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Diagnostic and Therapeutic Strategies to Severe Hyponatremia in the Intensive Care Unit

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Abstract

Hyponatremia is the most common electrolyte abnormality encountered in critically ill patients and is linked to heightened morbidity, mortality, and healthcare resource utilization. However, its causal role in these poor outcomes and the impact of treatment remain unclear. Plasma sodium is the main determinant of plasma tonicity; consequently, hyponatremia commonly indicates hypotonicity but can also occur in conjunction with isotonicity and hypertonicity. Plasma sodium is a function of total body exchangeable sodium and potassium and total body water. Hypotonic hyponatremia arises when total body water is proportionally greater than the sum of total body exchangeable cations, that is, electrolyte-free water excess; the latter is the result of increased intake or decreased (kidney) excretion. Hypotonic hyponatremia leads to water movement into brain cells resulting in cerebral edema. Brain cells adapt by eliminating solutes, a process that is largely completed by 48 h. Clinical manifestations of hyponatremia depend on its biochemical severity and duration. Symptoms of hyponatremia are more pronounced with acute hyponatremia where brain adaptation is incomplete while they are less prominent in chronic hyponatremia. The authors recommend a physiological approach to determine if hyponatremia is hypotonic, if it is mediated by arginine vasopressin, and if arginine vasopressin secretion is physiologically appropriate. The treatment of hyponatremia depends on the presence and severity of symptoms. Brain herniation is a concern when severe symptoms are present, and current guidelines recommend immediate treatment with hypertonic saline. In the absence of significant symptoms, the concern is neurologic sequelae resulting from rapid correction of hyponatremia which is usually the result of a large water diuresis. Some studies have found desmopressin useful to effectively curtail the water diuresis responsible for rapid correction.

Keywords

hyponatremia, syndrome of inappropriate antidiuresis, hypertonic saline, desmopressin, osmotic demyelination syndrome

Introduction

Hyponatremia is the most common electrolyte disorder encountered in clinical practice with prevalence rates up to 30% in the critically ill. Hyponatremia has been associated with increased morbidity, mortality, and healthcare utilization. In this manuscript, we review the literature regarding its epidemiology, pathogenesis, etiology, diagnosis, and management especially what it pertains to the patient with plasma sodium (PNa) < 120 mmol/L in the intensive care unit.

Epidemiology and Clinical Outcomes

Epidemiology

Hyponatremia is the most common electrolyte disorder encountered in clinical practice. The prevalence of hyponatremia varies with the definition of hyponatremia and the nature of the population studied. It is estimated that in the United States, there are between 3.2 and 6.1 million people with hyponatremia yearly[1] with a prevalence of up to 30% in critically ill patients when hyponatremia is defined as a PNa <135 mmol/L.[2]

Clinical Outcomes

Hyponatremia has been associated with increased mortality, morbidity, and healthcare utilization.

Inpatient mortality rates as high as 51% have been observed in some studies of patients with severe hyponatremia (PNa <120 mmol/L).[3,4] However, whether this observed heightened mortality is due to an effect of the electrolyte disturbance itself or other cofounders remains unclear. Several studies have documented an increase in mortality rates as PNa decreases suggesting a direct effect.[5–7] This is biologically plausible as hyponatremia of enough severity can potentially lead to cerebral edema, especially in the acute setting.

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However, other investigator groups have found divergent results. Chawla et al examined the mortality of hyponatremia in a cohort of over 45 000 patients admitted to a single community hospital over the course of 11 years.[8] They found that the mortality in those with PNa <135 mmol/L was 6.1%, and the mortality tended to increase as the PNa decrease from 134 to 120 mmol/L. However, as the PNa drop below 120 mmol/L, the trend reversed: the mortality of those with PNa <115 mmol/L (6.8%) was significantly less than the one in patients with PNa between 120 and 124 mmol/L (11.2%). This reversal of mortality as PNa falls has been observed in other studies.[9] They also observed that two-thirds of fatal cases of patients with an initial PNa <120 mmol/L died despite PNa returning to normal or near normal (≥128 mmol/L) before death, and greater than half of the deaths occurred ≥1 week after the nadir PNa occurred. In addition, 70% of patients who died with admission-uncorrected hyponatremia had 2 or more severe illnesses (commonly sepsis and multiorgan failure) with an average Charlson comorbidity index of 5.5. After a thorough review, they only found 3 deaths (5.6%) where hyponatremia seemed to play a causal role. Neurologic symptoms attributed to hyponatremia were uncommon and observed in only 4% of fatal cases. In contrast, survivors with PNa ≤110 mmol/L had a low comorbidity burden with an average Charlson comorbidity index of 1.8. The hyponatremia in this group was mostly attributed to medications including thiazide diuretics and selective serotonin reuptake inhibitors. The investigators concluded that the nature of the underlying illness rather than the severity of hyponatremia best explained the increased mortality associated with hyponatremia.

