Diagnosis and Management of Disorders of Body Tonicity—Hyponatremia and Hypernatremia: Core Curriculum 2020

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Overall body fluid concentration is regulated within a narrow range by the concerted action of the hypothalamic-pituitary axis to influence water intake through thirst and water excretion via the effect of vasopressin, or antidiuretic hormone, on renal collecting duct water permeability. Sodium is the principal extracellular cation; abnormalities in overall effective body fluid concentration, or tonicity, manifest as disturbances in serum sodium concentration. Depending on its severity and chronicity, hyponatremia can lead to significant symptoms, primarily related to central nervous system function. Failure to correct hyponatremia can lead to permanent neurologic damage, as can over rapid correction. It is thus essential to stay within specific limits for correction, particularly for chronic hyponatremia. Hypernatremia also leads to central nervous system dysfunction, although goals for its correction rate are less well established. This Core Curriculum article discusses the normal regulation of tonicity and serum sodium concentration and the diagnosis and management of hypo- and hypernatremia.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

The most common electrolyte disturbances observed in hospitalized patients, hyponatremia, and its opposite, hypernatremia, are defined as the presence of a serum sodium concentration ($[Na^+]$) < 135 or >145 mEq/L, respectively. Although total-body salt content may be abnormal, the vast majority of dysnatremias arise from a primary imbalance in electrolyte-free water intake and loss. The perturbation in water balance rather than any change in salt content is the problem. It is perhaps unfortunate that these disorders come to attention when the laboratory reports an abnormal $[Na^+]$. Clinicians should resist any temptation to consider body sodium content initially and should acquire the reflex to focus on what is wrong with water balance. Numerous disease processes, each meriting a specific treatment strategy, can be responsible. In light of the morbidity and mortality attributed to dysnatremias and the potential complications of their treatment, appropriate management requires a thorough understanding of the human osmoregulatory system and the conceptual framework used to approach these complex electrolyte aberrations. In this Core Curriculum, we discuss the characterization and treatment of these disorders of water balance after briefly reviewing the physiology of osmotic homeostasis.

Regulation of Body Tonicity and the Relationship Between Serum Sodium Concentration, Osmolality, Osmolarity, and Tonicity

As sodium is the most abundant cation in the extracellular fluid, $[Na^+]$ is the primary determinant of plasma osmolality, defined as the concentration of osmoles dissolved per kilogram of plasma water. Osmolarity is the concentration of osmoles per liter of plasma water and has virtually the same numerical value; osmolality is preferred when discourse is rigorous. Plasma osmolality is estimated using the equation delineated in Box 1. Plasma osmolality is a colligative property that is directly measurable with an osmometer. Tonicity, which is potentially confused with osmolality, denotes the concentration of osmoles—also known as effective osmoles—that do not freely cross cell membranes. With the exception of specialized epithelia in the distal nephron, the concentration inside and outside body cells must be the same since their cell membranes are freely permeable to water due to the constitutive presence of aquaporins. Therefore, the accumulation of effective osmoles in either the intra- or extracellular compartment provides a driving force for water movement into the compartment of greater tonicity to equalize concentration. Hypotonic plasma causes movement of water intracellularly, leading to cellular swelling. Conversely, hypertonic plasma begets cellular shrinkage. Sodium and glucose (in the presence of insulin lack) as obligate extracellular solutes are thus effective osmoles and contribute to both osmolality and tonicity, whereas membrane-permeable urea contributes to osmolality without affecting tonicity. Potassium, as the principal intracellular cation, also contributes to overall body concentration and tonicity as

described by the Edelman equation (Box 1). Plasma tonicity cannot be measured directly but is calculated by subtracting the contribution of urea to the measured plasma osmolality (Box 1).

While hypernatremia is always indicative of hyperosmolal and hypertonic plasma, hyponatremia can occur with low, normal, or elevated tonicity or osmolality. For instance, an elevation of SUN level will increase serum osmolality without affecting tonicity. Depending on the degree of azotemia, when concomitant water retention that reduces tonicity is present, hypotonic hyponatremia with normal or even elevated serum osmolality can be observed.

Case 1: *A 65-year-old woman presents with productive cough, shortness of breath, and fever. She is taking hydrochlorothiazide, 12.5 mg, daily for hypertension. Physical examination reveals temperature of 38.5°C, blood pressure of 90/50 mm Hg, heart rate of 100 beats/min, respiratory rate of 28 breaths/min, and oxygen saturation of 87% while breathing room air, along with dry mucus membranes, left lower-lobe crackles, and absence of edema. Laboratory results include [Na^+] of 128 mEq/L, serum urea nitrogen (SUN) level of 68 mg/dL, serum creatinine level of 3.4 mg/dL, and serum osmolality of 280 mOsm/kg H_2O.*

Question 1: This patient's serum is correctly described as:

a) Hypotonic and hypo-osmolal
b) Hypotonic and iso-osmolal
c) Isotonic and hypo-osmolal
d) Isotonic and iso-osmolal

Answer: The patient's serum osmolality is within the normal range of 275 to 295 mOsm/kg H_2O. Her effective serum osmolality, or tonicity, is ~256 mOsm/kg H_2O (Effective serum osmolality = S_{Osm} − SUN/2.8 = 280 − 68/2.8 = 256). She is thus iso-osmolal and hypotonic, making (b) the correct answer.

Additional Reading

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Pituitary Regulation of Tonicity

Plasma tonicity is tightly regulated by antidiuretic hormone (ADH), also known as arginine vasopressin. The pre-prohormone of ADH is synthesized in the hypothalamus and cleaved into ADH, neurophysin II, and copeptin. ADH is then stored in the posterior pituitary gland. A hypertonic extracellular environment induces shrinkage of hypothalamic osmoreceptors. The subsequent opening of stretch-inactivated cation channels triggers membrane depolarization, intracellular signaling, and release of vasopressin (ADH) from the posterior pituitary gland into the systemic circulation. Vasopressin then acts on the collecting duct of the nephron to increase water reabsorption and decrease serum tonicity.

Although plasma hypertonicity serves as the primary stimulus for vasopressin release, hypovolemia also can promote vasopressin secretion (Fig 1). Though mild changes in blood pressure do not affect vasopressin release, modest decreases in perfusion sensed by carotid baroreceptors stimulate pituitary vasopressin release at the expense of potentially lowering serum tonicity. Teleologically, one could argue that retaining water to foster volume expansion and thus preserve perfusion in the hypovolemic state was evolutionarily advantageous.

Renal Regulation of Tonicity

Vasopressin binds to vasopressin V2 receptors on the basolateral surface of principal cells of the collecting duct of the distal nephron. In the absence of vasopressin, impermeability of the collecting duct to water gives rise to dilute urine; water remains behind in the tubular lumen as solute

Box 1. Selected Formulas Useful for the Classification and Management of Dysnatremias

Plasma osmolality, mOsm/kg H_2O: (2 × [Na^+] (mEq/L)) + SUN (mg/dL)/2.8 + glucose (mg/dL)/18
Plasma tonicity, mOsm/kg H_2O: Measured plasma osmolality (mOsm/kg H_2O) − SUN (mg/dL)/2.8 or (2 × [Na^+] (mEq/L)) + glucose (mg/dL)/18
Edelman formula, simplified: [Na^+] = (eNa^+ + eK^+)/TBW
Urine to serum electrolyte ratio: (U_{Na} + U_K)/[Na^+][a]
Electrolyte-free water excretion: Urine Volume × (1 − (U_{Na} + U_K)/[Na^+])
Infusion rate, hypertonic saline solution: 1 mL/kg/h can be expected to increase [Na^+] 1 mEq/L/h
Infusion rate, D5W, to relower [Na^+]: 3 mL/kg/h
Free-water deficit: TBW (L) × (([Na^+]/140 mEq/L) − 1)[b]

Note: The formula for calculated plasma osmolality does not reflect the contribution of ethanol, methanol, or other toxic ingestions. Measured plasma osmolality should not be used for decision making in hyponatremia if an ingestion is suspected. A difference between plasma osmolality calculated with this formula and measured plasma osmolality can be used to infer the presence of a foreign substance. Infusion rates are approximations and do not take into account ongoing losses of water or solute; [Na^+] should be monitored frequently during infusion.
Abbreviations: D5W, 5% dextrose in water; eK^+, exchangeable potassium content; eNa^+, exchangeable sodium content; [Na^+], serum sodium concentration; SUN, serum urea nitrogen; TBW, total-body water; U_{Na}, urine sodium concentration; U_K, urine potassium concentration.
[a]Ratio > 1 predicts treatment failure with fluid restriction alone and worsening of hyponatremia in response to normal saline solution.
[b]TBW = 0.6 × body weight (kg).

