 mOsm/kg suggests conditions such as psychogenic polydipsia and low-solute potomania.[1–7,29]

Psychogenic polydipsia (primary polydipsia) occurs most frequently among schizophrenic patients and is characterized by excessive water intake, often in excess of 10 L/day. Nonetheless, euvolemia is maintained by osmotic suppression of AVP release and renal excretion of free water.[40] Therefore, urine is appropriately dilute and osmolality is low (usually < 100 mOsm/kg). The mechanism of hyponatremia is unclear but may involve a reduction in the osmotic threshold for AVP release and dysregulation of the osmotic stimulus for thirst.[41] Moreover, typical antipsychotics have been reported to worsen polydipsia, favoring the use of atypical antipsychotics in these patients.[42]

Low-solute potomania is caused by excessive intake of low-solute fluids, resulting in euvolemic hypotonic hyponatremia. A classic example is alcohol potomania, a condition characterized by excessive intake of beer, which is low in solute (often < 5 mEq/L of sodium).[43] Low-solute fluids can cause or worsen hyponatremia, especially in alcoholic cirrhotic patients, who often have elevated circulating AVP and renal insufficiency. Both beer and non-beer low-solute potomania have been described, including cider potomania and the classic tea and toast diet.[43,44] Reset osmostat syndrome (variable urine osmolality) and cerebral salt-wasting syndrome (CSWS; high urine osmolality) have also been reported to cause hyponatremia in alcoholics.[43] However, potomania alone is usually insufficient to produce hyponatremia given the large capacity of the kidney to excrete free water. Therefore, some dysregulation or impairment in renal free water excretion is required for hyponatremia to develop in this setting.

Euvolemic hypotonic hyponatremia in patients with urine osmolality exceeding 100 mOsm/kg suggests conditions in which AVP levels are increased or its activity is mimicked, resulting in less dilute urine.[1–7,29] Such conditions include endocrinopathies and the syndrome of inappropriate antidiuresis (SIAD), of which the syndrome of inappropriate antidiuretic hormone (SIADH) secretion and the nephrogenic syndrome of inappropriate antidiuresis (NSIAD) are subsets.[21,45] Moreover, increased urinary excretion of uric acid is common in SIAD, and calculation of the fractional excretion of uric acid (FE_{UA}) may provide an important diagnostic clue, with normal patients exhibiting a FE_{UA} less than 10%.[46]

Endocrinopathies, including thyroid and adrenal disorders, are important to consider in the differential diagnosis of euvolemic hypotonic hyponatremia as they can cause an increase in circulating AVP levels.[47,48] Hypothyroidism is a rare cause of euvolemic hypotonic hyponatremia that sometimes manifests as severe hyponatremia (105–110 mEq/L), and although the underlying mechanism is unclear, inappropriately elevated circulating AVP is thought to be the cause of fluid retention.[49] Hypocortisolism can also cause euvolemic hypotonic hyponatremia, although the underlying mechanism is also unclear as is the association between adrenal insufficiency and elevated plasma AVP.[50,51]

Historically, SIADH has been characterized by euvolemic hypotonic hyponatremia and impaired free water excretion in the absence of renal insufficiency, adrenal insufficiency, or any other known appropriate stimulus of AVP release.[19–21,52] The principle of antidiuresis was identified many years before the clinical syndrome of SIADH was first described in patients with bronchogenic carcinoma.[53,54] Likewise, SIADH was described several years before the identification of AVP as the causative hormone. Initially, AVP release was thought to be independent of plasma osmolality, but this did not hold true for all patients with SIADH. For example, in some hyponatremic patients who present with dilute urine, AVP release is appropriately suppressed, although at a lower than normal plasma sodium concentration, a condition termed *reset osmostat syndrome.*[1–7,20,21] Moreover, some cases of SIAD are due to identifiable genetic mutations that result in concentrated urine in the absence of AVP, a phenomenon appropriately termed NSIAD.[45] Examples include activating mutations of the V_2 receptor, mutations in genes that control renal collecting tubule expression of aquaporin water channels, and mutations producing molecules that mimic AVP. Accordingly, the term SIAD has recently been gaining acceptance as a more appropriate description of this syndrome, since elevated AVP levels are not an essential feature of antidiuresis. Therefore, both SIADH and NSIAD are technically subsets of SIAD.