Hyponatremia, especially chronic and even of mild degrees, has also been associated with increased morbidity. Several studies report the association of chronic hyponatremia with attention deficits and gait disturbances,[10] falls,[10] osteoporosis,[11] and bone fractures.[12]

Heightened healthcare utilization has also been associated with hyponatremia. Hyponatremia has been associated with increased length of hospital stay. It is also estimated that the direct costs of treating hyponatremia in the United States on an annual basis are between $1.6 billion and $3.6 billion with 70% of this cost incurred in the inpatient setting.[1]

It is unclear whether the treatment of hyponatremia has any impact on the heightened morbidity and mortality observed. Garrahy et al performed a prospective observational study of patients with severe hyponatremia (PNa <120 mmol/L) over a 10-year period and observed that specialist consultation to facilitate active management was associated with a reduction in mortality (relative risk [RR] = 0.09, 95% confidence interval [CI]: 0.03-0.26, $P < .001$).[13] Corona et al performed a meta-analysis of 15 observational studies with a total of 13 186 patients and observed that any improvement of hyponatremia was associated with a reduced risk of overall mortality (odds ratio [OR] = 0.57, 95% CI = 0.4-0.81).[14] In addition, only a few studies have reported improvement in morbidity related to hyponatremia correction.[15]

Physiological Determinants of PNa Concentration

Plasma Osmolality and Plasma Tonicity

It is important to distinguish plasma osmolality from plasma tonicity. Plasma osmolality is simply the number of solutes (in mOsm) present in 1 kg of plasma water. Plasma osmolality can be estimated using the following formula:

$$\text{POsm (mOsm / kg)} = 2 \times \text{PNa (mmol / L)} + \frac{\text{Glucose (mg / dL)}}{18} + \frac{\text{BUN (mg / dL)}}{2.8}$$

where POsm is plasma osmolality, glucose is the plasma glucose, and BUN is the blood urea nitrogen.

In contrast, plasma tonicity refers to only the number of *effective* osmoles present in 1 kg of plasma water. *Effective* osmoles are those solutes that do not cross cell membranes and generate osmotic water shifts when their concentration in plasma is elevated. Examples of effective osmoles include sodium, glucose (in the absence of insulin), and mannitol. Since urea (BUN) crosses cell membranes, then it does not generate osmotic water shifts, and it is considered an *ineffective* osmole. Other *ineffective* osmoles include ethanol and toxic alcohols (eg, ethylene glycol). Plasma tonicity (PTon) can be estimated with the following formula:

$$\text{PTon (mOsm / kg)} = 2 \times \text{PNa (mmol / L)} + \frac{\text{Glucose (mg / dL)}}{18}$$

Since the normal plasma glucose is ≈90 mg/dL, then glucose only contributes 5 mOsm/kg to the plasma tonicity. Therefore, PNa is the main determinant of plasma tonicity where

$$\text{PTon (mOsm / kg)} \approx 2 \times \text{PNa (mmol / L)}$$

Plasma Sodium Concentration and the Edelman Equation

In 1958, *Edelman* et al empirically demonstrated that PNa is a function of the ratio between total exchangeable body cation sodium (NaE) and potassium (KE) and total body water (TBW).[16] This relationship can be illustrated in a simplified form[17] (Edelman equation) as follows:

