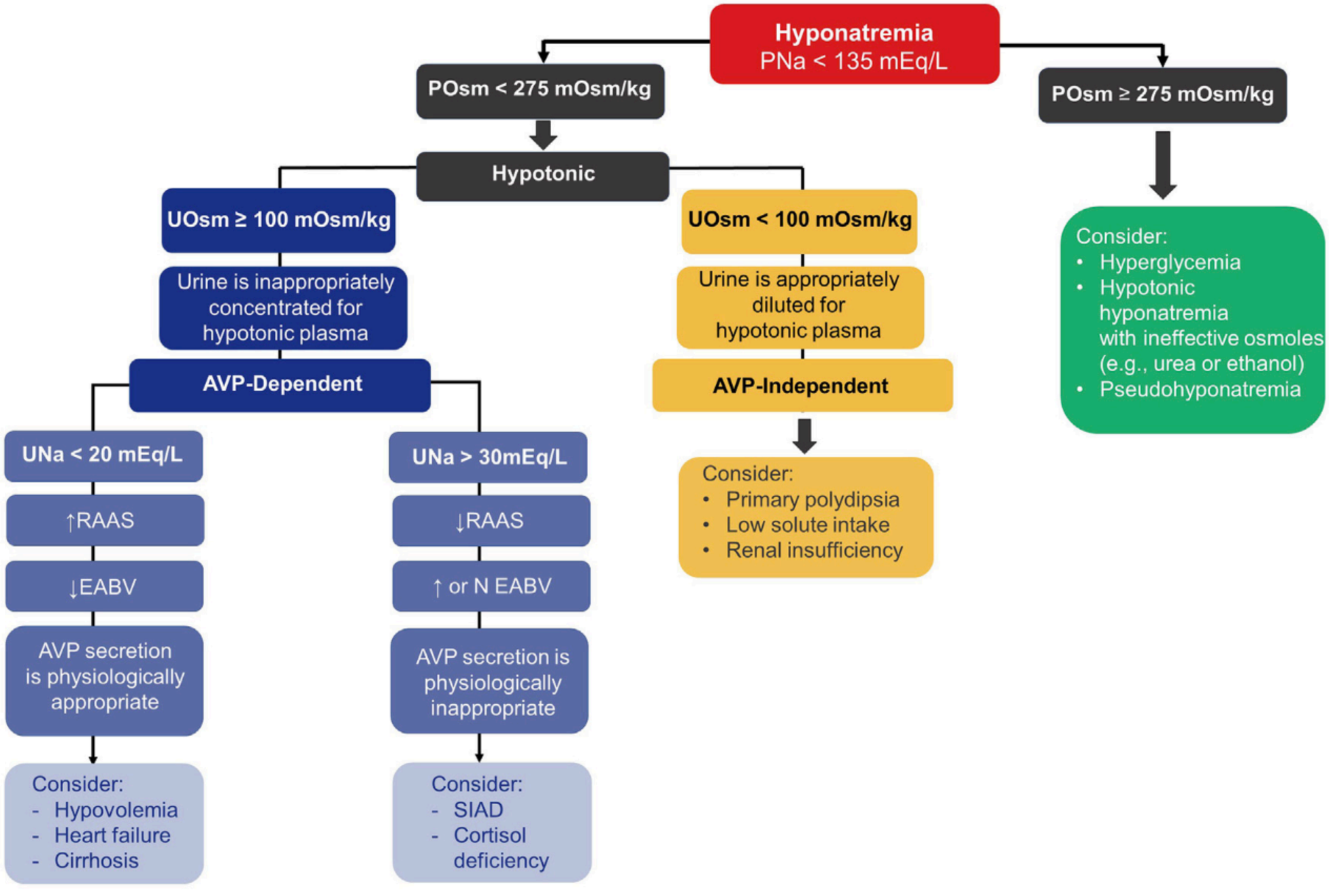

Figure 4. Diagnostic approach to hyponatremia. Abbreviations: AVP, arginine vasopressin; EABV, effective arterial blood volume; PNa, plasma sodium concentration; POsm, plasma osmolality; RAAS, renin-angiotensin-aldosterone system; SIAD, syndrome of inappropriate antidiuretic hormone; UNa, urine sodium concentration; UOsm, urine osmolality. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Hyponatriämie und SIADH

Bei schwerer *symptomatischer Hyponatriämie* → Therapie ad ICU mit *3% NaCl* (nach komplett abgenommener Diagnostik, incl. Urin)

- ❑ Anamnese: *Medikamente*, Gewichtsverlauf, *Erbrechen, Übelkeit*, Stürze, Schwäche, Müdigkeit, akute Verbrennung, Trinkmenge/Tag, subj. Durstgefühl, *neurologische Symptome*, quant/qualitat. *Bewusstseinsstörung*
- ❑ PA: Pneumopathie, Hirnpathologien, Operation, frühere Dysnatriämien
- ❑ Volumenstatus: Blutdruck (stehend und liegend), Herzfrequenz, Halsvenen, Unterschenkelödeme, Aszites, Pleuraerguss, Orthopnoe
- ❑ Labor: *Blut: Osmolarität*, CG, BGA; *Urin: Osmolarität*, Natrium, Kalium, Chlor, Harnstoff, Harnsäure, Kreatinin

Hyponatriämie (Na^+<135mmol/l)

P_{osm}> 280 mmol

Pseudo- oder Translocational Hyponatriämie

P_{osm}<280mmol/l

$Urin_{osm}$<200mmol/kg

- Primäre Polydipsie
- Biertrinker-Potomanie

Therapie
Wasserrestriktion auf 500ml/24h

$Urin_{osm}$>200mmol/kg

***FE_{H-St} <35% + FE_{H-Sre}<20%**
oder
FE_{H-St} >35% + FE_{H-Sre}<12%

FE_{H-St} >35% + FE_{H-Sre}>12%

- Chron./*Akute Niereninsuff*
- *SIADH*

ausser

- *Diarrhoe*, Vomitus
- Verlust in den 3. Raum
- Diuretika
- Mineralokortikoid Mangel

Therapie
0.9% NaCl, max. 1/25 des Gewichtes (in Liter)

Klinische Hypervolämie
(Ödeme, *Aszites*, Orthopnoe)

- *Herzinsuffizienz*
- Leberzirrhose
- Nephrotisches Syndrom

Therapie
Wasserrestriktion auf 500ml/24h,
Auslöser behandeln

*Kalkulator MD+CALC

2012/07

Hyponatriämie und SIADH: Berechnungsformeln

- **Osmolarität (mmol/l):** $2_x\,(Na^+)$ + Glucose + Harnstoff

  Norm *Plasma*: 275-290 mOsm/l
  Urin: 50-1200 mOsm/l

- **Renale Natrium Extraktionsfraktion**:

  $100 \times (Urin_{Na} \times Plasma_{krea}) : (Plasma_{Na} \times Urin_{krea})$

  Norm: 1-2%

- **Na-Aenderung nach Infusion von 1 l in Abhängigkeit der Na-Konzentration**

  NaCl 0.9%: 154 mmol/l Na
  NaCl 3%: (=1l NaCl 0.9% + 80 ml NaCl 29%): 513 mmol/L)

Veränderung des Na^+_{Plasma} pro $L_{Infusion}$ = ($Na_{Infusat}$ – Na_{Plasma}) : (total body water (TBW*) + 1)

*TBW für Frauen = kgKG x 0.5
*TBW für Männer = kgKG x 0.6

Hyponatremia Demystified: Integrating Physiology to Shape Clinical Practice

Biruh T. Workeneh, Priti Meena, Mirjam Christ-Crain, and Helbert Rondon-Berrios

Hyponatremia is one of the most common problems encountered in clinical practice and one of the least-understood because accurate diagnosis and management require some familiarity with water homeostasis physiology, making the topic seemingly complex. The prevalence of hyponatremia depends on the nature of the population studied and the criteria used to define it. Hyponatremia is associated with poor outcomes including increased mortality and morbidity. The pathogenesis of hypotonic hyponatremia involves the accumulation of electrolyte-free water caused by either increased intake and/or decrease in kidney excretion. Plasma osmolality, urine osmolality, and urine sodium can help to differentiate among the different etiologies. Brain adaptation to plasma hypotonicity consisting of solute extrusion to mitigate further water influx into brain cells best explains the clinical manifestations of hyponatremia. Acute hyponatremia has an onset within 48 hours, commonly resulting in severe symptoms, while chronic hyponatremia develops over 48 hours and usually is pauci-symptomatic. However, the latter increases the risk of osmotic demyelination syndrome if hyponatremia is corrected rapidly; therefore, extreme caution must be exercised when correcting plasma sodium. Management strategies depend on the presence of symptoms and the cause of hyponatremia and are discussed in this review.

Key Words: Hyponatremia, Plasma tonicity, Arginine vasopressin, Urea, Osmotic demyelination syndrome

Hyponatremia, defined as a plasma sodium concentration (PNa) < 135mEq/L, is one of the most common problems in clinical practice and one of the least-understood because accurate diagnosis and management require some familiarity with the water homeostasis physiology, making the topic seemingly complex. Hyponatremia has been associated with increased morbidity, mortality, and increased health care–related expenses with an estimated annual direct cost ranging between $1.6 billion and $3.6 billion in the United States alone.[1] This article reviews the epidemiology, diagnosis, clinical manifestations, risk factors for complications, and management approaches of hyponatremia based on the best available evidence. Our objective is to equip the reader with the knowledge and confidence to approach this critical, often knotty, clinical problem almost every clinician is likely to encounter.