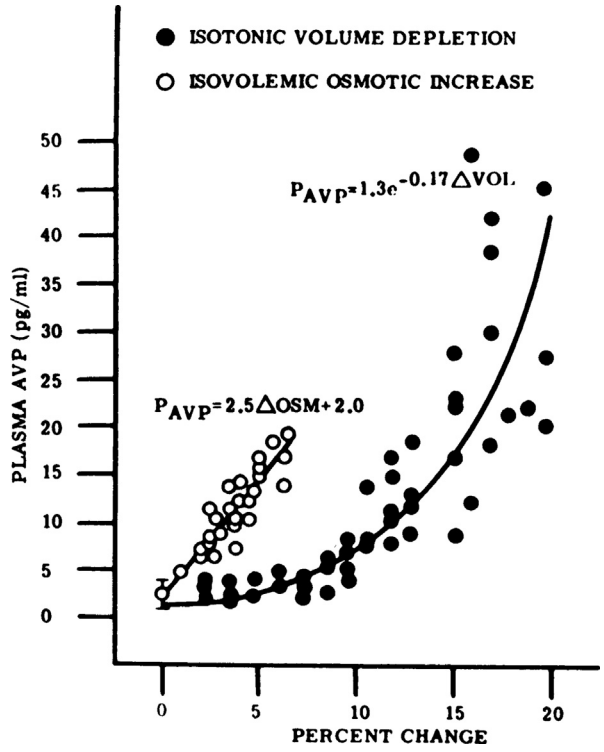

Figure 1. Relationship between plasma vasopressin (P_{AVP}) and change from baseline in either blood volume or plasma osmolality in rats. Plasma hypertonicity serves as the primary stimulus for vasopressin release; very small changes are associated with significant linear increases in AVP secretion. A greater degree of volume depletion is required to promote AVP release, which is exponential, and the magnitude of release may exceed that due to osmolality changes. Original figure is ©1973 American Society for Clinical Investigation; reproduced from Dunn et al (The role of blood osmolality and volume in regulating vasopressin secretion in the rat. *J Clin Invest.* 1973;52(12):3212-3219) with permission of the copyright holder.

is reabsorbed. V2 receptor activation stimulates translocation to and fusion of aquaporin 2–containing vesicles with the apical membrane of the principal cell, allowing water to flow into the cell, from which it exits into the hypertonic medullary interstitium through constitutively active basolateral aquaporin channels (Fig 2). Reabsorption of water in this manner leads to concentrated urine and lowers serum osmolality. Urine osmolality (U_{Osm}) is hence a surrogate measure of vasopressin activity; high and low U_{Osm} equate to high and low vasopressin levels, respectively. In the healthy state, vasopressin levels are undetectable when plasma tonicity is low and rise in a linear fashion as tonicity increases above normal. The normal human kidney can produce urine with osmolality ranging from 50 to 1,200 mOsm/kg H_2O. However, in advanced chronic kidney disease, this range narrows significantly. Concentrating ability is markedly impaired, and a more modest diluting defect occurs as well.

Thiazide diuretics, which block reabsorption of sodium chloride at the distal nephron diluting site, can also impair urinary dilution and account for ~90% of cases of diuretic-associated hyponatremia. By inhibiting loop of Henle sodium reabsorption, loop diuretics reduce renal medullary hypertonicity and thereby reduce the driving force for water reabsorption in the collecting duct. As a result, loop diuretics—in contrast to thiazides—tend to hinder renal concentrating ability and can contribute to the development of hypernatremia.

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Hyponatremia

Clinical Manifestations of Hyponatremia

The severity of hyponatremia symptoms correlates with the acuity of hyponatremia onset and its magnitude. As hyponatremia develops, all cells take up water and swell. This is problematic for the brain in the nondistensible cranium. Astrocytes are particularly sensitive to osmotic stress, though expulsion of potassium and electrolytes over 6 to 12 hours and organic osmolytes including glutamine and taurine over a 24- to 48-hour period decreases intracellular solute content and mitigates swelling with hypotonic hyponatremia. Taking into account the time course of brain compensation, acute hyponatremia is defined by expert opinion as developing over less than 48 hours. Chronic hyponatremia is present for longer and represents the vast majority of cases of hyponatremia. Given the consequences of over rapid correction of chronic hyponatremia (see later discussion), cases in which the hyponatremia is not known with certainty to be of less than 48 hours' duration, including virtually all cases of hyponatremia that have developed outside the hospital (hyponatremia following endurance exercise or MDMA [3,4-methylenedioxy-methamphetamine] ingestion are notable exceptions), should be treated as if chronic. In cases of severe hyponatremia, that is, $[Na^+] < 125$ mEq/L, evolving over less than 48 hours, in which brain water uptake outstrips the compensatory mechanisms described, symptoms are primarily neurologic and progress from mild nausea and vomiting to lethargy, headaches, confusion, and muscle cramps. Serious complications of acute profound hyponatremia include cerebral edema, seizures, coma, brainstem herniation, and neurogenic pulmonary edema. Thiazide-associated hyponatremia, exercise-associated hyponatremia, MDMA ingestion, administration of hypotonic fluids in the setting of postoperative pain treated with opiates, and primary polydipsia confer higher risk. Although hyponatremia of long duration may be symptomatic if severe, most patients with chronic mild to moderate hyponatremia will not be overtly symptomatic. Observational studies in patients with heart failure, cirrhosis, end-stage kidney disease, and other serious