There are specific criteria for diagnosis of SIAD.[21] To be diagnosed with SIAD, patients must be euvolemic, have a urine osmolality greater than 100 mOsm/kg, and have a low effective plasma osmolality. Moreover, excessive water intake is necessary for hyponatremia to develop.[19–21,52] The underlying causes of SIAD are numerous

Table 5. Common Known Causes of the Syndrome of Inappropriate Antidiuresis

Neoplasms	Pulmonary (small cell lung carcinoma, mesothelioma)
	Gastrointestinal, urologic, prostate, and endometrial carcinomas
	Other (thymoma, lymphoma, Ewing's sarcoma)
Pulmonary conditions	Infectious (pneumonia, tuberculosis, empyema)
	Ventilatory (acute respiratory failure, chronic obstructive pulmonary disease)
Intracranial conditions	Inflammatory (meningitis, systemic lupus erythematosus)
	Trauma, mass or fluid (surgery, tumors, subarachnoid hemorrhage, hydrocephalus)
	Other (multiple sclerosis, Guillain-Barré syndrome, delirium tremens)
Drugs	AVP analogues or mimics (vasopressin, desmopressin, oxytocin)
	Stimulate AVP release or enhance its action (chlorpropamide, meperidine, theophylline, amiodarone, SSRIs, tricyclic antidepressants, carbamazepine, chlorpromazine, clozapine, cyclophosphamide, vincristine, angiotensin-converting enzyme inhibitors, nicotine, 3,4-methylenedioxymethamphetamine [ecstasy])
Other	Genetic mutations (AVP or receptors, water channels)
	Postoperative (pain, nausea, inappropriate fluid administration)
	Exercise-associated (marathons, endurance athletes, extreme temperatures)
	AIDS
	Idiopathic

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AVP = arginine vasopressin; SSRIs = selective serotonin-reuptake inhibitors.

(**Table 5**).[19–21,45,52,55–58] Drugs known to mimic the action of AVP, stimulate its release, or enhance its action resulting in SIAD include AVP analogues as well as drugs ranging from narcotics to antipsychotics.[56,58–60] For example, oxytocin has an AVP-like effect that can result in water intoxication.[61] Selective serotonin-reuptake inhibitors can also enhance the AVP effect, especially in the elderly, females, those taking diuretics, or those with low baseline plasma sodium concentrations.[56,59]

Exercise-associated hyponatremia also fulfills the essential diagnostic criteria of SIAD. Hypotonic fluids ingested during endurance exercise are subject to delayed absorption, resulting in prolonged elevation of circulating AVP and water retention.[62,63] This cycle is further potentiated by the use of nonsteroidal anti-inflammatory agents among athletes.[64] Excess water intake and hormone-related changes during exercise are thought to be the main factors along with several other mechanisms.[65,66] Multiple nonosmotic stimuli also coexist during prolonged endurance exercise. Even when intravascular volume is restored, nonosmotic stimuli continue to evoke AVP release. Lastly, abnormal regulation of extracellular fluid volume and translocation of circulating osmotically active sodium to an osmotically inactive internal store, or "third space," have also been suggested as contributing factors.[67]