EPIDEMIOLOGY AND CLINICAL OUTCOMES

Prevalence

The prevalence of hyponatremia depends on the nature of the patient population studied (eg, hospital type and department) and the criteria used to define hyponatremia. When hyponatremia is defined as a PNa < 135 mEq/L, prevalence rates up to 30% are seen in acutely and chronically ill hospitalized patients.[2] When hyponatremia is defined as PNa < 130 mEq/L, the prevalence is expectedly lower ranging between 1% and 4%.[3] The risk of developing hyponatremia increases with age, and in institutionalized geriatric patients, it is as high as 50%.[4] Interdepartmental differences in hyponatremia rates are also observed, with one study showing that rates were higher in departments of surgery (32%), internal medicine (36%), and intensive care (38%) than those in all other hospital departments.[5]

Mortality

Several observational studies report an association of hyponatremia with an increased risk of mortality.[6] However, whether these associations indicate a causal relationship has not been established. It is also possible that hyponatremia is a surrogate marker for the severity of an underlying condition.[7] The results of ongoing trials should reveal information about the effects of a targeted correction of PNa on the mortality and rehospitalization rate (NCT03557957). In the absence of prospective data, the result of a large retrospective study suggests that there may be an association with increased risk of short-term adverse events, including in-hospital mortality.[8] Similarly, other investigations have shown that hyponatremia is associated with worse prognosis in several different disease states including cirrhosis,[9] pneumonia,[10] stroke,[11] pulmonary embolism,[12] end-stage kidney disease,[13] patients admitted to the intensive care unit,[14] myocardial infarction,[15] and heart failure.[16] For the latter, a large meta-analysis of 8 cohort studies showed that improvement of hyponatremia was associated with lower mortality

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risk during follow-up, particularly short-term mortality.[17] Furthermore, a meta-analysis of 15 observational studies with a total of 13,816 patients reported that any improvement of hyponatremia was associated with a reduced risk of overall mortality (odds ratio 0.57; 95% confidence interval 0.40-0.81).[18]

Morbidity

Chronic hyponatremia has often been thought to be asymptomatic or pauci-symptomatic. However, several studies have shown that hyponatremia, even if mild, is associated with gait instability,[19] falls, attentional deficits,[20] and increased risk of fractures.[21] In addition, hyponatremia is associated with an increased risk of osteoporosis compared with normonatremia, mainly as a result of increased osteoclast activity and mobilization of sodium stored within the bone matrix.[22] Again, most of these studies show associations, and only a few have shown reversibility of symptoms by correction of hyponatremia in randomized controlled studies.[23]

PHYSIOLOGY OF WATER HOMEOSTASIS

Homeostasis is defined as the ability of living organisms to keep a constant internal environment despite great fluctuations in external conditions. Homeostasis is essential for health and survival; as Claude Bernard puts it, "the constancy of the internal environment is the condition of a free and independent existence."[24] The extracellular fluid (ECF) constitutes the body's internal environment. Normal cell functioning requires that the ECF maintains specific physiological parameters (eg, temperature, pH, electrolyte concentration) within a very narrow range. One of these essential physiological parameters is plasma tonicity (PTon).

CLINICAL SUMMARY

- Chronic hyponatremia, even mild and apparently asymptomatic, has been associated with neurocognitive impairment including attention deficits, gait disturbances, falls, and osteoporosis.
- A physiological approach to the diagnosis of hyponatremia that calls for the sequential confirmation of hypotonicity, presence of arginine vasopressin, and mechanism for arginine vasopressin release is recommended.
- Potassium and sodium are osmotically equivalent, and adjustment of hypertonic saline infusion rate should be considered when supplementing potassium.
- Desmopressin can be used to prevent overly rapid correction of hyponatremia as water diuresis frequently occurs when arginine vasopressin release is turned off.

Plasma Osmolality and Tonicity

The importance of maintaining a constant PTon is linked to the control of cell volume; in hypertonic conditions, cells shrink, and in hypotonic conditions, cells swell. It is important to make the distinction between plasma osmolality (POsm) and PTon.[25] POsm simply refers to the number of solute particles (osmoles) dissolved in a kilogram of plasma water and can be estimated by using the following formula:

(equation 1): $POsm = 2 \times PNa + glucose/18$ and $BUN/2.8$,

where PNa is the plasma sodium concentration (in mEq/L), glucose refers to the plasma glucose concentration (in mg/dL), and BUN refers to the blood urea nitrogen concentration (in mg/dL). Normal POsm ranges between 280 and 295 mOsm/kg.

In contrast, PTon refers to the number of *effective* osmoles dissolved in a kilogram of plasma water. Effective osmoles refer to solutes that cannot cross cell membranes and, therefore, are able to generate osmotic water movement. Urea, as well as ethanol and toxic alcohols, readily cross cell membranes in muscle tissue and are considered *ineffective* osmoles, and hence, do not contribute to PTon. Urea is therefore excluded from equation 1:

(equation 2): $PTon = 2 \times PNa + Glucose/18$

Because normal plasma glucose level is about 90 mg/dL, the contribution of plasma glucose to PTon is small, only ~5 mmol/L (and in the case of an infusion of dextrose 5% in water, the effect is short-lived because dextrose is quickly metabolized). Therefore, PNa is the major determinant of PTon where PTon is $\approx 2 \times PNa$.

Plasma Sodium Concentration

As mentioned previously, PNa generally reflects PTon because sodium is the most important effective osmole in the ECF. By contrast, potassium is the most important effective osmole in the intracellular fluid and the most important contributor to intracellular fluid tonicity. On the basis of these principles, Edelman and colleagues in 1958 showed that PNa is a ratio between the total body exchangeable sodium (Na_E) and total body exchangeable potassium (K_E) and total body water (TBW).[26] This relationship can be illustrated as follows:

(equation 3): $PNa = 1.11 \times [(Na_E + K_E)/TBW] - 25.6$

Mathematically, the Edelman equation has the slope-intercept form of the equation of a straight line, that is, $y = mx + b$; where $y = PNa$, $m = 1.11$ (slope), $x = (Na_E + K_E)/TBW$, and $b = -25.6$ (intercept). The importance of the slope and intercept of the Edelman equation were not recognized until recently where analysis performed by Nguyen and Kurtz demonstrated that these are determined by several physiological parameters.[27] The slope is determined by the Gibbs-Donnan effect and the osmotic coefficient of sodium salts. The Gibbs-Donnan effect alters the distribution of sodium between the intravascular and interstitial compartments due to the presence of anionic impermeant plasma proteins, resulting in a higher concentration of sodium in the

intravascular compartment. The osmotic coefficient of sodium refers to the percentage of sodium salts (NaCl and NaHCO3) that completely dissociate into sodium ions in plasma. Under physiological conditions, only 94% of sodium salts completely dissociate. On the other side, the intercept of the Edelman equation likely represents a measure of the quantity of the osmotically inactive Na_E and K_E per unit of body water. Sodium exists in osmotically active and inactive forms. The latter form is found bound to anionic groups in glycosaminoglycans in bone, muscle, cartilage, and skin and does not contribute to PNa.[28]

A simplified form of equation 3 is more commonly used in clinical practice and is shown below:

(equation 4): $PNa = (Na_E + K_E)/TBW$

The importance of the variables Na_E and TBW in determining PNa can be readily appreciated. Decreasing the numerator (Na_E) and/or increasing the denominator (TBW) will decrease PNa. However, the effect of K_E is less apparent but has important clinical implications. Hypokalemia due to potassium losses can contribute to the genesis of hyponatremia,[29] and conversely, hypokalemia correction can lead to an increase in PNa.[30] If potassium is lost from the ECF, the ECF potassium concentration will decrease, creating a chemical gradient for potassium movement out of the cells. Potassium efflux into the ECF prevents water from entering the cells, resulting in PNa dilution.[29]

Water Balance

As it is evident from the Edelman equation, TBW is a major determinant of PNa. The kidneys play a major role in the homeostasis of PNa (and therefore PTon) by matching rates of water intake with water excretion. Only hypertonic or hypotonic fluid gains or losses alter PNa, while isotonic fluid changes do not. Therefore, this can be better described as electrolyte-free water balance, which defines the nonisotonic components of water input and output to determine their effects on PNa.[31]

Tonicity-Sensing Mechanisms

We do not possess sensors that directly monitor changes in electrolyte-free water, rather, we have osmoreceptors, which detect changes on a water balance surrogate, that is, PTon. There are central and peripheral osmoreceptors. The central osmoreceptors are the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT), which are circumventricular organs that lack the blood-brain barrier and can readily detect PTon changes. Mechanosensitive neurons located in the SFO and OVLT respond to hypertonicity by shrinking, which leads to the activation of the truncated N-terminal variant of the transient receptor potential vanilloid type-1 (ΔN-TRPV1) channels that generate inward currents resulting in depolarization, producing an action potential. In contrast, hypotonicity leads to an increase in cell volume in these neurons with the activation of transient receptor potential vanilloid type-4 (TPRV4) channels. The end result is hyperpolarization and a reduction in neuron basal activity. Direct coupling of these transient receptor potential vanilloid channels to microtubules/cytoskeleton networks is responsible for mechanical gating of the channels during cell volume changes in SFO and OVLT neurons.[32,33] Polymorphisms of the *TRPV4* gene have been associated with hyponatremia in healthy aging men.[34]