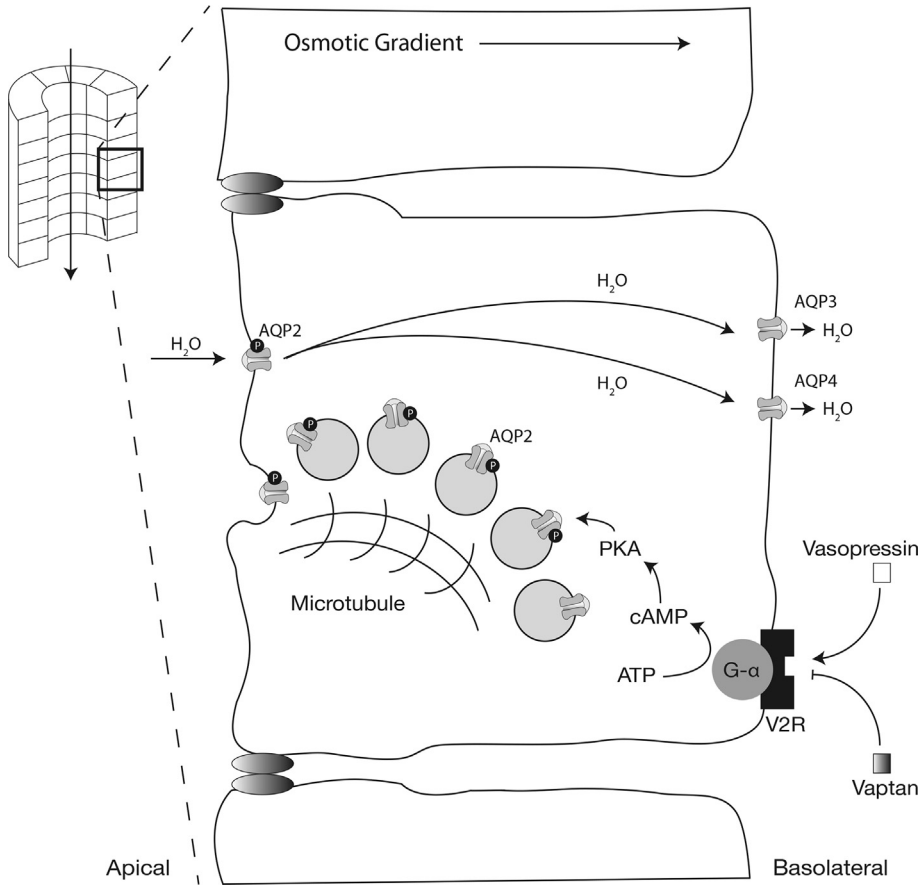

Figure 2. Vasopressin–induced increase in water permeability in the collecting duct. Vasopressin binds to the vasopressin 2 receptor (VR2), leading to an increase in intracellular cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA). The latter leads to translocation of preformed vesicles containing aquaporin 2 (AQP2) along cytoskeletal elements toward the apical membrane, where exocytic insertion of AQP2 into the apical membrane renders the membrane permeable to water. Using the osmotic gradient from tubular lumen to medullary interstitium, tubular water can now move to the interstitium through constitutively activated basolateral AQP3 and AQP4 channels. Of note, vasopressin receptor antagonists (vaptans) compete with vasopressin for the V2 receptor–binding site. Abbreviation: ATP, adenosine triphosphate. Original figure ©2013 National Kidney Foundation; reproduced from Lehrich et al (Role of vaptans in the management of hyponatremia. *Am J Kidney Dis.* 2013;62(2):364-76) with permission of the copyright holder.

chronic illnesses, however, have demonstrated an association with adverse outcomes including mortality with even modest reductions in [Na^+], as listed in Box 2. It remains uncertain whether chronic hyponatremia is itself a cause of the increased mortality risk or simply a marker for the severity of the underlying disorder that actually confers the risk. Similarly, although clinicians agree that treating chronic hyponatremia is valuable, there is a paucity of studies documenting improvement in any functional parameter after correction of hyponatremia.

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Box 2. Adverse Outcomes Associated With Chronic Mild to Moderate Hyponatremia

- Cognitive impairment and decline
- Falls
- Fractures and osteoporosis
- Gait instability
- Mortality
- Calcium-forming kidney stones

Note: Clinical associations demonstrated in observational studies.

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Classification of Hyponatremia—Tonicity

As mentioned, hyponatremia can arise in varying states of tonicity. Apparent hyponatremia coupled with an effective serum osmolality of 275 to 295 mOsm/kg H_2O is consistent with either isotonic hyponatremia or pseudohyponatremia. As its name implies, pseudohyponatremia does not represent true hyponatremia but rather laboratory artifact. Widely used serum multianalyzers measure [Na^+] using indirect potentiometry and specimen dilution. This method assumes that water constitutes 93% of plasma. However, high plasma lipid or protein concentrations will lower the aqueous contribution to plasma volume, leading to a falsely decreased calculated [Na^+] value. Hyponatremia reported in patients with marked hyperlipidemia or paraproteinemia should thus raise suspicion for pseudohyponatremia. Erroneous [Na^+] measurement in hyperlipidemia can be mitigated by ultracentrifugation to separate out lipid layers. Alternatively, direct potentiometry, which is commonly used in blood gas analyzers, is not subject to this error.

Hyponatremia combined with plasma tonicity > 295 mOsm/kg H_2O is indicative of hypertonic hyponatremia. This phenomenon, termed translocational hyponatremia, is most commonly observed in hyperglycemia; extracellular hypertonicity associated with hyperglycemia favors efflux of water into the extracellular space, in turn decreasing the [Na^+]. [Na^+] decreases by ~1.6 mEq/L for every 100 mg/dL increase in serum glucose level, though as serum glucose level increases to >400 mg/dL, the incremental decrease in [Na^+] can approximate 2.4 mEq/L. [Na^+] can decrease in a similar fashion with administration of mannitol.

Hypotonic hyponatremia occurs with an effective serum osmolality < 275 mOsm/kg H_2O and merits further evaluation.

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Hypotonic Hyponatremia and Urinary Dilution

In hypotonic hyponatremia, the presence of low U_{Osm} indicative of maximally dilute urine—typically < 100 mOsm/kg H_2O—suggests that vasopressin is appropriately suppressed but ongoing water ingestion exceeds the kidney's capacity for electrolyte-free water excretion. In individuals consuming a typical Western diet, ~800 mOsm of solute is generated and then excreted in urine on a daily basis. Assuming urine can be maximally diluted to 50 mOsm/kg H_2O, this corresponds to a maximal electrolyte-free water clearance of 16 L/d (800 mOsm solute/50 mOsm/kg H_2O = 16 L). Ingestion of a greater volume of water as observed in primary polydipsia will cause hypotonic hyponatremia despite maximally dilute urine. Similarly, if the rate of solute ingestion diminishes to 200 mOsm/d, as in the case of a "tea-and-toast" diet or beer potomania, the electrolyte-free water excretory capacity decreases to 4 L/d (200 mOsm solute/50 mOsm/kg H_2O = 4 L), placing such patients at risk for hypotonic hyponatremia despite more modest fluid intake and preserved urinary dilution.

The most common cause of hypotonic hyponatremia is vasopressin-mediated impairment in urinary dilution. Because hyponatremia in this setting directly reflects a defect in electrolyte-free water clearance rather than sodium balance, total-body sodium content and extracellular fluid volume are functions not of the hyponatremia but of the underlying disease process. Patients with vasopressin-mediated hypotonic hyponatremia may be hypovolemic, euvolemic, or hypervolemic.

Hypotonic Hyponatremia With Impaired Urinary Dilution—Classification by Volume Status

Hypovolemia

Assessment of volume status in a patient with hypotonic hyponatremia with less than maximally dilute urine is diagnostically critical, if often challenging. As mentioned, significant hypoperfusion is a potent nonosmotic stimulus for vasopressin release. Hypovolemic hypotonic hyponatremia may thus occur as a consequence of true intravascular volume depletion of any cause, including but not limited to hemorrhage, gastrointestinal fluid loss, diuretics, or salt wasting due to mineralocorticoid deficiency in Addisonian crisis. Much overdiagnosed, cerebral salt-wasting can complicate subarachnoid hemorrhage and lead to hypovolemic hyponatremia. Much more frequently, a high-sodium diuresis in this setting is due to an appropriate effort to maintain sodium balance in the face of saline expansion mistakenly prescribed to patients with syndrome of inappropriate antidiuretic hormone secretion (SIADH). Correctly diagnosing cerebral salt-wasting relies on scrutiny of volume balance and vital signs to establish that spontaneous natriuresis resulting in volume depletion actually antedated the hyponatremia.

Hypervolemia

Hypervolemic hypotonic hyponatremia can be a consequence of decompensated heart failure or advanced cirrhosis. In the former, hypoperfusion with a reduced effective circulating volume leads to non–osmotically-mediated vasopressin release (Fig 1) and water retention. In

the latter, worsening arterial underfilling provokes nonosmotic vasopressin release and hyponatremia. As a surrogate for altered hemodynamics in these conditions, hyponatremia is a strong predictor of mortality.

Euvolemia

Hypotonic hyponatremia also occurs in euvolemic patients. The leading cause, SIADH, refers to persistent vasopressin secretion in the absence of an osmotic or hemodynamic stimulus. The criteria for diagnosis and potential causes of SIADH are delineated in Boxes 3 and 4, respectively.

A diagnosis of SIADH notably requires that other causes of euvolemic hypotonic hyponatremia with impaired urinary dilution be excluded. Because cortisol inhibits vasopressin release, isolated glucocorticoid deficiency manifests as euvolemic hyponatremia with hypoglycemia (note that combined glucocorticoid and mineralocorticoid deficiency will be accompanied by volume depletion and hyperkalemia). Although incompletely understood, hypotonic hyponatremia associated with profound hypothyroidism, that is, myxedema, is thought to be due to nonosmotic vasopressin release provoked by reduced cardiac output. Unlike individuals with other causes of heart failure, patients with hyponatremia attributable to hypothyroidism are typically euvolemic.