Euvolemic hypotonic hyponatremia in patients with variable, urine osmolality may suggest reset osmostat syndrome, especially if urine osmolality rises progressively in response to fluid restriction.[1–7,29] This syndrome represents a well-recognized pattern of AVP release in response to hypertonic saline infusion (Table 1). AVP release can be rapid and progressive, resulting in variably dilute urine. Although abnormal, AVP levels are closely related to increasing plasma osmolality, and AVP release is appropriately suppressed at very low plasma osmolality. However, as plasma osmolality approaches normal, AVP release is seemingly inappropriate because the normal osmotic threshold has been lowered. AVP release at this subnormal threshold is actually appropriate but is calibrated to a lower threshold of normal. Appropriately dilute urine can still be attained, just at a lower plasma osmolality. Reset osmostat syndrome is often seen in the elderly, patients with pulmonary disease (eg, tuberculosis), and malnutrition.[68,69] Lastly, physiologic reset osmostat syndrome can occur during pregnancy, causing plasma osmolality to decrease by approximately 10 mOsm/kg of water. When necessary, a water-loading test can be performed to distinguish reset osmostat syndrome from other patterns of AVP release.[69,70]

Hypovolemic hypotonic hyponatremia. Hypovolemic hypotonic hyponatremia may result from renal or extrarenal losses, and the underlying cause of the losses may be differentiated based on urine sodium concentration (Table 4).[1–7,29] In the setting of total body sodium depletion, AVP release increases and free water is retained to maintain intravascular volume. However, free water retention alone is not sufficient to restore extracellular fluid volume in hypovolemia. Moreover, replacement of sodium and water losses with free water alone potentiates inappropriately high plasma AVP levels, which may worsen hyponatremia. Hypovolemia with urine sodium less than 20 mEq/L or FE_{Na} less than 1% suggests active renal sodium retention to compensate for extrarenal losses, such as gastrointestinal or insensible losses with free water replacement. Hypovolemic patients with urine sodium exceeding 20 mEq/L or FE_{Na} exceeding 1% suggests renal sodium losses due to diuretics, osmotic diuresis, salt-losing nephropathies, metabolic

alkalosis, adrenal insufficiency, or CSWS. Most cases of diuretic-induced primary natriuresis are caused by thiazide rather than loop diuretics.[60] Thiazide diuretics can cause excessive renal sodium loss and volume depletion, resulting in the development of severe hyponatremia soon after initiation of therapy, especially in susceptible patients.[71] Salt-losing nephropathies include renal tubular acidosis, polycystic kidney disease, and obstructive uropathy. Both type II renal tubular acidosis and metabolic alkalosis cause hyponatremia as a result of bicarbonaturia, which obligates sodium excretion. Both primary and secondary adrenal insufficiency can result in glucocorticoid and/or mineralocorticoid deficiency, resulting in hyponatremia.[47,48]

CSWS has been described as the development of excessive primary natriuresis, followed by hypovolemic hypotonic hyponatremic dehydration, in patients with intracranial disorders (eg, subarachnoid hemorrhage [SAH], meningitis, metastatic carcinomas) and in patients who have undergone neurosurgical procedures.[57,72–75] However, there is considerable controversy as to whether CSWS and SIAD are distinct clinical entities.[72,75] The major purported distinguishing factor has been volume status, with euvolemia associated with SIAD and hypovolemia associated with CSWS. However, accurate determination of volume status under these conditions can be difficult, and hypovolemia in CSWS has yet to be documented as there is no gold standard measure of volume depletion.[30,75] Interestingly, FE_{UA} has been reported as a means of distinguishing these syndromes. In both SIAD and CSWS, FE_{UA} may be elevated above 10%, but correction of hyponatremia normalizes FE_{UA} to less than 10% in SIAD but not in CSWS.[46] Moreover, random urine sodium concentrations tend to exceed 100 mEq/L in CSWS, but rarely, if ever, in SIAD. While the pathogenesis of CSWS remains unclear, several mechanisms have been proposed.[57,72–75] Inappropriately low plasma renin and aldosterone levels may be due to disruption of sympathetically mediated renal reabsorption of sodium and water in the proximal tubules. Inappropriate natriuresis and volume depletion may also involve release of dopamine and/or natriuretic factors (eg, brain natriuretic peptide, C-type natriuretic peptide).[73] For example, SAH causes release of brain natriuretic peptide as well as suppression of aldosterone.[76] Moreover, hyponatremia after SAH may be delayed and is often inappropriately attributed to CSWS. One recent study found that the hyponatremia after SAH was due to SIADH in most cases (69.2%), followed by hypovolemic hyponatremia (21.0%), CSWS (6.5%), and combined CSWS/SIADH (4.8%).[77] Finally, volume depletion in CSWS may further potentiate elevated plasma AVP. In any case, differentiation of CSWS from SIAD is important because although both syndromes have similar clinical presentations, the treatments are theoretically different with respect to volume status.[57,74,78]