Changes in SFO and OLVT neuron cell volume are maintained as long as the osmotic stimulus persists. OVLT and SFO neurons then relay this information to median preoptic nucleus. Neurons from all 3 structures, but predominantly from the median preoptic nucleus, then project to the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus, which synthesize arginine vasopressin (AVP) as well as neurons in the insular and cingulate cortex to generate thirst. In addition, osmoreceptors outside the central nervous system (peripheral osmoreceptors) have been described in the oropharyngeal cavity, gastrointestinal tract, splanchnic mesentery, portal vein, and liver. These detect the osmotic strength of ingested food and induce an anticipatory response that might buffer changes in PTon associated with diet.[32]

Arginine Vasopressin

AVP is a hormone manufactured as prohormone in the magnocellular neurons of the PVN and SON of the hypothalamus and transported via their axons to the posterior pituitary. During transport, the prohormone undergoes enzymatic cleavage generating 3 peptides: AVP, neurophysin-2, and copeptin (Fig 1). Under physiological conditions, AVP and the other peptides are released in equimolar amounts from the posterior pituitary into the circulation triggered by 2 physiologic stimuli: plasma hypertonicity (ie, POsm >280-285 mOsm/kg) and decreased effective arterial blood volume (EABV). However, the PTon threshold for AVP release falls when EABV decreases and rises when EABV increases. This explains why, in patients with hypovolemic hyponatremia, AVP continues to be released despite the inhibitory effect of hypotonicity, indicating that the body prioritizes volume regulation over osmoregulation. The latter phenomenon known as osmosensory gain seems to be mediated by the stimulatory actions of angiotensin II over SFO and OVLT neurons.[35]

Once AVP is released, it then travels in the circulation and binds to the vasopressin 2 receptor (V2) in the basolateral membrane of the principal cells of the connecting tubule and collecting duct (CD) activating adenylyl cyclase and generating cyclic adenosine monophosphate, which in turn activates protein kinase A, phosphorylating aquaporin 2 water channels (AQP2) present in cytosolic vesicles causing shuttling and fusion of these AQP2 vesicles to the apical plasma membrane. This allows the reabsorption of water from tubular lumen into the blood. In addition, AVP also binds to the V2 receptors present in the cells of the thick ascending limb of the loop of Henle (TAL) and the inner medullary CD to increase the activity of the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) and urea transporters UT-A1 and UT-A3, respectively, resulting in

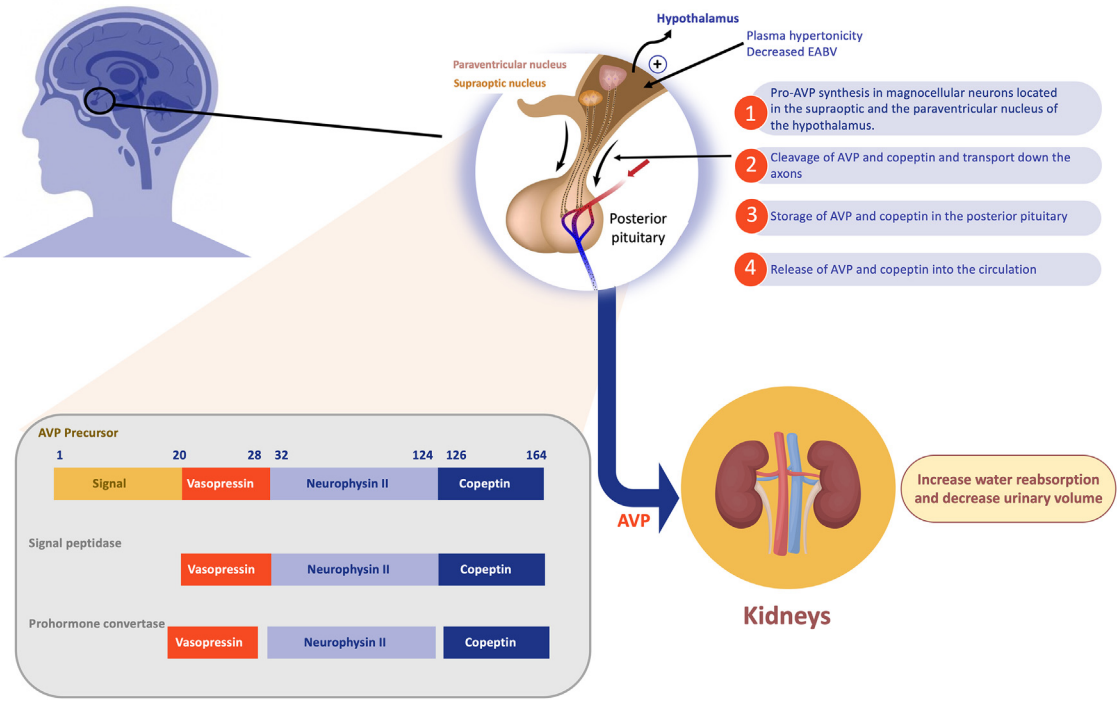

Figure 1. Synthesis of arginine vasopressin and copeptin. Abbreviations: AVP, arginine vasopressin; EABV, effective arterial blood volume. The prohormone pro-AVP is synthesized in the magnocellular neurons located in the supraoptic and paraventricular nucleus of the hypothalamus. During the axonal transport of the granules from the hypothalamus to the posterior pituitary, enzymatic cleavage of the prohormone generates the final products of AVP, neurophysin II and the COOH-terminal glycoprotein copeptin. When afferent stimulation depolarizes the AVP-containing neurons, the 3 end products are released into the capillaries of the posterior pituitary in equimolar manner. Main stimuli for release are an increase in plasma osmolality and a drop in blood pressure or volume. AVP acts on the collecting duct to increase water absorption and decrease urine volume. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

increased delivery of sodium chloride and urea to the medulla and simultaneously increasing the osmotic gradient for water reabsorption.[36]

Thirst

The sensation of thirst is a complex behavior that drives water intake. Neuroimaging data suggest that the anterior cingulate cortex and the insular cortex in the brain are key anatomic structures responsible for the subjective thirst experience.[37] The 2 main physiologic stimuli for thirst are plasma hypertonicity (osmotic thirst) and angiotensin II as a consequence of decreased EABV (hypovolemic thirst). Furthermore, the use of angiotensin-converting enzyme inhibitors in patients with end-stage kidney disease has been found to reduce thirst and intradialytic weight gain.[38,39] It is not clear whether osmotic thirst and AVP secretion share the same POsm threshold. Some have suggested that the onset of thirst sensation is ≈ 10 mOsm/kg above the osmotic threshold for AVP release (ie, 294 mOsm/kg)[40] while other studies have concluded that they have a similar threshold.[41] Rapid ingestion of liquid (gulping) stimulates rapid satiation that quenches thirst even before any significant changes in POsm occurs, suggesting that tactile signals through vagal or other cranial nerves from oropharyngeal and gastric distension also mediate initial thirst suppression.[42]

Mechanisms of Urinary Dilution

The kidneys' ability to generate electrolyte-free water in response to a water load protecting against hyponatremia depends on several factors:

1. Glomerular filtration. An adequate glomerular filtration will ensure an adequate amount of filtrate is delivered to the diluting segments for electrolyte-free water generation.
2. Proximal tubule reabsorption. Proximal tubule reabsorbs between 65% and 80% of filtrate. The less filtrate that is reabsorbed in this segment, the more that will be presented to the diluting segments for electrolyte-free water generation.
3. Tubular fluid dilution. Dilution of filtrate as it passes along the nephron generates electrolyte-free water. This is accomplished by the remarkable ability of the TAL and, to a lesser extent, the distal convoluted tubule (DCT) to reabsorb NaCl in the absence of water. The luminal membrane of the cells located in these nephron