$$\text{PNa} = \frac{\text{NaE} + \text{KE}}{\text{TBW}}$$

The contributions of NaE and TBW to PNa are intuitively evident. However, the contributions of KE to PNa are much less apparent. While sodium is the main solute in the extracellular fluid compartment and the main determinant of plasma and extracellular fluid tonicity, potassium is the major of intracellular tonicity. Total body potassium depletion can lead to hyponatremia, and potassium replacement can lead to its correction. It is commonly assumed that potassium depletion leads to a

compensatory potassium exit from cells leading to a commensurate sodium shift into the cells. When potassium is repleted, the reverse occurs. Rather, the reason for hypokalemia-induced hyponatremia is not that sodium shifts into the cells per se but rather that the compensatory potassium exit prevents water from entering the cells with sodium resulting in a dilution of PNa.[18]

Pathogenesis and Etiology

Since PNa is the main determinant of plasma tonicity, hyponatremia is usually associated with a hypotonic plasma; however, hypertonic and isotonic forms of hyponatremia can also occur.

Hypertonic Hyponatremia

Hypertonic hyponatremia, also known as translocational hyponatremia, occurs due to the presence of large amounts of *effective* osmoles in plasma such as hyperglycemia and mannitol. Hyponatremia occurs because of the translocation of intracellular water to the extracellular space causing PNa dilution. Hypertonic hyponatremias are true hyponatremias and should not be confused with pseudohyponatremia. In the case of hyperglycemia, various correction factors have been proposed to estimate PNa when glucose is normalized, but the most accurate[19] is the conversion coefficient proposed by Katz[20] where PNa increases by 1.6 mmol/L for every 100 mg/dL of plasma glucose over 100 mg/dL.[21]

Isotonic Hyponatremia

Isotonic hyponatremia is usually caused by a laboratory artifact, that is, pseudohyponatremia. PNa is measured using ion selective electrodes (ISEs) where a sodium-specific electrode is submerged into the sample to measure sodium ion activity in water (sodium ions only distribute in the water fraction of plasma). The ISE electrode produces a potential change which is then converted into concentration using the Nernst equation. There are 2 methods that utilize ISE: indirect and direct. Most clinical laboratories routinely measure PNa in automated analyzers using the *indirect* ISE method.[22] In this method, an aliquot of plasma or serum first undergoes a significant dilution step (1:16-1:34). Under normal conditions, plasma is 93% water and 7% solids (proteins and lipids). In patients with severe hyperproteinemia, hypertriglyceridemia, or hypercholesterolemia (lipoprotein X in cholestasis),[23] the solid phase of plasma is greater than 7% and the water fraction less than 93%. Because sodium ions only distribute in the water fraction of plasma, the sample with a lower water fraction will contain less sodium ions. If this sample undergoes a significant dilution, the effect of the solids coming from the original sample will be negligible, and the electrode will measure a lower sodium ion activity in water and hence a lower PNa. Therefore, *indirect* ISE methods are affected by the distribution of solutes and water in the sample, a phenomenon known as "electrolyte exclusion effect." In contrast, *direct* ISE methods used with blood gas analyzers and point-of-care devices do not involve a dilution step, and the presence of a lower water fraction will not affect the results. PNa values using *direct* ISE is ≈2 mmol/L lower than the one obtained with *indirect* ISE.[24]

Hypotonic Hyponatremia

Based on the simplified Edelman equation, hypotonic hyponatremia can be the result of a decrease in the numerator (total exchangeable body cations, NaE + KE) and/or an increase in the denominator (TBW). Four different scenarios can be encountered leading to hypotonic hyponatremia (Figure 1):

1. Normal total exchangeable body cations with an increase in TBW, for example, primary polydipsia.
2. Decrease in both total exchangeable body cations and TBW with a greater decrease in total exchangeable body cations, for example, hypovolemia.
3. Increase in both total exchangeable body cations and TBW with a greater increase in TBW, for example, cirrhosis and heart failure.
4. Decrease in total exchangeable body cations with an increase in TBW, for example, syndrome of inappropriate antidiuresis (SIAD, formerly known as SIADH).

A common theme in all the above scenarios is that TBW is always proportionally greater than total exchangeable body cations, that is, hypotonic hyponatremia is due to electrolyte-free water excess which could be the result of either an increase in intake and/or a decrease in (kidney) excretion.