Box 3. Diagnostic Criteria and Clinical Data Consistent With SIADH

Bartter & Schwartz Criteria for SIADH

- Hypotonic hyponatremia (effective S_{Osm} < 275 mOsm/kg H_2O)
- Euvolemia
- Less than maximally dilute urine (U_{Osm} > 100 mOsm/kg H_2O)
- Elevated urine sodium excretion commensurate with lack of avid sodium retention during normal intake of sodium and water (U_{Na} > 30 mEq/L)
- Absence of advanced kidney disease, cirrhosis, or heart failure
- Absence of alternative causes of euvolemic hypotonic hyponatremia with less than maximally dilute urine including but not limited to hypothyroidism, glucocorticoid insufficiency, or diuretic use

Additional Data Supporting Diagnosis of SIADH

- Serum uric acid < 4 mg/dL
- Fractional excretion of uric acid > 10%
- Worsening of hyponatremia with IV normal saline solution infusion
- Plasma vasopressin or copeptin level inappropriately elevated relative to serum osmolality
- Abnormal response to water load (excretion of < 80% of 20 mL/kg load in 4 h with failure to dilute urine to <100 mOsm/kg H_2O)

Abbreviations: IV, intravenous; S_{Osm}, serum osmolality; U_{Na}, urine sodium concentration; U_{Osm}, urine osmolality; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Beyond glucocorticoid insufficiency and hypothyroidism, rarer entities can mimic SIADH. The nephrogenic syndrome of inappropriate antidiuresis is a hereditary disorder stemming from a gain-of-function mutation of the distal tubule V2 receptor. It is X-linked, presents with hyponatremia in male infants, and is the mirror image of some forms of nephrogenic diabetes insipidus (DI). Unlike SIADH, vasopressin levels are low. Marathon runners are at highest risk for exercise-associated hyponatremia, which arises from nonosmotic vasopressin release in the setting of pain, stress, or discomfort coupled with excessive ingestion of hypotonic fluids. Reset osmostat occurs in patients with tuberculosis or other causes of inanition and is characterized by hypotonic hyponatremia with an [Na^+] that never falls below the mid to upper 120s. Vasopressin secretion is fully suppressed below that level and the hyponatremia is not progressive. Whether it is a distinct disorder or a variant of SIADH is debated. Diagnosis requires a high index of suspicion and a formal water load test.

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Box 4. Common Causes of SIADH

CNS disease: Brain abscess, encephalitis, head trauma, intracranial hemorrhage, meningitis, tumor

Drugs: Amiodarone, carbamazepine, oxcarbazepine, 3,4-methylenedioxy-methamphetamine (MDMA, "Ecstasy"), nicotine, phenothiazines, opioids, selective serotonin re-uptake inhibitors, tricyclic antidepressants, cyclophosphamide, chlorpropamide, vincristine

Malignancy: Most commonly small cell carcinoma of the lung followed by head and neck cancer and non–small cell lung cancer

Pulmonary disease: Acute respiratory failure, COPD, pneumonia, tuberculosis

Other: HIV infection, idiopathic, postoperative state, reset osmostat

Note: This list is not exhaustive. Numerous other drugs and tumors are reported to cause SIADH. Some authorities classify reset osmostat as a separate entity rather than a subset of SIADH.
Abbreviations: CNS, central nervous system; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
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Diagnostic Approach to Hyponatremia

Because treatment of hyponatremia varies by cause, recognition of the underlying disease process is integral to management. A suggested algorithm for the diagnosis of hyponatremia is shown in Figure 3. First, the presence of hypotonicity should be confirmed by measurement of serum osmolality. If azotemia is present, tonicity will need to be calculated using the formula provided in Box 1. Pseudohyponatremia should be considered if hypertriglyceridemia or hyperproteinemia are present. Translocational hyponatremia will be evident if hyperglycemia is present and should also be suspected if mannitol has been administered recently. The correction of $[Na^+]$ for glucose or measurement of serum osmolality will be confirmatory.

When it is certain that hypotonic hyponatremia is present, that disorder should be further characterized as vasopressin mediated or vasopressin independent by assessing U_{Osm}. If urinary dilution is impaired, clinical assessment of volume status can elucidate the mechanism for vasopressin release. Because the differentiation of subtle hypovolemia from euvolemia is difficult, urine sodium concentration should be measured in any patient not plainly hypervolemic due to congestive heart failure or cirrhosis. For patients who are euvolemic and consuming a diet with normal salt and water content, maintenance of body sodium balance dictates that urine sodium concentration will be >30 mmol/L. Use of diuretics can increase urine sodium concentration, and urine sodium concentration may be low despite normal total body sodium content when urine flow rate is high. It is thus not an infallible indicator of volume status. Even so, one should be very circumspect about making the diagnosis of SIADH when urine sodium concentration is low. Retention of other osmolytes such as urea and uric acid is observed in the setting of reduced true or effective circulating volume but typically not with SIADH, in which subclinical volume

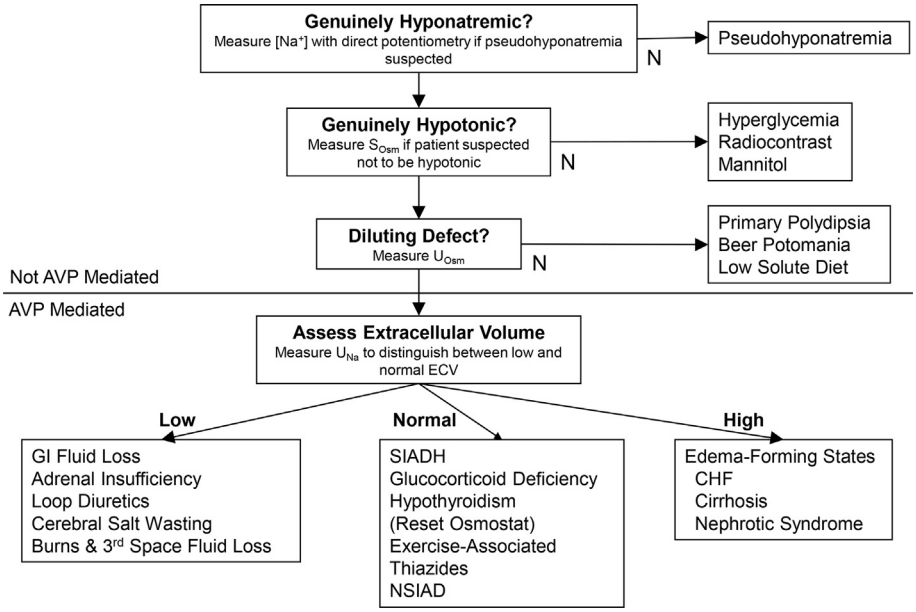

Figure 3. Diagnostic approach to hyponatremia. Urine sodium concentration (U_{Na}) > 30 mEq/L suggests that volume depletion is absent, but numerous exceptions exist. See text for details. Patients with thiazide-induced hyponatremia typically appear clinically euvolemic, but they may be hypovolemic, and their U_{Na} is variable. Abbreviations: AVP, vasopressin; CHF, congestive heart failure; ECV, extracellular fluid volume; GI, gastrointestinal; $[Na^+]$, serum sodium concentration; NSIAD, nephrogenic syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate antidiuretic hormone secretion; S_{Osm}, serum osmolality; U_{Osm}, urine osmolality.

expansion from electrolyte-free water retention reduces urea and uric acid reabsorption. Accordingly, high SUN level, serum uric acid level > 4 mg/dL, or fractional excretion of uric acid < 10% should raise suspicion that SIADH is not the cause of hyponatremia. Given the difficulty establishing that patients are euvolemic, a trial of volume expansion with saline solution can be an appropriate diagnostic maneuver to exclude hypovolemia. This should be done with great caution. Careful monitoring of [Na^+] and urine output is essential. Patients with SIADH can generate and retain electrolyte-free water from normal saline solution with a resultant further lowering of [Na^+]. Correction of hypovolemia can result in a high-volume water diuresis with rapid [Na^+] correction, risking over rapid correction. Consequently, while uncertainty about volume status persists, only a modest amount of fluid, that is, ≤1 L, should be infused slowly, particularly if the starting [Na^+] is very low. If low enough that any further reduction would be dangerous, use of 3% saline solution for the volume trial should be considered.