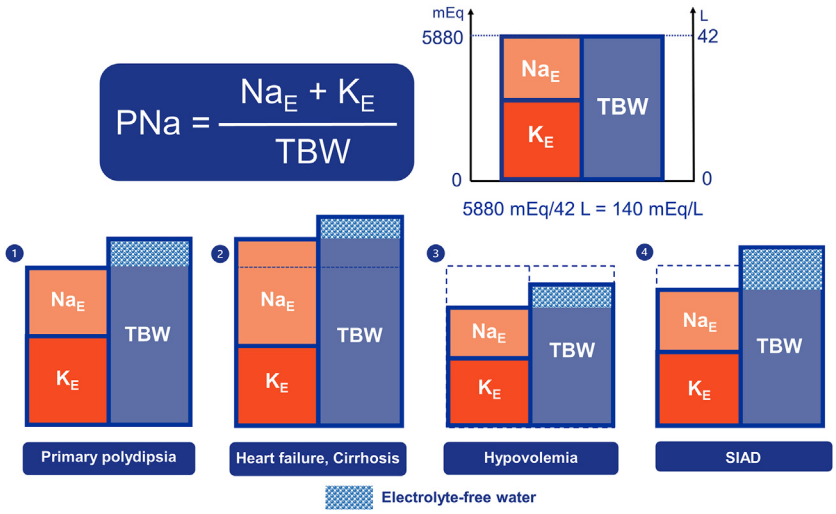

Figure 2. Edelman Gamblegrams. Edelman and colleagues empirically demonstrated that plasma sodium concentration (PNa) is a function of total body exchangeable sodium (Na_E), total body exchangeable potassium (K_E), and total body water (TBW). The main variables of the equation are depicted in a Gamblegram. Based on this equation, hypotonic hyponatremia will occur when the ratio between the sum of total body exchangeable sodium (Na_E) and total body exchangeable potassium (K_E) and total body water (TBW) decreases. There are 4 different scenarios where this can occur leading to hypotonic hyponatremia: (1) normal Na_E and K_E with increased TBW, eg, primary polydipsia; (2) increased Na_E and K_E and increased TBW but with a proportionally higher increase in TBW, eg, cirrhosis and heart failure; (3) decreased Na_E and K_E and decreased TBW but with a proportionally higher decrease in NaE + KE, eg, hypovolemia; and (4) decreased Na_E and K_E with increased TBW, eg, syndrome of inappropriate antidiuresis (SIAD). As inferred from the figure, hypotonic hyponatremia is always caused by electrolyte-free water (EWF) excess, ie, TBW is proportionally higher to the sum of Na_E and K_E. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

segments possesses active sodium transporters (NKCC2 in TAL, and the Na^+-Cl^- cotransporter, NCC, in DCT) but lacks aquaporins making them impermeable to water.

4. Osmolar excretion rate. Under solute balance conditions, osmolar excretion rate equals dietary solute intake. An optimal dietary solute intake will guarantee appropriate levels of solutes present in cortical CD tubular fluid, creating a lower osmotic gradient between tubular fluid and renal interstitium leading to decreased water reabsorption allowing more electrolyte-free water to be excreted.
5. AVP. Generated electrolyte-free water is excreted by keeping the CD relatively impermeable to water, which requires AVP to be absent.

PATHOGENESIS AND ETIOLOGY OF HYPONATREMIA

Because PNa is the main determinant of PTon, hyponatremia is usually associated with hypotonicity, but in certain circumstances, it can be associated with hypertonicity or isotonicity.

Hypertonic Hyponatremia

Hypertonic hyponatremia occurs when there is a significant accumulation of effective osmoles (eg, glucose and mannitol) in plasma, increasing PTon. Hypertonicity leads to translocation of water out of the cells and into the ECF, causing PNa dilution. In the case of hyperglycemia, several conversion coefficients and formulas have been put forward to estimate PNa after correction of hyperglycemia; however, the conversion coefficient of 1.6 proposed by Katz[43] and refined by Al-Kudsi and colleagues (PNa decreases by 1.6 mEq/L for every 100 mg/dL of plasma glucose over 100 mg/dL)[44] is the most reliable.[45]

Isotonic Hyponatremia

The most common cause of isotonic hyponatremia is pseudohyponatremia, a laboratory artifact. Ninety-three percent of plasma is water, and 7% is proteins and lipids. Sodium is distributed in the aqueous fraction. When PNa is measured in total serum or plasma using *indirect* ion-selective electrode (ISE), a dilution step is required. However, when plasma triglycerides, cholesterol (Lipoprotein-X in cholestasis),[46] or proteins are increased, the volume of the nonaqueous fraction also increases and displaces the water fraction so that the total plasma now contains less water per unit volume (and hence less sodium per unit volume). Under these circumstances, measuring PNa will lead to a dilution error, causing a falsely reduced PNa. *Direct* ISE (eg, blood gas analyzer) avoids this error

as sodium activity is measured in the aqueous fraction of an undiluted blood sample. Pseudohyponatremia is not a vestige of the past as most US clinical laboratories continue to routinely measure PNa using the indirect ISE method.[47]

Hypotonic Hyponatremia

Hypotonic hyponatremia develops when electrolyte-free water input is greater than electrolyte-free water output. Based on the Edelman equation, hypotonic hyponatremia will occur when the ratio between Na_E and K_E and TBW decreases. There are 4 possible scenarios where this can occur (Fig 2).[48] As inferred from the figure, hypotonic hyponatremia is always caused by excess electrolyte-free water, that is, TBW is proportionally higher to the sum of Na_E and K_E. This electrolyte-free water excess could be the result of (1) an increase in electrolyte-free water intake and/or (2) a decrease in the kidneys' ability to generate electrolyte-free water. It is important to note that more often than not, more than one mechanism comes into play, making the etiology of hypotonic hyponatremia multifactorial.

Increased Electrolyte-Free Water Intake

Humans can ingest large volumes of water without problems because the kidneys have the ability to produce diluted urine and excrete large volumes of electrolyte-free water up to a certain limit, after which hyponatremia develops. The maximal volume of ingested water that will result in hyponatremia when the limit is exceeded can be estimated from the urine osmolality calculation:

(equation 5): $UOsm = OER/V$,

where UOsm is the urine osmolarity (in mOsm/L), OER is the osmolar excretion rate (in mOsm/d), and V is the daily urine volume (in liters). Therefore, the daily urine volume can be estimated with the following formula:

(equation 6): $V = OER/UOsm$

Because the lowest UOsm is $\approx$ 50 mOsm/L, the osmolar excretion rate becomes the main determinant of V. Under solute balance conditions, osmolar excretion rate equals daily solute intake. A typical daily diet contains 600 to 900 mOsm of solute. Assuming a maximal intake of 900 mOsm/d, the osmolar excretion rate will be the same. Replacing this in equation 6, we have

$V = 900$ mOsm/d / 50 mOsm/L $= 18$ L/d

Hence, only intake of water that exceeds the maximal V of 18 L/d would result in hyponatremia. However, the presence of other comorbidities (eg, schizophrenia, neuroleptic drugs) associated with AVP stimulation often reduces the volume of water required to cause hyponatremia. A recent systematic review reported that a median water intake of 8 L/d was sufficient to cause hyponatremia in these patients.[49]

Decreased Kidney's Ability to Generate Electrolyte-Free Water

Increased AVP. This is by far the most common mechanism of hyponatremia. AVP release could be physiologically appropriate or inappropriate. Physiological AVP secretion is in response to decrease in EABV (10%-15% reduction of intravascular volume).[50–52] EABV is a concept that refers to the volume of arterial blood effectively perfusing tissues. EABV cannot be directly measured, but its status can be ascertained using surrogates such as plasma renin activity, plasma aldosterone concentration, urine sodium, fractional excretion of sodium, urea, or uric acid.[53] EABV is a function of the ECF volume, cardiac output, and peripheral resistance. EABV is decreased because of hypovolemia, heart failure, or vasodilation (eg, cirrhosis) causing decreased organ perfusion. Decreased EABV is sensed by cardiopulmonary and arterial baroreceptors which project via cranial nerves IX and X into the nucleus of tractus solitarius in the medulla oblongata causing a reduction in tonic inhibitory input. From here, neural projections reach the PVN and SON to stimulate AVP release. The stimulatory effect of decreased EAVB on AVP release overrides the inhibitory effect of hypotonicity.

When AVP is released independent of physiologic stimuli, the release is considered inappropriate. The latter can be seen in the syndrome of inappropriate antidiuresis (SIAD) and low cortisol states. Cortisol is a well-known inhibitor of AVP release.[54] Both corticotropin-releasing hormone and AVP are synthesized in the hypothalamus, and the absence of cortisol leads to an increase in corticotropin-releasing hormone, along which AVP is also secreted.[55] In addition, cortisol increases vascular smooth muscle sensitivity to the actions of catecolamines.[56] Therefore, cortisol deficiency can contribute to vasodilation and reduced EABV, stimulating AVP release. In addition to cortisol deficiency, primary adrenal insufficiency is also characterized by aldosterone deficiency leading to kidney sodium wasting and hypovolemia adding an additional stimulus for AVP release.[57]

Low Solute Intake. From equation 6, one can infer that the urine volume, and hence electrolyte-free water excretion, is dependent on the osmolar excretion rate and, therefore, the daily solute intake.[58] Ingestion of protein and sodium and potassium salts generates meaningful solutes, but ingestion of carbohydrates does not. For instance, if a patient consumes 150 mOsm/d of solute, the osmolar excretion rate will also be 150 mOsm/d under solute balance conditions. Assuming a maximally dilute urine (UOsm = 50 mOsm/kg), urine solutes will be excreted in a volume of urine equal to 150/50 = 3 L/d (equation 6), and fluid intake exceeding this will result in hyponatremia. Typical examples of this mechanism are beer potomania (large volumes of beer which is 90%-95% water and

containing very low quantities of electrolytes, coupled with poor dietary intake of protein and salt) and "tea-and-toast" diet (relatively high fluid intake coupled with adequate caloric intake mainly in the form of carbohydrates but with very little protein and salt intake).