MANAGEMENT

General Approach to Therapy

Plasma osmolality provides the basis for an initial approach to management of hyponatremia. In hypertonic hyponatremia (ie, factitious hyponatremia), treatment is directed at the underlying cause. No specific treatment is indicated for isotonic hyponatremia (ie, pseudohyponatremia) other than treating the underlying lipid and/or protein disorder.

Treatment of hypotonic hyponatremia is guided foremost by the presence or absence of symptoms, then by clinical volume status (**Table 6**). In hypotonic hyponatremia, symptoms usually become evident when plasma sodium concentration is less than 120 mEq/L. Mortality is high in symptomatic patients who receive delayed treatment or have confounding coexisting medical conditions. Severe symptoms include severe mental status changes, seizure, coma, and respiratory arrest; moderate symptoms include disorientation, confusion, weakness, and lethargy; and mild symptoms include anorexia, cramping, nausea, vomiting, headache, and irritability. Depending on volume status, treatment of hypotonic hyponatremia generally involves a stepwise approach that may range from hypertonic saline in severe symptomatic cases, to isotonic saline in moderate or mild symptomatic cases, to simple free water restriction in asymptomatic cases. Severely symptomatic patients should be treated aggressively with hypertonic or isotonic saline to prevent progression to life-threatening neurologic complications.[28,78–83] Hypertonic saline should only be used for severely symptomatic patients in an intensive care setting with expert consultation, and typically only for a brief period of time. Loop diuretics may be used to treat or curtail potential volume overload. When symptoms subside, treatment should become less aggressive and focus on correcting the underlying cause of water to sodium imbalance. Serial reevaluation and careful step-down in treatment intensity toward reaching the goal of steady-state euvolemic normonatremia is a good approach.

Acute hypotonic hyponatremia, defined as onset at less than 48 hours, can be corrected immediately.[3,79,82,83] However, correction of asymptomatic chronic hyponatremia may be inappropriate or unnecessary, as may occur in cirrhotic patients or reset osmostat syndrome. Moreover, overaggressive management may lead to significant

Table 6. Approach to Treatment of Hypotonic Hyponatremia Based on Volume Status and Symptomatology

All patients		Treat underlying cause if possible Serial reevaluation of volume status Step-down in treatment intensity as symptoms resolve Serial measurement of electrolytes to monitor progress Consider additional pharmacotherapy as indicated (see Table 7)
Any volume status	Severely symptomatic*	Hypertonic saline ± diuretics‡ Correction rate: 1–2 mEq/L/hr until major symptoms resolve *then*
	Mild or moderately symptomatic†	Isotonic saline ± diuretics Correction rate: 0.5–1 mEq/L/hr until asymptomatic *then* Transition to volume-specific asymptomatic treatment
Hypervolemic	Asymptomatic	Restrict free water to 0.5–1 L/day ± diuretics Correction rate: 0.5 mEq/L/hr
Euvolemic	Asymptomatic	Restrict free water to 0.5–1 L/day Correction rate: 0.5 mEq/L/hr
Hypovolemic	Asymptomatic	Isotonic saline Correction rate: 0.5 mEq/L/hr

NOTE: Volume status is determined by physical examination.

*Severe symptoms include severe mental status changes, seizure, coma, and respiratory arrest.

†Moderate symptoms include disorientation, confusion, weakness, and lethargy. Mild symptoms include anorexia, cramping, nausea, vomiting, headache, and irritability.