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Case 2: *A 70-year-old woman is brought to the emergency department with a day of confusion, nausea, and vomiting. She was started on treatment with chlorthalidone, 25 mg, daily 1 week earlier to treat newly diagnosed hypertension. Physical examination is notable for temperature of 37°C, heart rate of 105 beats/min, blood pressure of 95/60 mm Hg, respiratory rate of 14 breaths/min, and oxygen saturation of 100% while breathing room air. She is acutely ill appearing and not oriented to person, place, or date. Mucous membranes are dry, and no edema is present. Saline solution, 0.9%, is begun with a plan to administer 1 L over the first 2 hours. Laboratory results return, revealing [Na^+] of 104 mmol/L, serum potassium level of 2.8 mmol/L, SUN level of 27 mg/dL, and serum creatinine level of 1.4 mg/dL. She experiences a generalized seizure.*

Question 2: Which of the following is the most appropriate next step in management?

a) Increase rate of normal saline solution
b) Administer tolvaptan
c) Bolus 100 mL of 3% saline solution over 10 minutes
d) Infuse 500 mL of 3% saline solution over 15 minutes

Question 3: After appropriate treatment, no further seizure activity occurs, and repeat [Na^+] is 108 mEq/L. In addition to infusion of isotonic IV fluids and monitoring [Na^+] every 2 hours, which of the following is the most appropriate management strategy?

a) Aim for an [Na^+] of 120 mEq/L over the first 24 hours
b) Aim for an [Na^+] of 114-116 mEq/L over the first 24 hours
c) Aim for an [Na^+] of 114-116 mEq/L over the first 24 hours and monitor urine output hourly and U_{Osm} every few hours
d) Aim for an [Na^+] of 110-112 mEq/L over the first 24 hours
e) Aim for an [Na^+] of 110-112 mEq/L over the first 24 hours and monitor urine output hourly and U_{Osm} every few hours

Answer to Question 2: Hypertonic saline solution is indicated for severely symptomatic hyponatremia with a seizure. Acutely increasing the [Na^+] by 4 to 6 mEq/L can prevent further seizure activity, reduce brain swelling, and eliminate the risk for tentorial herniation due to cerebral edema. In a setting in which increasing [Na^+] is a genuine emergency, this can be accomplished by administration of up to three 100-mL boluses of 3% saline solution 10 minutes apart. Tolvaptan and 0.9% saline solution will not increase [Na^+] quickly or reliably enough. Thus, (c) is the correct answer.

Answer to Question 3: This patient has multiple risk factors for ODS with over rapid correction, namely presenting serum [Na^+] < 105 mEq/L, hypokalemia, and thiazide diuretic use. A more conservative goal of correcting [Na^+] ideally by 4 to 6 mEq/L and no more than 8 mEq/L in the first 24 hours is appropriate. [Na^+] should be monitored every 2 hours. Because an increase in urine output and decrease in UOsm will precede any increase in [Na^+], hourly urine output should be followed up, which will likely require bladder catheter placement. UOsm should be measured every few hours. Thus, (e) is the correct response.

Treatment of Hyponatremia

Treatment of Hypertonic Hyponatremia

Translocational hyponatremia secondary to hyperglycemia should improve with lowering of blood glucose level. Aggressive volume repletion with isotonic fluid is also typically required to correct volume depletion from the glucosuria-driven osmotic diuresis and make up for intracellular translocation of water with glucose in response to insulin.

Complications of Treatment of Hypotonic Hyponatremia

While a brain cell depleted of its organic osmolytes resists swelling in a hypotonic environment, it may dehydrate and shrink if its surrounding tonicity increases faster than it can reaccumulate effective osmoles. Osmotic demyelination syndrome (ODS) can occur if correction of hyponatremia is achieved too rapidly. Sequelae of ODS are often irreversible and include dysphagia, dysarthria, spasticity, behavioral disturbance, cognitive impairment, delirium, seizures, quadriparesis, coma, and "locked in" syndrome.

ODS classically presents as neurologic deterioration several days after an initial treatment-induced improvement in the neurologic symptoms from the hyponatremia itself. Because of this delay, over rapid correction should be promptly addressed despite the lack of any symptoms. However, acute hypotonic hyponatremia developing over less than 24 to 48 hours lacks complete brain adaptation and thus carries no risk for ODS. ODS is also unlikely to complicate treatment of patients with an initial $[Na^+] > 125$ mEq/L. Among patients with chronic hypotonic hyponatremia, a presenting $[Na^+] < 105$ mEq/L, alcoholism, advanced liver disease, and malnutrition are notable risk factors for ODS. Because potassium is exchangeable with sodium, repletion of potassium deficits leads to translocation of sodium out of cells and a further increase in $[Na^+]$; hypokalemia is also a risk factor for ODS.

Goals of Treatment of Hypotonic Hyponatremia

Treatment of hypotonic hyponatremia must balance the risk for morbidity or mortality from persistent hyponatremia against that of ODS from over rapid correction. Because normalization of $[Na^+]$ in acute hyponatremia carries no risk for ODS, the rate of increase need not be constrained when the duration of hyponatremia is known to be less than 48 hours. With chronic hyponatremia, clinicians should increase $[Na^+]$ enough to abrogate the risk for serious complications of hyponatremia such as seizures or brain herniation without putting the patient at risk for ODS. In a key retrospective study of 56 patients treated for chronic hyponatremia with a $[Na^+] < 105$ mEq/L, posttherapeutic neurologic complications did not occur among patients for whom $[Na^+]$ corrected < 12 mEq/L in 24 hours or <18 mEq/L in 48 hours. They were absent as well in patients for whom $[Na^+]$ increased <0.55 mEq/L per hour to a concentration of 120 mEq/L (Fig 4). These findings are the basis for recommendations and guidelines for the maximal rate of $[Na^+]$ correction in chronic hyponatremia. The potential of augmented risk for ODS should also be taken into account. Current goals and limits for $[Na^+]$ correction are shown in Table 1.

Beyond chronicity, the severity of attributable symptoms should also guide therapy. Most patients presenting with chronic hyponatremia have mild or no symptoms, leaving providers ample time to fix the electrolyte disturbance gradually. For patients who are severely symptomatic with marked alterations in sensorium or seizures, rapid elevation of the $[Na^+]$ (irrespective of presumed duration of hyponatremia) by just 4 to 6 mEq/L in 1 to 2 hours can significantly reduce brain swelling and abort any seizure or seizure risk. This can be accomplished by administration of up to three 100-mL boluses of hypertonic saline solution given 10 minutes apart.

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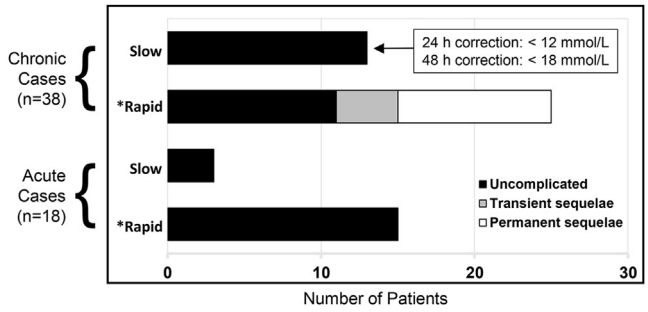

Figure 4. Rate of correction of chronic or acute severe hyponatremia. In this retrospective analysis, 56 patients with a starting serum sodium concentration ($[Na^+]$) < 105 mEq/L were treated for chronic hyponatremia. Transient and permanent neurologic sequelae occurred only when hyponatremia was rapidly corrected in chronic cases. Posttherapeutic neurologic complications did not occur when $[Na^+]$ corrected < 12 mEq/L in 24 hours or <18 mEq/L in 48 hours and at a rate < 0.55 mEq/L/h to a value of 120 mEq/L. Figure drawn from data in Sterns et al (Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. *J Am Soc Nephrol*. 1994;4(8):1522-1530).