Dilution Defect. Dilution of intratubular fluid in TAL, DCT, connecting tubule, and CD is essential for the generation of electrolyte-free water by the kidneys and the defense against hyponatremia. Diuretics interfere with solute reabsorption in different nephron segments and impair urinary dilution. In that sense, all diuretics have been reported to cause hyponatremia, but hyponatremia is more commonly associated with thiazide diuretics although the mechanism is complex. Thiazides exert their action by inhibiting NCC in the DCT. However, hyponatremia is rarely a reported complication in patients with Gitelman syndrome, a disorder caused by NCC-inactivating mutations. Hypovolemia has also been postulated as a mechanism, but hyponatremia can occur in the absence of AVP (eg, Brattleboro rats, a strain of laboratory rats with congenital central diabetes insipidus, develop hyponatremia when exposed to thiazide diuretics).[59] In addition, a significant number of patients with thiazide-induced hyponatremia are euvolemic, and their laboratory parameters can mimic those of SIAD.[60] Another study found that polydipsia and reduced urine urea excretion (suggesting low solute intake) are frequent features in patients with thiazide-induced hyponatremia.[61] Furthermore, patients with a history of thiazide-induced hyponatremia rapidly develop hyponatremia upon rechallenge with a single dose, suggesting a genetic predisposition.[62] A recent genome-wide association study of 2 cohorts of patients admitted with thiazide-induced hyponatremia shed some light into the latter hypothesis.[63] About half of the patients in these cohorts carried a single-nucleotide polymorphism in the *SLCO2A1* gene encoding for a prostaglandin transporter (PGT). CD cells synthesize prostaglandin E_2 (PGE_2) that acts in a paracrine and autocrine manner to regulate water transport. These effects are mediated by specific receptor subtypes (EP1, EP3, and EP4). EP4 is located on the apical membrane and, when stimulated, leads to AQP2 insertion resulting in water reabsorption. EP1 and EP3 are expressed on the basolateral side and, when stimulated, exert the opposite effect. Normally, PGT directs PGE_2 to the basolateral membrane, where stimulation of EP1 and EP3 decreases water reabsorption. However, decreased PGT activity leads to luminal PGE_2 accumulation, favoring stimulation of EP4 leading to AQP2 insertion and increase in water permeability even in the absence of AVP. Further in vitro studies suggested that this polymorphism significantly decreases PGT activity.

Reduced Glomerular Filtration Rate. The urine-diluting ability of the kidneys is typically compromised when the glomerular filtration rate drops below 20-25 mL/min.[64] When glomerular filtration rate is reduced below that threshold, the minimal achievable UOsm is around 200 mOsm/kg. Using equation 6, at a solute intake of 600-900 mOsm/d, the urine volume would be 600/200 = 3 L/d to 900/200 = 4.5 L/d, and any fluid intake above this will lead to hyponatremia.[65]

CLINICAL MANIFESTATIONS OF HYPONATREMIA

Brain Adaptation to Hyponatremia

An acute drop in PTon leads to a rise in brain water content culminating in cerebral edema. Astrocytes, a type of glial cell, swell with relative sparing of neurons.[66] To counteract this brain swelling, the first adaptive mechanism is the movement of fluid from the brain cells into the cerebrospinal fluid and then into the systemic circulation.[67] The second compensatory adaptive mechanism consists of extrusion of electrolytes and organic osmolytes from the intracellular to the extracellular region to equilibrate osmolalities and mitigate further brain edema.

During the initial 3 hours, there is mainly a loss of inorganic ions such as potassium and chloride. The astrocyte utilizes ATP-dependent mechanisms to achieve this requiring the Na^+-K^+-ATPase pump, which is of primary importance for the extrusion of ions. Certain factors such as estrogens (premenopausal women) and hypoxia inhibit the activity of the Na^+-K^+-ATPase pump and impair the ability of the brain to adapt to hypotonicity increasing the risk of cerebral edema.[68]

Subsequently, an efflux of organic osmolytes such as glutamate, taurine, glycine, and myoinositol occurs with the consequent loss of brain water to halt cellular swelling and normalize brain volume.[69] Full brain adaptation to hypotonicity takes 48 hours. Extrusion of neurotransmitters like glutamate has been proposed as a possible mechanism for mild neurocognitive deficits associated with chronic hyponatremia.[19]

Symptoms of Hyponatremia

The severity of symptoms of hyponatremia correlates with the degree of brain edema. Factors such as the magnitude and the rapidity of decline in PNa are the primary determinants of the severity of symptoms, with symptoms occurring more frequently in acute hyponatremia (duration $<$48 hours) where full brain adaptation to hypotonicity has not occurred yet and less frequently in chronic hyponatremia (duration $\geq$48 hours) where full brain adaptation has taken place (Fig 3). Symptoms can vary in severity as mild, moderate, and severe. Severe symptoms include seizures and coma representing a significant degree of cerebral edema. However, controversy exists as to what constitutes mild and moderate symptoms. The 2014 European clinical practice guidelines on diagnosis and treatment of hyponatremia consider nausea without vomiting, confusion, and headaches as moderate symptoms but do not define what mild symptoms are.[70] However, nausea, vomiting, and headaches only represent ominous signs of cerebral edema in patients with self-induced water intoxication such as patients with hyponatremia due to primary polydipsia, exercise, or ecstasy. Otherwise, these symptoms are very common in patients with chronic hyponatremia and do not portend a poor

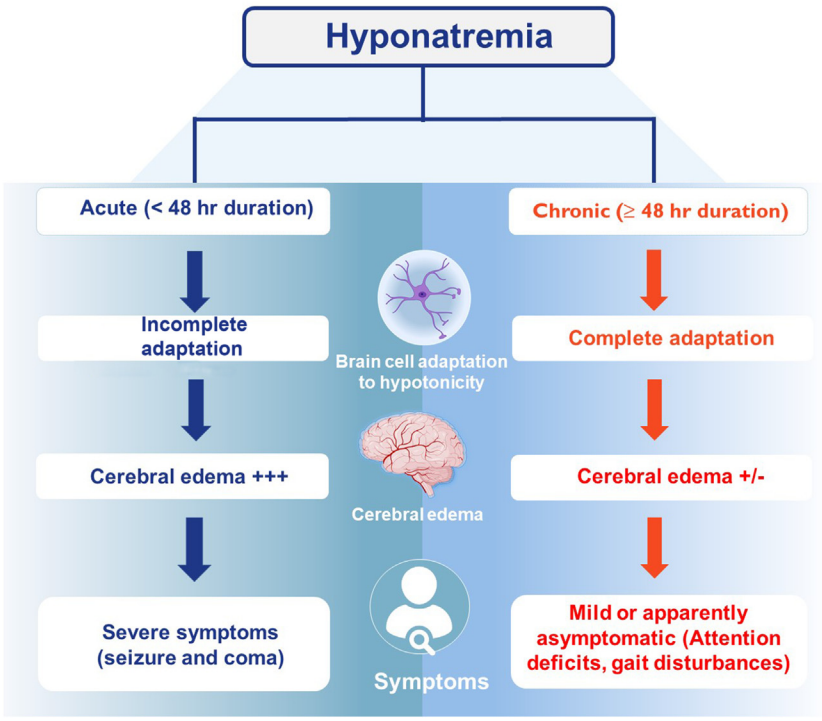

Figure 3. Brain adaptation to acute and chronic hyponatremia. Severity of symptoms of hyponatremia correlates with the degree of brain edema. Severe symptoms occur more frequently in acute hyponatremia (duration <48 hours) where full brain adaptation to hypotonicity has not occurred yet and less frequently in chronic hyponatremia (duration ≥48 hours) where full brain adaptation has taken place. However, the adaptation to chronic hyponatremia has also been proposed as possible mechanism for mild neurocognitive deficits, gait disturbances, and falls associated with chronic hyponatremia. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

prognosis.[71–73] In contrast, the 2013 American expert panel for the diagnosis, evaluation, and treatment of hyponatremia did not specifically define neither mild nor moderate symptoms but implied these to be symptoms attributed to hyponatremia that are less severe than those mandating urgent correction within 1 hour.[74]

DIAGNOSIS OF HYPONATREMIA

The main goals of the diagnostic approach to hyponatremia are to determine whether hypotonicity exist, and if so, whether AVP mediates the hyponatremia, and if so, whether a physiologic stimulus is responsible for the AVP secretion[75] (Fig 4).

Is Hyponatremia Hypotonic?

If the serum osmolality (SOsm) is <275 mOsm/kg, then a hypotonic hyponatremia exists. However, if SOsm is ≥275 mOsm/kg, then this does not rule out hypotonic hyponatremia as this can occur when hypotonic hyponatremia coexist with large concentrations of ineffective osmoles (eg, urea and ethanol). Caution should be used when interpreting SOsm in this context. Having ruled out hypotonicity, an SOsm of ≥275 mOsm/kg indicates either hypertonic hyponatremia (eg, hyperglycemia and mannitol) or isotonic hyponatremia (eg, pseudohyponatremia).

Does AVP Mediate Hypotonic Hyponatremia?

AVP-dependent hyponatremia can be identified by urine that is not maximally diluted (UOsm ≥100 mOsm/kg), while AVP-independent hyponatremia is associated with a maximally dilute urine (UOsm <100 mOsm/kg). Typical examples of the latter include primary polydipsia, low solute intake, and reduced kidney function with the caveat that, in patients with reduced kidney function, UOsm is typically less than SOsm but not <100 mOsm/kg.

Is AVP Secretion in Hypotonic Hyponatremia Physiologically Appropriate?