‡Hypertonic saline should only be used with expert consultation in an intensive care setting and may be relatively contraindicated in hypervolemic hypernatremia, favoring the use of isotonic saline as initial treatment in severely symptomatic patients.

morbidity and mortality.[26,81] Permanent brainstem damage may result from osmotic myelinolysis syndrome, which is characterized by central pontine myelinolysis resulting from osmotically-induced demyelination.[81,82] In general, approximately one half of the total sodium deficit can be safely replaced in the first 12 hours, at a rate of 0.5 mEq/L/hr (12 mEq/L/day). The following equation can be used to estimate the effect of 1 L of sodium infusate on plasma sodium concentration:[1]

$$\text{Change in plasma sodium} = \frac{(\text{Infusate sodium} - \text{Plasma sodium})}{(\text{Total body water} + 1)}$$

Total body water (in liters) is calculated by multiplying total body weight (in kilograms) by 0.5 in nonelderly women, 0.6 in nonelderly men, 0.45 in elderly women, and 0.5 in elderly men. Infusate sodium concentrations are as follows: 3% saline = 513 mEq/L, 0.9% saline = 154 mEq/L, and 0.45% saline = 77 mEq/L. Other formulas also exist that take into account sodium infusates containing potassium and other electrolytes.

Nonpeptide arginine vasopressin receptor (AVP-R) antagonists are a new class of drugs that promote aquaresis, a term used to describe the excretion of electrolyte-free water without sodium or potassium excretion.[84–89] Commonly referred to as "vaptans" or "aquaretics" to contrast their effects with diuretics, AVP-R antagonists directly inhibit the action of AVP at its receptors, specifically targeting both V_{1A} receptors on vascular smooth muscle cells and V_2 receptors on renal collecting duct cells. Conivaptan is currently the only aquaretic approved by the US Food and Drug Administration; it is indicated for treatment of symptomatic euvolemic and hypervolemic hyponatremia in hospitalized patients, specifically SIADH and CHF.[83–89] Because thirst is a commonly reported side effect, some free water restriction may be required.

Treatment of Hypervolemic Hypotonic Hyponatremia

A reasonable approach to initial therapy in severely symptomatic patients with hypervolemic hypotonic hyponatremia is to correct the plasma sodium concentration by 1 to 2 mEq/L/hr using either hypertonic saline or isotonic saline, sometimes in combination with loop diuretics, until major symptoms (eg, severe mental status changes, seizures) subside. It is important to note that hypertonic saline may be relatively contraindicated in hypervolemia, favoring the use of isotonic saline in severely symptomatic patients as initial therapy. Once major symptoms subside, treatment should then become less aggressive and redirected at correcting the underlying cause of hyponatremia. Ultimately, free water restriction is the preferred treatment, on the order of 0.5 to 1 L/day, with or without diuretics, correcting by no more than 0.5 mEq/L/hr. AVP-R antagonists may be considered in hospitalized symptomatic patients with CHF (**Table 7**).[84–89] Initial treatment of asymptomatic patients is free water restriction with or without loop diuretics to correct hyponatremia and improve volume status.

Treatment of Euvolemic Hypotonic Hyponatremia

A reasonable approach to initial therapy in severely symptomatic patients with euvolemic hypotonic hyponatremia is to correct the plasma sodium concentration by 1 to 2 mEq/L/hr using hypertonic saline until major symptoms subside, then switch to isotonic saline and correct by 0.5 to 1 mEq/L/hr thereafter. Loop diuretics may be used to curtail fluid overload during treatment, but their use should be minimized. Once