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Treatment of Hypotonic Hyponatremia

Suggested treatment strategies for hypotonic hyponatremia are provided in Table 1. Electrolyte-free water restriction can prevent worsening hyponatremia irrespective of the cause. Thiazide diuretic treatment should be discontinued. If urine is maximally dilute, restricting fluid ingestion in primary polydipsia or increasing solute intake and thus the potential for electrolyte-free water excretion in a patient following an otherwise solute-deficient diet is usually sufficient. Patients with severe hyponatremia due to primary polydipsia may experience rapid correction of $[Na^+]$ with fluid restriction. Close monitoring is warranted, and measures to replace or retard water loss (see later discussion) may be necessary.

Hypovolemic Hyponatremia. Impaired urinary dilution due to hypovolemia should prompt volume repletion with isotonic fluids such as 0.9% saline solution or

Table 1. Suggested Treatment Strategies for Management of Hyponatremia According to Chronicity, Symptom Severity, and Risk for ODS

Presentation	Risk for ODS	Goal Increase in $[Na^+]$	Limit to Increase in $[Na^+]$	Treatment Strategy
Acute Hypotonic Hyponatremia (duration verified to be <48 h)				
Severe symptoms	Negligible	Rapid increase by 4-6 mEq/L, then gradual increase to normalization	Normalization	Rapidly increase $[Na^+]$ by 4-6 mEq/L with up to three 100-mL boluses of hypertonic saline solution given over 10 min at a time, followed by hypertonic saline solution at 1 mL/kg/h until substantial normalization. If rapid spontaneous correction occurs, it need not be constrained.
Mild or moderate symptoms	Negligible	Normalization	Normalization	Fluid restriction alone if cause rapidly reversible. Otherwise, hypertonic saline solution at 1 mL/kg/h until substantial normalization.
Chronic Hypotonic Hyponatremia (duration known to be >48 h or uncertain)				
Severe, moderate, or mild symptoms	High[a]	4-6 mEq/L in 24 h	8 mEq/L in any 24-h period	Treatment according to cause (volume repletion for hypovolemic hyponatremia, water restriction with SIADH or hypervolemic hyponatremia, etc) and severity of symptoms. Hypertonic saline solution for severely symptomatic hyponatremia with risk for seizures or herniation or a vaptan or urea for mild to moderate refractory euvolemic or hypervolemic hypernatremia. During early phase, closely monitor $[Na^+]$ every 2-4 h and urine output. Re-lower $[Na^+]$ with IV D5W or enteral water ± desmopressin, 1-2 μg, every 6 h if correction over rapid.
Severe, moderate, or mild symptoms	Intermediate	4-8 mEq/L in 24 h	10-12 mEq/L in any 24-h period and no more than 18 mEq/L in any 48-h period	Same strategy as high-risk ODS patients, except with less strict $[Na^+]$ correction limits.
Moderate or mild symptoms	Low (initial $[Na^+]$ > 125 mEq/L)	Normalization	Normalization	Treatment according to cause. Consider vaptan or urea for refractory euvolemic or hypervolemic hypernatremia.

Note: In patients with substantial risk for ODS (especially those with starting $[Na^+]$ < 120 mEq/L) who experience an increase in $[Na^+]$ exceeding the recommended limit, consider re-lowering $[Na^+]$ to a value below target by administration of electrolyte-free water. Urine output and/or osmolality should also be followed to detect onset of a spontaneous water diuresis (especially with volume depletion or thiazide-associated hyponatremia) that can lead to over rapid correction. Desmopressin may be useful in this setting to limit ongoing urinary water loss.

Abbreviations: D5W, 5% dextrose in water; IV, intravenous; $[Na^+]$, serum sodium concentration; ODS, osmotic demyelination syndrome; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Based on recommendations from Verbalis et al (Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med.* 2013;126(10)(suppl 1):S1-S42).

[a]$[Na^+]$ ≤ 105 mEq/L, hypokalemia, alcoholism, malnutrition, and advanced liver disease.

Ringer's lactate solution. Because restoration of euvolemia is accompanied by suppression of nonosmotic vasopressin release, this may lead to the abrupt onset of a brisk water diuresis and the consequent risk for over rapid correction of $[Na^+]$. Clinicians should anticipate the occurrence of this phenomenon. Close observation of hourly urine output is mandatory in severe cases, and frequent measurement of U_{Osm} in this setting is useful. Slow correction of hypovolemia (if shock is absent and the patient is not compromised by hypoperfusion), may be beneficial in preventing this complication.

Hypervolemic Hyponatremia. Management of vasopressin-mediated hypervolemic hyponatremia depends on the cause. For both heart failure and cirrhosis, fluid and salt restriction are cornerstones of treatment, although their feasibility and efficacy are limited. Because worsening volume overload may exacerbate a low cardiac output state in decompensated heart failure and in turn potentiate nonosmotic vasopressin release, loop diuretics should be considered first-line therapy for hyponatremia attributed to heart failure. As mentioned, loop diuretics tend to impair free-water reabsorption. They can be cautiously used in cirrhosis as well. When fluid restriction and loop diuretics fail, a vasopressin antagonist (vaptan) like tolvaptan or conivaptan can be used to promote aquaresis and is indicated as second-line therapy for mild to moderate symptomatic hyponatremia related to heart failure. Caution is indicated before the use of a vaptan in patients with cirrhosis due to their potential to cause splanchnic vasodilatation (conivaptan) or hepatotoxicity (tolvaptan; see Pharmacologic Therapies). In practice, these medications are nonetheless used in patients awaiting liver transplantation to optimize volume status and increase $[Na^+]$ to a level acceptable for transplantation listing.

Euvolemic Hyponatremia. If the cause is hypothyroidism or isolated glucocorticoid deficiency, management consists of fluid restriction plus hormone replacement therapy. However, the overwhelming majority of patients with euvolemic hyponatremia have SIADH. This disorder is ideally managed by eliminating its cause. SIADH due to pulmonary or central nervous system infection will resolve with appropriate antimicrobial therapy. Treatment with culprit medications should be discontinued, if possible. Eliminating tumors responsible for ectopic vasopressin production may not be feasible, and other causes of SIADH (Box 4) may be difficult to remove. Beyond treating the cause, SIADH is also initially managed with water restriction. The degree of water restriction that will mitigate hyponatremia can be estimated using the ratio of the sum of urinary sodium and potassium concentrations to the $[Na^+]$ (Box 1). A ratio < 1 allows for more liberal limits (ie, <1 L/d). A ratio > 1 may call for prohibitively strict measures (<500 mL/d) and predicts worsening of hyponatremia with IV isotonic fluid saline administration because the sodium chloride is excreted in a smaller volume of more highly concentrated urine with the remaining electrolyte-free water retained.

Fluid restriction alone is unlikely to be successful in many cases of SIADH when the underlying cause is persistent. Increasing solute intake with protein or salt supplementation may prove helpful by increasing solute excretion in urine and with it obligatory water excretion. Oral urea supplementation functions in a similar fashion as a nonreabsorbable urinary solute. When these interventions are unsuccessful, a vaptan can be used.