Reduced EABV is the only physiologic stimuli for AVP secretion in hypotonic hyponatremia. States of reduced EABV (eg, hypovolemia, heart failure, and cirrhosis) are characterized by sodium-avid kidneys (urine sodium concentration [UNa] <20 mEq/L) as a result of renin-angiotensin-aldosterone system activation.[76] In contrast, a UNa >30 mEq/L usually indicates renin-angiotensin-aldosterone system inactivation due to normal or increased EABV, and AVP release in the latter scenario is, therefore, physiologically inappropriate (ie, SIAD).

We prefer the use of the aforementioned physiology-based approach in the diagnosis of hyponatremia over the traditional algorithm based on volume status since the clinical assessment of ECF volume in hyponatremia has poor sensitivity and specificity.[77] However,

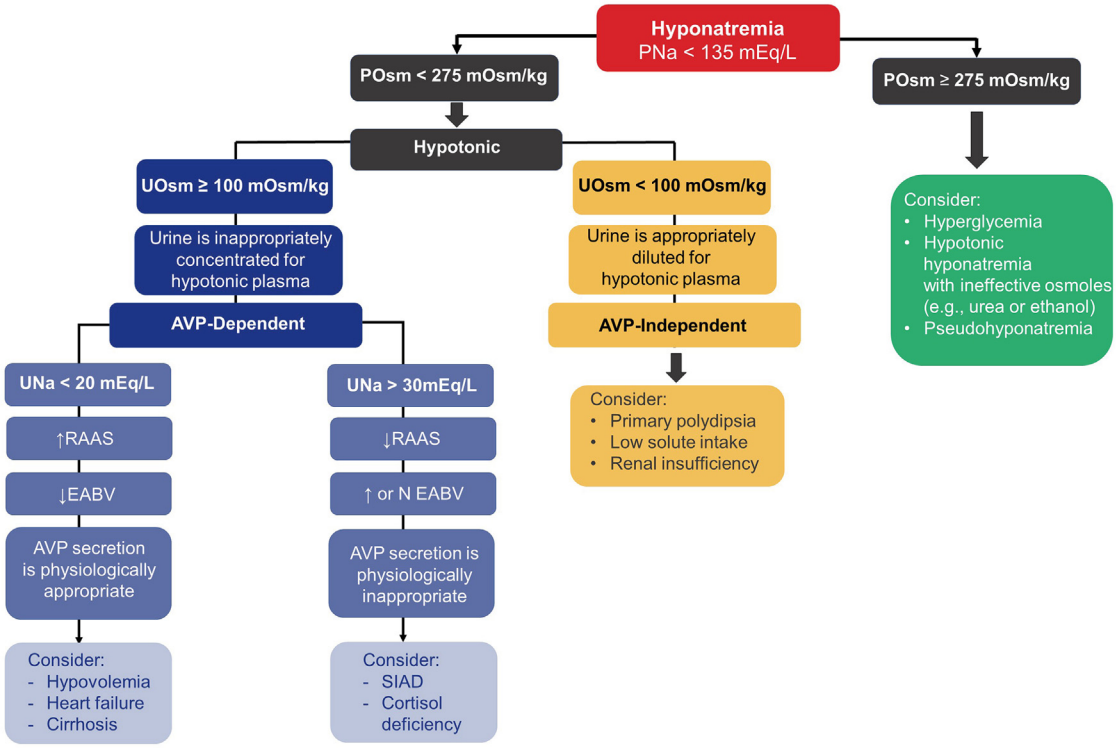

Figure 4. Diagnostic approach to hyponatremia. Abbreviations: AVP, arginine vasopressin; EABV, effective arterial blood volume; PNa, plasma sodium concentration; POsm, plasma osmolality; RAAS, renin-angiotensin-aldosterone system; SIAD, syndrome of inappropriate antidiuretic hormone; UNa, urine sodium concentration; UOsm, urine osmolality. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

point-of-care ultrasound has emerged in recent years as an effective tool to assess volume status in hyponatremic patients and may aid in the diagnosis.[78,79]

Diagnosis of SIAD

The diagnosis of SIAD deserves special mention. The clinical criteria necessary to diagnose SIAD go back to the definition by Schwartz and Bartter in 1967[80] and are outlined in Table 1. Cortisol deficiency is a key differential diagnosis, as secondary adrenal deficiency can present a biochemical picture identical to SIAD. Therefore, formal biochemical exclusion of adrenal insufficiency is mandatory in the evaluation of euvolemic hyponatremia. Thyroid-stimulating hormone measurement has been traditionally recommended to rule out hypothyroidism as part of the differential diagnosis of SIAD; however, clinically important hyponatremia is uncommon even in patients with severe hypothyroidism.[82] Several other criteria support but are not essential for a diagnosis of SIAD. Volume expansion and AVP acting on V_1 receptors in the kidney increase uric acid clearance, and therefore, hypouricemia is often found with SIAD.[83] A water-loading test can be helpful especially when reset osmostat is considered in the differential diagnosis since the inability to excrete a standard water load confirms the presence of SIAD. Unfortunately, measurement of AVP or copeptin as a reliable surrogate marker for AVP does not help in the diagnosis since some patients with SIAD do not have measurably elevated AVP or copeptin levels.[84] One study including 298 patients with profound hyponatremia showed that overall there is limited diagnostic utility of copeptin in hyponatremia, except very low levels pointing to primary polydipsia.[85] Once SIAD is diagnosed, the investigation for the etiology can be systematically considered, and it is helpful to categorize the various causes: malignancy, drugs (eg, antidepressants, anticonvulsants, antipsychotics), central nervous system disorders, pulmonary disorders, and miscellanea (eg, pain and nausea).[86]

TREATMENT OF HYPONATREMIA

The treatment of hyponatremia depends first and foremost on the presence and severity of symptoms which reflect underlying cerebral edema. Hyponatremia with moderate

Table 1. Diagnostic Criteria for the Syndrome of Inappropriate Antidiuresis

- Low SOsm <275 mOsmol/kg H_2O
- Elevated urine osmolality >100 mOsmol/kg H_2O (inappropriately concentrated)
- Clinical euvolemia (absence of signs of hypovolemia or hypervolemia)
- Elevated urinary sodium excretion >30 mEq/L with normal salt and water intake
- Absence of other potential causes of euvolemic hyposmolality (glucocorticoid insufficiency, hypothyroidism)
- Normal renal function and absence of diuretic use

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or severe symptoms (eg, seizures and coma) is a medical emergency requiring immediate therapy with hypertonic saline 3%. In the absence of significant symptoms, the treatment should focus on the underlying mechanism of hyponatremia. The American expert panel[74] and the European clinical practice guidelines[70] have put forward sets of guidelines.

Goals and Limits of Correction

Multiple case series and case reports demonstrate that increasing PNa by 4-6 mEq/L is enough to address even the most severe symptoms of hyponatremia.[87] Furthermore, a study in normonatremic neurosurgical patients has shown that increasing PNa by 5 mEq/L is enough to markedly reduce intracranial pressure and reverse impending herniation.[88] The American expert panel recommends correcting PNa by a goal of 4-6 within 1 hour for patients with acute and/or severely symptomatic hyponatremia, while the European clinical practice guidelines recommend correcting PNa by a goal of 5 mEq/L.

How much correction of PNa is "too much"? There is now general agreement that excessive correction of chronic hyponatremia can trigger osmotic demyelination syndrome (ODS). The American expert panel recommends a PNa correction limit of 10-12 mEq/L in any 24-hour period and 18 mEq/L in any 48-hour period for patients at average risk of ODS while recommending a PNa correction limit of 8 mEq/L in any 24-hour period for patients at high risk of ODS (see complications of therapy below). The European clinical practice guidelines recommend a PNa correction limit of 10 mEq/L during the first 24 hours and 8 mEq/L during every 24 hours thereafter. A recent study identified 21 patients who developed ODS despite PNa rates of correction between 8 and 10 mEq/L per day as suggested by the current guidelines and recommended a lower limit of daily PNa correction (7 mEq/L).[89]

Acute Hyponatremia and/or Hyponatremia With Moderate or Severe Symptoms

Patients with acute and/or moderately or severely symptomatic hyponatremia are at risk of brain herniation, requiring emergent therapy. For patients with severe symptoms (including those with acute hyponatremia), high risk of herniation, or self-induced water intoxication (eg, primary polydipsia, ecstasy, exercise-induced), the American expert panel recommends a 100-mL IV bolus of NaCl 3% for over 10 minutes, up to 3 times as needed. For patients with acute hyponatremia with mild to moderate symptoms, the American expert panel recommends a slow infusion of NaCl 3%. Similarly. the European practice guidelines recommend a 150-mL IV bolus of NaCl 3% over 20 minutes 2 times and then repeat twice or until the PNa goal (ie, increase in 5 mEq/L) is achieved for patients with severe symptoms while recommending a single bolus for patients with moderate symptoms.

It is unclear whether hypertonic saline should be given as a slow infusion or bolus. An observational study evaluated the clinical outcomes of patients with SIAD with severe symptoms after treatment with hypertonic saline as either bolus or slow infusion.[90] In response to the American expert panel recommendations, the investigators had changed hypertonic saline protocol from slow infusion to bolus. This allowed them to compare the outcomes in 22 patients treated by bolus to historical data from 28 patients given slow infusions. In comparison to the slow infusion, the bolus regimen was more effective at raising PNa at 6 hours, and this was associated with an improvement in the Glasgow Coma Scale.