Increase Electrolyte-Free Water Intake. The kidneys have an extraordinary capacity to excrete electrolyte-free water, but there is a limit. This limit can be estimated using the urine osmolarity calculation as follows:

$$\text{UOsm (mOsm / L)} = \frac{\text{OER (mOsm / day)}}{\text{V(L / day)}}$$

where UOsm is the urine osmolarity, OER is the osmolar excretion rate (daily urine solute excretion), and V is the 24 h urine volume. The above formula can be rearranged in the following way:

$$\text{V (L / day)} = \frac{\text{OER (mOsm / day)}}{\text{UOsm (mOsm / L)}}$$

Hyponatremia will occur when the volume of ingested water is greater than the maximal daily urine volume (assuming no insensible losses). In order to estimate the maximal daily urine volume, the osmolar excretion rate must be the highest possible and the urine osmolality must be the lowest possible. The osmolar excretion rate typically ranges between 600 and 900 mOsm/day while the urine osmolality ranges between 50 and 1200 mOsm/L. Therefore, the maximal daily urine

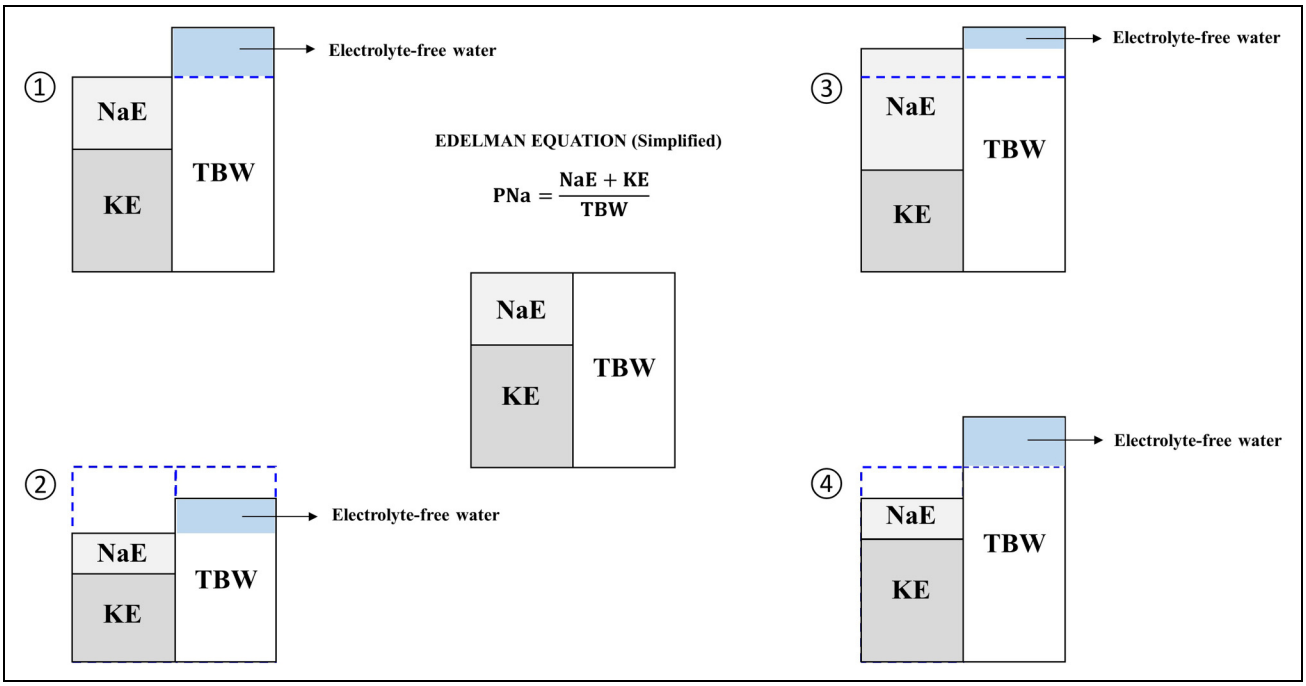

Figure 1. Edelman Gamblegrams. Edelman and colleagues empirically demonstrated that plasma sodium concentration (PNa) is a function of total body exchangeable sodium (Na_E), total body exchangeable potassium (K_E), and total body water (TBW). The main variables of the equation are depicted in a Gamblegram. Based on this equation, hypotonic hyponatremia will occur when the ratio between the sum of total body exchangeable sodium (NaE) and total body exchangeable potassium (KE) and total body water (TBW) decreases. There are 4 different scenarios where this can occur leading to hypotonic hyponatremia: (1) normal NaE and KE with increased TBW, for example, primary polydipsia; (2) decreased NaE and KE and decreased TBW but with a proportionally higher decrease in NaE + KE, for example, hypovolemia; (3) increased NaE and KE and increased TBW but with a proportionally higher increase in TBW, for example, cirrhosis and heart failure; and (4) decreased NaE and KE with increased TBW, for example, syndrome of inappropriate antidiuresis (SIAD). As inferred from the figure, hypotonic hyponatremia is always caused by electrolyte-free water (EWF) excess, that is, TBW is proportionally higher to the sum of NaE and KE. Reused with permission and adapted from Workeneh et al.[25]

volume can be calculated as

$$\text{V (L / day)} = \frac{900 \text{ mOsm / day}}{50 \text{ mOsm / L}} = 18 \text{ L / day}$$