Indications for and Dosing of Hypertonic Saline Solution

Note that neither urea nor vaptans increase $[Na^+]$ with predictability or reliability. Therefore, severe symptoms arising from SIADH or acute hyponatremia should prompt consideration of infusion of hypertonic saline solution. Given concerns for phlebitis associated with prolonged peripheral infusion of hyperosmolar solution, some centers require that continuous infusion of hypertonic saline solution be given through a central venous catheter, though data for adverse outcomes associated with peripheral IV infusion are lacking. A number of formulas of varying complexity have been proposed to guide hypertonic saline solution dosing. None is more than an approximation, and none takes into account the effect on $[Na^+]$ of concomitant ongoing renal water or sodium excretion. Therefore, we prefer this simple formula for initial guidance: each 1 mL/kg/h of 3% saline solution administered can be expected to increase $[Na^+]$ by 1 mEq/L/h. Whichever formula is selected, it is important to understand that the formulas may underestimate the change in $[Na^+]$, and results are highly variable. Serial laboratory measurements every 1 to 2 hours are mandatory to assess the effect of the infusion.

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Pharmacologic Therapies

Two pharmacologic therapies for hyponatremia, the vaptans and the osmotic agent urea, deserve more detailed discussion. Conivaptan is a nonselective vasopressin V1 and V2 receptor inhibitor. Tolvaptan is V2 selective. When administered according to protocol in placebo-controlled randomized clinical trials, conivaptan increased $[Na^+]$ by approximately 8 mEq/L over several days and tolvaptan increased $[Na^+]$ by about 5 mEq/L over 4 days when administered at a starting dose of

15 mg titrated up to 60 mg daily. Approximately 2% of patients given tolvaptan experienced over rapid correction of [Na^+]. The change in [Na^+] was greater in patients with lower starting values, a factor that may partly explain the far less predictable results observed in individual patients treated outside a clinical trial. Some patients will be exquisitely sensitive and others will be relatively refractory. Careful monitoring of [Na^+] changes is thus required when vaptans are initiated.

As these drugs underwent development, the initial expectation was that their ability to antagonize the effect of excessive vasopressin specifically would make them highly efficacious and that they would be widely used. As it turns out, neither agent can be used long term, which has greatly curtailed their use even for the short term because clinicians are reluctant to start a treatment for a long-lasting condition that can be used only briefly. Conivaptan is a potent CYP3A4 inhibitor with many drug-drug interactions. Consequently, although orally active, it received US Food and Drug Administration approval in only an IV formulation for short-term use. Long-term tolvaptan use is limited by 2 factors. After its initial approval for hyponatremia therapy, a significant risk for liver injury was noted in clinical trials in which tolvaptan was used to retard cyst growth in polycystic kidney disease. Thus, the potential to induce liver damage is a relative contraindication for long-term tolvaptan use. Because the drug dose used for polycystic kidney disease was much higher than that used in hyponatremia and liver injury test results can be followed serially, concerns about liver injury with long-term tolvaptan use are not insurmountable. The more important factor precluding long-term tolvaptan use is its cost, ~$450 for a single 15 mg tablet.

These agents are suitable when the duration of the underlying cause of hyponatremia is expected to be brief, as with pneumonia-induced SIADH or when [Na^+] must be increased for a specific reason, such as an upcoming surgical procedure. Although either agent can be used, additional concerns have been raised regarding the extrarenal effects of V1 antagonism by conivaptan. The V1 receptor is present, among other sites, in vascular smooth muscle, platelets, and myocardium. When activated, it effects vasoconstriction, platelet aggregation, and myocardial hypertrophy. Inactivation of the V1 receptor could induce hypotension and may account for the orthostatic hypotension observed in ~14% of patients receiving conivaptan. In light of the unfavorable splanchnic vasodilation that may occur, this agent is generally avoided in cirrhosis.

The most pronounced side effects for both tolvaptan and conivaptan are thirst, dry mouth, and polyuria. Vaptans should not be used in concert with hypertonic saline solution owing to case reports of associated ODS.

Urea is a long-standing and less-expensive alternative to the vaptans for treatment of SIADH. Excreted in urine, it increases urinary solute content and electrolyte-free water clearance. Retrospective studies suggest that administration of 7.5 to 90 g/d of urea is associated with an ~6-mEq/L increase in [Na^+] over 4 to 5 days. Save for dysgeusia, urea is not associated with serious adverse events such as [Na^+] overcorrection. Most of the reported experience with urea is from a single group in Belgium, and controlled trials versus vaptans or even placebo are lacking. Formerly, urea was available in the United States only through compounding formularies in an unpalatable form. Recently, a flavored preparation has become available in the United States, classified as a medical food that does not require a prescription. In a single-center US study, urea was reasonably well tolerated, safe, and effective.

Neither vaptans nor urea have been well studied in severe symptomatic hyponatremia. Patients with [Na^+] < 120 mEq/L and attributable neurologic symptoms were excluded from vaptan trials. The effect of urea is slow. Accordingly, at the present time, without further data, vaptans or urea should be considered for use only in patients with euvolemic or hypervolemic hyponatremia with mild to moderate symptoms, and not in circumstances in which [Na^+] must be increased emergently.

A large-scale registry that examined inpatient hospital treatment practices in 3,087 patients at 225 sites in the United States and European Union noted urea use in only 10 patients. Due to the heterogeneity of treatment patterns, more detailed analysis of the efficacy of individual agents was limited to initial monotherapies used; in the case of tolvaptan, 131 patients; and hypertonic saline solution, 72 patients. Because therapies were not randomized, definitive conclusions about relative efficacy cannot be drawn, but hypertonic saline solution and tolvaptan produced the largest changes in [Na^+]. Fluid restriction alone had little efficacy. Given the paucity of data for either urea or tolvaptan and the encumbrances to the use of tolvaptan, it is difficult to draw definitive conclusions about the best long-term therapy for hyponatremia.

The lack of data is reflected in discordant expert panel recommendations or guidelines. A principally US-based expert panel recommended use of tolvaptan because it is the only agent for which placebo-controlled trials are available. European Best Practice guidelines, conversely, recommended urea and described no role at all for vaptans. The issue is further obscured by the lack of trials with adequate power to assess any benefit on any long-term outcome besides [Na^+].

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Prevention and Management of Overcorrection

If the risk for ODS or the likelihood of over rapid correction is high, clinicians should monitor the response to therapy vigilantly. Particularly when hypertonic saline solution is used or severe hyponatremia complicates profound hypovolemia, $[Na^+]$ should be measured every 2 to 4 hours. In thiazide-induced and hypovolemic hyponatremia, aquaresis may follow the suppression of nonosmotic vasopressin release that occurs after volume repletion. This can result in a rapid increase in $[Na^+]$. Because the increase will be preceded by an increase in urine output and decrease in U_{Osm}, urine output should be monitored hourly and U_{Osm} should be measured frequently in this setting.

If overcorrection occurs, calculation of urine electrolyte-free water excretion can guide therapy (Box 1). Administering enteral water or IV 5% dextrose in water in an amount equal to urinary electrolyte-free water loss plus estimated extrarenal and insensible water losses should prevent a further increase in $[Na^+]$. If overcorrection occurs, consideration should be given to therapeutic relowering of the $[Na^+]$. In this scenario, we suggest increasing the calculated rate of enteral water or IV 5% dextrose in water administration by 3 mL/kg/h.

Particularly when urine output is high and urine is very dilute, desmopressin can be administered to abrogate any further urine electrolyte-free water loss and simplify fluid management. In patients at high risk for over rapid correction due to aquaresis, some authorities recommend preemptive administration of desmopressin, 1 - 2 μg, IV or subcutaneously every 6 hours to prevent any urine electrolyte-free water loss with 3% saline solution infused at a rate calculated to effect the desired rate of increase in $[Na^+]$. Irrespective of the strategy adopted, adherence to the recommended daily maximal $[Na^+]$ increase limit and frequent laboratory monitoring are key requirements for avoidance of ODS.

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Hypernatremia

Defense Against the Development of Hypernatremia

Hypernatremia is either caused by renal or nonrenal loss of water in excess of any accompanying salt loss or by concentrated salt intake. Water loss is overwhelmingly the more common cause. Small increases in plasma tonicity stimulate both vasopressin release and thirst. The resulting reduction in renal electrolyte-free water excretion and increase in water intake prevent the development of hypernatremia if the individual can sense and act on thirst. Thus, hypernatremia from water loss typically occurs in infants or individuals with altered sensorium, infirmity, or concurrent medical conditions such as stroke or endotracheal intubation that interfere with communication or access to water.