The SALSA (Efficacy and Safety of Rapid Intermittent Correction Compared With Slow Continuous Correction With Hypertonic Saline in Patients With Moderately Severe or Severe Symptomatic Severe Hyponatremia) trial was a randomized controlled trial that compared rates of overcorrection in 178 patients with symptomatic hyponatremia treated with hypertonic saline administered via bolus or slow infusion.[91] The investigators found no difference in the primary outcome. However, more patients in the bolus group achieved the PNa target within 1 hour and had a lower incidence of therapeutic relowering of PNa.

As formulas that estimate PNa changes after infusion of hypertonic saline are notoriously inaccurate,[92] a preferred strategy is to administer a volume of NaCl 3% calculated based on patient's weight: 1–1.5 mL/kg and infuse it over a 6-hour period (eg, for a 70-kg woman, the volume of NaCl 3% can be estimated as $70 \times 1.5 = 105$ mL and to be administered over 6 hours at a rate of 105/6 or 17.5 mL/h).[81] It is estimated that this volume of hypertonic saline will increase PNa by $\approx$ 1 mEq/L. This should be followed by frequent PNa measurement (at least every 2 hours) with titration of the hypertonic saline rate based on the results. Central venous access is not necessary as hypertonic saline 3% can be safely administered via peripheral vein.[93] As discussed previously in the section addressing the Edelman equation, potassium and sodium are osmotically equivalent (1 mEq of hypertonic KCl $\approx$ 2 mL of NaCl 3%), and NaCl 3% infusion rate should be adjusted when supplementing with hypertonic potassium solutions.

Chronic Hyponatremia Without Significant Symptoms

The treatment of chronic hyponatremia without significant symptoms should target the underlying mechanism of hyponatremia (eg, glucocorticoids for adrenal insufficiency). In this section, we will focus on the treatment of SIAD, the most common cause of hyponatremia.

Fluid Restriction

All published guidelines agree that fluid restriction is the first-line therapy for SIAD with mild-to-moderate hyponatremia. The ideal fluid restriction is not strictly defined. Importantly, for a successful fluid restriction, all fluids must be included in the restriction including water, juice, soup, and so on. In principle, the recommendation is to limit fluids to $<$0.8 L/d.

A recent randomized controlled study comparing patients with fluid restriction vs no treatment showed a modest but significant increase in PNa (4 mEq/L within 30 days compared to 1 mEq/L without treatment).[94] However, 39% patients assigned to fluid restriction did not

respond, with PNa persistently below 130 mEq/L after 3 days. Several other, nonrandomized larger observational data failed to show a relevant effect of fluid restriction. In addition, this therapy is often poorly tolerated because of an associated increase in thirst leading to poor compliance with long-term therapy.

A predictor for nonresponse to fluid restriction is a high urinary osmolality (>500 mOsm/L), UNa (>130 mEq/L),[95] or a (UNa + UK)/PNa > 1.[96]

Loop Diuretics and Salt Tablets

Loop diuretics block NKCC2 in TAL and decrease delivery of sodium and chloride to the kidney medulla, decreasing the medullary gradient necessary for water reabsorption in CD.

Salt tablets could also potentially enhance electrolyte-free water excretion. From equation 6, we can infer that increasing the solute load will increase urine volume and electrolyte-free water. However, the amount of solute delivered with the traditional regimen of salt tablets of 6 g per day is rather small (≈198 mOsm/d). In contrast, 30 g/d of urea provides 500 mOsm/d of solute (the equivalent of 15.1 g of NaCl). Therefore, the main utility of salt tablets is only to replace loop diuretic-induced sodium losses. They are listed in the European practice guidelines as a second-line therapy for SIAD in combination with salt tablets. However, a recent randomized controlled trial comparing the effect of fluid restriction alone vs fluid restriction plus loop diuretics vs fluid restriction plus loop diuretics plus salt tablets did not show a significant additive effect of loop diuretics or salt tablets.[97] Acute kidney injury and hypokalemia were more common in patients receiving furosemide; therefore, caution should be taken when adopting this strategy.

Urea

Urea works as an osmotic diuretic to correct hyponatremia in SIAD, but in contrast to mannitol, urea decreases natriuresis. It is usually prescribed in a dose of 15 to 60 g/d (slow uptitration). Overcorrection of PNa in association with urea has been observed with no reports of ODS.[98] Furthermore, there are data suggesting urea might be protective against ODS.[99] Side effects include distaste and nausea. The findings of a small cohort of SIAD patients suggested that urea may have comparable efficacy to vaptans in reversing hyponatremia due to chronic SIAD.[100] A prospective study looking at the long-term efficacy and safety of urea is currently ongoing (NCT04588207).

Vasopressin Antagonists

Tolvaptan is an oral vasopressin V2-receptor antagonist that blocks AVP action in the kidney, inducing water diuresis and thereby raising PNa. An intravenous alternative, conivaptan, is also approved, but its use is limited to a maximum duration of 4 days because of drug interaction effects with other agents metabolized by the CYP3A4 hepatic isoenzyme.

The efficacy of tolvaptan vs placebo was investigated in the randomized placebo-controlled SALT-1 and SALT-2 trials in patients with chronic euvolemic or hypervolemic hyponatremia.[101] The results showed that tolvaptan increased PNa (within 4 days) by 4 mEq/L compared to only 1 mEq/L in the placebo group and an even higher increase within 30 days. The American expert panel recommends its use as a second-line treatment, whereas the European clinical practice guidelines recommend against the use of tolvaptan in moderate to profound hyponatremia, mainly due to the lack of a proven outcome benefit aside from the increase in PNa and the concern of overly rapid PNa correction. Importantly, discontinuing fluid restriction when vaptans are started, initiation of treatment in the hospital, and regular sodium monitoring limit the risk of overcorrection. A lower initial dose of tolvaptan, 7.5 mg, which has been associated with lower rates of overcorrection, should be considered.[102] Common side effects of tolvaptan include dry mouth, thirst, and urinary frequency.

Sodium-Glucose Cotransporter 2 Inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are successfully used for patients with type 2 diabetes and heart failure, showing benefit.[103,104] SGLT2 inhibitors induce glycosuria and osmotic diuresis and were therefore investigated in SIAD due to their possible action on electrolyte-free water excretion. A randomized trial in patients with SIAD comparing empagliflozin or placebo, in addition to fluid restriction, showed an increase in PNa of 10 mEq/L over 4 days as compared to only 7 mEq/L in the placebo (fluid restriction only) group.[105] However, some of the SIAD might have been transient due to pain, trauma, or nausea, and the autocorrection rates may have differed between the groups. A randomized controlled double-blind study evaluating the effect of SGLT2 inhibitors on PNa and clinical signs and symptoms of hyponatremia in SIAD and in hypervolemic hyponatremia is currently ongoing (NCT04447911).

Complications of Therapy

Overcorrection of Hyponatremia. Overcorrection of hyponatremia is a medical emergency and is defined as PNa correction exceeding the recommended limits. Excessive PNa correction typically occurs during the treatment of AVP-mediated hyponatremia when the underlying stimuli for AVP release vanishes and AVP secretion ceases restoring the ability of the kidneys to generate electrolyte-free water.

Risk factors for rapid correction of hyponatremia include:[87]

- Volume expansion in hypovolemia or patients with low solute intake
- Glucocorticoid replacement in adrenal insufficiency
- Resolution of transient selective serotonin reuptake inhibitors (eg, recent surgery, pneumonia, discontinuation of SSRI)
- Discontinuation of desmopressin or thiazide diuretics
- Initiation of vasopressin antagonists

Use of Desmopressin to Prevent or Manage Overcorrection of Hyponatremia. Desmopressin has been used to address the spontaneous water diuresis that leads to rapid

Table 2. Strategies to Prevent and Treat Overly Rapid Correction of Hyponatremia Using Desmopressin

Strategy	Indications	Description
Proactive ("DDAVP clamp")	Start immediately when PNa <120 mEq/L AND: • High risk for rapid correction*, AND/OR • High risk for ODS†	• Desmopressin 2 – 4 mcg IV/SC every 6 – 8 h, AND • NaCl 3% 100 mL bolus for seizures, coma, or rapidly falling PNa‡, OR • NaCl 3% 1 – 1.5 mL/kg IV over 6 h (to increase PNa by ≈ 1 mEq/L every 6 h)
Reactive	Worrisome PNa trajectory: • PNa goal of 6 mEq/L in a 24-h period has been achieved, AND/OR • UOP > 1 mL/kg/h	• Desmopressin 2 – 4 mcg IV/SC every 6 – 8 h
Rescue	Overly rapid correction of hyponatremia has already occurred: • Increase in PNa ≥ 8 mEq/L in any 24-h period	• Desmopressin 2 – 4 mcg IV/SC every 6 – 8 h, AND • Dextrose 5% in water 3 mL/kg IV (to decrease PNa by ≈ 1 mEq/L) until PNa is just below the correction limit

Abbreviations: IV, intravenously; ODS, osmotic demyelination syndrome; PNa, plasma sodium; SC, subcutaneously; SIAD, syndrome of inappropriate antidiuresis; UOP, urine output.
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*Low solute intake, hypovolemia, adrenal insufficiency, transient SIAD, thiazide diuretics, desmopressin, vasopressin antagonists.
†Alcohol use disorder, hypokalemia, liver disease, malnutrition, PNa ≤ 105 mEq/L.
‡Self-induced water intoxication or acute postoperative hyponatremia (risk that PNa will fall due to delayed absorption of ingested water or excretion of hypertonic urine).

correction of hyponatremia. Three distinctive strategies have been identified in the literature,[106] which are described in detail along with their indications in Table 2 and represented graphically in Figure 5.