Table 7. Pharmacotherapy for Hypotonic Hyponatremia

Medication	Indication	Mechanism	Dose Range
Demeclocycline (antibiotic)	Water restriction failure in chronic euvolemic hypotonic hyponatremia (eg, SIAD)	Inhibits cAMP Idiosyncratically induces nephrogenic diabetes insipidus	300–600 mg orally twice daily
Furosemide (loop diuretic)	Chronic hypervolemic hypotonic hyponatremia (eg, CHF) Chronic euvolemic hypotonic hyponatremia (eg, SIAD)	Inhibits renal $Na^+/K^+/Cl^-$ cotransport in the ascending loop of Henle and distal tubule Increases excretion of free water along with natriuresis and kaliuresis	Dosage and route vary per individual Typically 40 mg IV over 1–2 min; repeat if response not satisfactory; oral route for maintenance
Conivaptan (aquaretic)	Symptomatic hypervolemic hypotonic hyponatremia (approved for CHF) Symptomatic euvolemic hypotonic hyponatremia (approved for SIADH)	AVP-R antagonist Increases excretion of electrolyte-free water	20 mg IV loading dose over 30 min; followed by 20 mg IV over 24 hr May increase to 40 mg over 24 hr maximum; may continue for 1–4 days maximum
Fludrocortisone (corticosteroid)	Cerebral salt-wasting syndrome	Increases sodium reabsorption and potassium loss in renal distal tubules	0.05–0.2 mg orally daily

AVP-R = arginine vasopressin receptor; cAMP = cyclic adenosine monophosphate; CHF = congestive heart failure; IV = intravenously; SIAD = syndrome of inappropriate antidiuresis.

asymptomatic, patients can be transitioned to free water restriction. Initial treatment of asymptomatic patients is free water restriction on the order of 0.5 to 1 L/day, with correction by no more than 0.5 mEq/L/hr over a period of several days.

There is a wide array of clinical presentations of SIAD due to the broad spectrum of identifiable underlying causes of osmoregulatory dysfunction. As a result, significant individual differences exist in the response to therapy. Treatment of SIAD can range from free water restriction in asymptomatic patients, to isotonic or hypertonic saline infusion in severely symptomatic patients, to pharmacotherapy in select cases. For patients who do not respond to or cannot adhere to water restriction, pharmacotherapy with demeclocycline is warranted. This agent antagonizes the effect of AVP on the distal tubule, essentially inducing a state of nephrogenic diabetes insipidus (Table 7).[27,28,85] However, demeclocycline has a slow onset of action, thereby limiting its usefulness to chronic SIAD. AVP-R antagonists are indicated for hospitalized symptomatic patients with SIADH (Table 7).[84–89]

Treatment of Hypovolemic Hypotonic Hyponatremia

The cornerstone of treatment for hypovolemic hypotonic hyponatremic patients is volume replacement with saline solutions (Table 6). A reasonable approach in severely symptomatic patients is to correct the plasma sodium concentration by 1 to 2 mEq/L/hr using hypertonic saline until major symptoms subside, then switch to isotonic saline and correct by 0.5 to 1 mEq/L/hr thereafter. Initial treatment of asymptomatic patients is isotonic saline, with correction by no more than 0.5 mEq/L/hr to avoid osmotic demyelination. Finally, empiric corticosteroids can be used if hypocortisolism is suspected, and fludrocortisone can be used if hyponatremia is due to CSWS (Table 7).[90]

CONCLUSION

Evaluation of hyponatremia requires a systematic approach. In addition to history and physical examination, measurement of plasma osmolality provides an important diagnostic clue. Hypotonic hyponatremia requires accurate assessment of volume status, and measurement of urine sodium and osmolality further narrows the differential of underlying causes. Symptomatic patients should be treated aggressively to prevent life-threatening complications. If hypertonic saline is deemed necessary, it should only be initiated in an intensive care setting with expert consultation. Asymptomatic hypervolemic patients are treated with free water restriction, often in combination with loop diuretics. Asymptomatic euvolemic patients are treated with free water restriction. Asymptomatic hypovolemic patients are treated with judicious volume replacement with isotonic saline. Rapid correction can cause central pontine myelinolysis and permanent brainstem damage and thus should be avoided. **HP**

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