When factors contributing to hypernatremia were compared in individuals admitted to the hospital with hypernatremia and individuals who developed it in the hospital, 2 patterns emerged. Patients with hypernatremia on admission were older, often came from a long-term care facility in which their access to fluid may have been impaired, and mostly had preserved urinary concentrating capacity. Patients who developed hypernatremia in the hospital had an age similar to that of the overall hospital population. Eighty-six percent lacked free access to water, 74% had enteral water intake < 1 L/d, and virtually all received < 1 L/d of electrolyte-free water during the period when hypernatremia developed. Renal concentrating ability was impaired in 89% due principally to the use of diuretics or an osmotic diuresis. In this adult population, hypernatremia acquired outside the hospital was principally a geriatric disorder, whereas hospital-acquired hypernatremia was due to an insufficient fluid prescription, that is, iatrogenic.

One unusual cause of hypernatremia bears mention. Rarely, a defect in thirst perception caused by hypothalamic lesions leads to reduced water ingestion, a condition termed essential hypernatremia.

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Classification of Hypernatremia

Apart from impaired thirst and water intake the cause of hypernatremia can be separated among 3 categories using the history and laboratory data (Table 2). In the first group, the route of electrolyte-free water loss is extrarenal. Except for pure transpirational skin loss, the fluid lost is sodium-containing but hypotonic. U_{Osm} is usually > 600 mOsm/kg H_2O, indicating preserved urinary concentrating ability.

In the second group, a renal concentrating defect is responsible, with renal fluid loss driven by natriuretic diuretics, an osmotic diuresis from hyperglycemia, or pure water loss due to DI. The third group has no water loss. Their hypernatremia has developed because of excessive salt administration. The clinical settings are diverse but inevitably involve accidental or iatrogenic administration of large salt loads with limited or no fluid.

Table 2. Causes of Hypernatremia

Cause	Proximate Cause	Findings Supporting Diagnosis
Inadequate water intake	Lack of access to water	• Altered sensorium, immobility, endotracheal intubation • Chronic care facility residence • Fluid prescription that does not take into account insensible losses • U_{Osm} > 600 mOsm/kg H_2O
Extrarenal hypotonic fluid loss	GI losses or perspiration	• History of diarrhea, febrile illness, gastric suction, or enteric fistula • U_{Osm} > 600 mOsm/kg H_2O
Renal concentrating defect	Diuretics	• History of loop diuretic use • Isosthenuric urine
	Osmotic diuresis	• Hyperglycemia with glucosuria • Urea-induced osmotic diuresis • Isosthenuric urine (eg, recovery from ATN)
	Central diabetes insipidus	• Presence of brain trauma, surgery, tumor, infiltrative disease, or infection including tuberculosis • Maximally or submaximally dilute urine • Persistently dilute urine during water deprivation test • Low copeptin levels • U_{Osm} increases in response to desmopressin
	Nephrogenic diabetes insipidus	• Treatment with lithium or demeclocycline, hypercalcemia, hypokalemia, renal tubulointerstitial disease, especially sickle cell nephropathy and obstructive uropathy • U_{Osm} < 300 mOsm/kg H_2O • Persistently dilute urine during water deprivation test • High copeptin levels • U_{Osm} fails to increase in response to desmopressin
Excessive salt intake	Hypertonic fluid administration	• Receipt of hypertonic sodium bicarbonate solution during cardiac arrest or hypertonic saline solution • History of dilution error for powdered feeding formulas in infants • Administration of TPN or concentrated enteral tube feeds • U_{Osm} > 600 mOsm/kg H_2O • U_{Na} > 100 mEq/L

Note: Even if not specifically noted, impaired thirst or access to water is typically also present.
Abbreviations: ATN, acute tubular necrosis; GI, gastrointestinal; TPN, total parenteral nutrition; U_{Na}, urine sodium concentration; U_{Osm}, urine osmolality.

Diabetes Insipidus

If hypernatremia develops and urine is submaximally concentrated, DI is present. Central DI is characterized by the lack of vasopressin, which may be complete or partial. Among the causes of central DI (Table 2), pituitary trauma is characterized by a classic triphasic response. An initial period of DI is followed by SIADH due to uncontrolled release of vasopressin from necrosing pituitary cells followed by sustained DI. The urine will be persistently maximally dilute or submaximally concentrated if the vasopressin lack is complete or partial, respectively. Symptoms of polyuria and polydipsia may not be severe, though hypernatremia will develop if access to water is impaired. Nephrogenic DI is caused by an absent or incomplete response to vasopressin (Table 2). The hereditary forms are typically caused by inactivating mutations of the principal cell V2 receptor. Aquaporin defects are less frequently responsible.

Overnight water deprivation testing is used to diagnose DI. In this setting, body weight, blood pressure, and serum chemistries are measured while water is withheld. Because patients with complete DI may become significantly water depleted and hypernatremic after less than 12 to 16 hours of water deprivation, the test should be stopped if >3% of body weight is lost. After water deprivation, urine concentration before and after desmopressin administration is determined. Individuals with central DI concentrate urine in response to desmopressin; patients with nephrogenic DI are refractory. Confusion may arise if a patient with polyuria due to primary polydipsia is mistakenly assumed to have DI and undergoes diagnostic water deprivation. Long-term polydipsia can wash out the medullary interstitial concentration gradient and downregulate aquaporin 2 leading to impaired urinary concentration and falsely suggesting the presence of nephrogenic DI. Notably, such patients will not have a history of hypernatremia. Direct measurement of vasopressin is difficult due to instability of the hormone and has led to persistent reliance on diagnostic water deprivation. Recently, measurements of the more stable vasopressin prohormone carboxy-terminal cleavage peptide, copeptin, have been used to differentiate between primary polydipsia, central DI, and

nephrogenic DI. Copeptin testing may supplant use of the water deprivation test.

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Treatment

The initial step in management is identification of the cause of hypernatremia and its correction, if possible. Depending on the responsible disorder, specific treatment may include insulin for hyperglycemia, symptomatic management of gastrointestinal symptoms, correction of hypercalcemia or hypokalemia, and, for central DI, long-term administration of desmopressin.

To protect against brain shrinkage as hypernatremia develops, brain cells take up solute. Dissipating those added osmoles during correction takes time. Rapid correction can result in neuronal water uptake and cerebral edema. However, in contrast to hyponatremia, an extensive body of experimental studies and reports of clinical experience with complications of treatment are lacking. Thus, recommendations for rate of correction are less well grounded and largely opinion based.

If hypernatremia develops rapidly (<48 hours), rapid correction is appropriate, with correction to normal over 24 hours. How quickly to correct hypernatremia of longer duration is uncertain. Until recently, opinion-based expert recommendations, based principally on small retrospective studies in children with hypernatremia that reported a lower incidence of cerebral edema when $[Na^+]$ was lowered at 0.5 vs 1.0 mEq/L/h, called for lowering the $[Na^+]$ at a rate of 10 to 12 mEq/L/d. This recommendation was challenged by a recent retrospective study of hypernatremic adults that found no difference in mortality or complications of treatment with rapid (>0.5 mEq/L/h) versus slow (≤0.5 mEq/L/h) correction of either community- or hospital-acquired hypernatremia. Absent definitive data, our approach is to correct chronic hypernatremia over a 48-hour period.

The standard formula for calculation of free-water deficit is noted in Box 1. This formula is a starting point and does not take into account ongoing water losses, which must be added to the fluid prescription. As with hyponatremia, $[Na^+]$ and ongoing fluid losses should be measured frequently and the fluid prescription adjusted accordingly. Hypotonic salt-containing IV fluids are of course only partially electrolyte free. Choice of IV fluids must take into account the fraction of the fluid that can be considered to be electrolyte free. A simple method is to administer 5% dextrose in water IV or water enterally at a rate targeted to the water deficit and give a separate infusion of isonatric fluid, if required, to correct any volume depletion resulting from the hypotonic fluid loss that generated the hypernatremia.

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