In patients with severe hyponatremia (PNa < 120 mEq/L), PNa should be checked at least every 2 hours. Because the PNa values using direct and indirect ISE methods can differ significantly,[110] we recommend sticking to a single method while monitoring PNa. We prefer using whole blood sodium (ie, direct ISE) as the turnaround time is shorter. UOsm should be checked at least once daily to confirm that urine remains concentrated (eg, UOsm > 400-500 mOsm/kg) while on desmopressin, and dose and/or frequency should be adjusted if not. Patients need to be fluid-restricted while on desmopressin (eg, 800 mL/d) to prevent worsening of hyponatremia.

To avoid overcorrection, desmopressin should be continued until PNa reaches 125 to 130 mEq/L, after which the risk of ODS becomes negligible. Before stopping desmopressin, the previous day's correction should be assessed to be sure that the 48-hour limit is not exceeded.

Desmopressin should not be used in patients with self-induced water intoxication due to psychosis. In those patients, one cannot be assured of the control of water intake. Other patients where this regimen is not advised are patients who are not at risk of developing a spontaneous water diuresis such as patients whose hyponatremia can be confidently attributed to heart failure or cirrhosis and patients who clearly have chronic SIAD with no other confounders.

Osmotic Demyelination Syndrome. ODS is a complication of rapid correction of chronic hyponatremia in susceptible individuals. The adaptation to chronic hyponatremia is the extrusion of organic osmolytes making the brain vulnerable to injury if the PNa is corrected too rapidly because organic osmolytes reaccumulate slowly as hyponatremia is normalized (5 to 7 days).[111] The imbalance in organic osmolytes in the setting of rapid correction results in astrocyte dehydration and injury with subsequent oligodendrocyte damage.

Recognition of neurologic damage can be complex because clinically apparent symptoms of ODS can be delayed for up to 7 days after rapid PNa correction. Affected individuals frequently have lesions in pontine and extrapontine areas, but these might not be detected by MRI until after 4 weeks of the onset of symptoms.[112] Symptoms can include altered mentation, pseudobulbar palsy, seizures, cerebellar ataxia, and even more dramatic consequences such as locked-in syndrome.[113]

There are specific factors that have been identified that raise the risk of ODS:[74]

- Overcorrection of chronic hyponatremia
- PNa ≤ 105 mEq/L
- Alcohol use disorder
- Hypokalemia
- Malnutrition
- Cirrhosis.

The role of alcohol use disorder, malnutrition, and associated electrolyte deficiencies in the pathogenesis of ODS cannot be overstated. An adequate supply of substrates and cofactors is required during slow correction of PNa to promptly enhance intracellular osmolality via cellular uptake and/or release of effective osmoles and synthesis

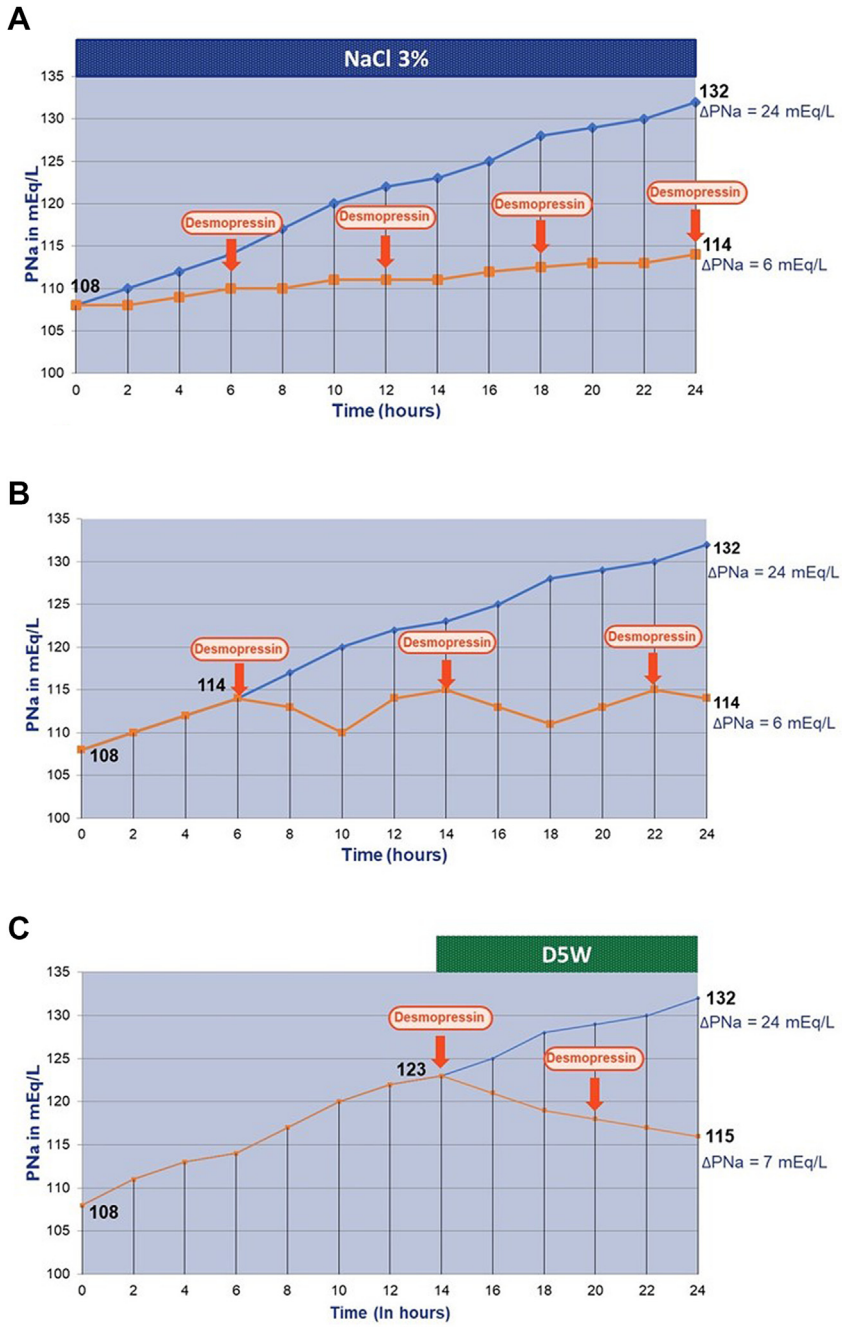

Figure 5. Desmopressin strategies to prevent and manage overly rapid correction of hyponatremia. Abbreviations: D5W, dextrose 5% in water; PNa, plasma sodium concentration. The figure illustrates hypothetical scenarios where a patient presents with an initial PNa of 108 mEq/L. Desmopressin has been used to prevent or treat excessively rapid correction. Desmopressin is usually given at a dose of 2–4 mcg IV every 6–8 hours. Three distinctive strategies have been described: (1) The proactive approach integrates the use of desmopressin with hypertonic saline from the start of PNa correction[107]; (2) The reactive approach is indicated when the trajectory of PNa correction is worrisome and seems likely to result in overcorrection (ie, a PNa goal of 6 mEq/L/24 h has been achieved)[108]; (3) The rescue approach is indicated when overcorrection had occurred and combines the use of desmopressin with hypotonic fluids such as D5W aiming to relower PNa just below the therapeutic limits.[109] The recommended volume of NaCl 3% to increase PNa by ≈ 1 mEq/L is 1-1.5 mL/kg, and this volume is to be administered over 6 hours (rate of 0.16 to 0.25 mL/kg/h). Alternatively, in symptomatic patients, a bolus of 100 or 150 mL can be administered intermittently. The recommended volume of D5W to decrease PNa by ≈ 1 mEq/L is 3 mL/kg. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of necessary organic osmolytes.[114] The latter may require close monitoring and prompt supplementation of phosphate, potassium, magnesium, and glucose particularly in patients with malnutrition or those at risk (eg, elderly, alcohol use disorder).

Management of established ODS is supportive. Early studies prior to 1990 observed an excess morbidity and mortality associated with this disorder. More recent data published over the last 20 years show that most patients with ODS survive and recover without significant sequelae.[115]

CONCLUSIONS

Our aim with this review is to promote the understanding of the physiologic principles of behind hyponatremia and to fortify the knowledge and expertise in the evaluation of management hyponatremia. The reader should conclude from the evidence presented that hyponatremia can contribute to increased mortality and morbidity. We should be aware of the very serious clinical consequences of acute or symptomatic hyponatremia requiring prompt therapy with hypertonic saline. On the other side, chronic hyponatremia, once thought to be asymptomatic, can lead to subtle neurocognitive deficits. Finally, caution should be taken when correcting chronic hyponatremia to prevent ODS.

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