This means that ingesting over 18 L/day would overwhelm the kidneys' excretory capacity leading to hyponatremia. This is the primary mechanism behind primary polydipsia. Rangan et al performed a systematic review of 177 studies reporting hyponatremia in the context of excess water intake and found that the average water intake on presentation was only 8 L/day.[26] This is considerably less than our estimate, and it is likely that other factors (eg, antipsychotic drugs) associated with arginine vasopressin (AVP) release play a role in reducing the volume of ingested water needed to develop hyponatremia. Other disorders characterized by self-induced water intoxication include 3,4-methylenedioxymethamphetamine intoxication (MDMA or "ecstasy") and exercise-associated hyponatremia (eg, marathon-runner hyponatremia). However, the genesis of hyponatremia associated with these conditions is not solely caused by increased water intake. Increased nonosmotic AVP release triggered by exercise, pain, nausea, and other factors also plays a significant role.[27,28]

Decreased (Kidney) Electrolyte-Free Water Excretion. The ability of the kidneys to excrete electrolyte-free water depends on several factors.

An adequate glomerular filtration rate (GFR) will guarantee a sufficient volume of filtrate to be delivered to the diluting segments of the nephron for electrolyte-free water generation. Patients with GFR <20-25 mL/min (eg, acute kidney injury and advanced chronic kidney disease) will have difficulty excreting electrolyte-free water.[29]

The proximal tubule reabsorbs between 65% and 80% of glomerular filtrate and plays an important role in determining the proportion of fluid delivered to the diluting segments. The more volume reabsorbed in the proximal tubule, the less volume to be delivered to the diluting segments for electrolyte-free water generation. Increased proximal tubular fluid reabsorption is common in conditions associated with renal hypoperfusion such as heart failure and cirrhosis.

Dilution of tubular fluid as it passes along the thick ascending limb of the loop of Henle and, to a lesser extent, the distal convoluted tubule generates electrolyte-free water. Any diuretic, which interferes with tubular dilution, can result in hyponatremia although thiazide diuretics are more commonly associated. In contrast, loop diuretics are less likely to cause

hyponatremia as they also interfere with the urinary concentration mechanism, resulting in diluted urine.[30]

The osmolar excretion rate, which depends on dietary solute intake, also obligates electrolyte-free water excretion.[31] Ensuring an optimal intake of dietary solutes is crucial for maintaining appropriate levels of solutes in the tubular fluid of the cortical collecting duct. This, in turn, helps create a lower osmotic gradient between the tubular fluid and the renal interstitium. As a result, there is reduced water reabsorption and a greater ability to excrete electrolyte-free water. Suboptimal solute intake (<600 mOsm/day) will limit the kidneys' ability to excrete electrolyte-free water. For instance, for a given daily solute intake of 200 mOsm, the maximal volume of urine can be calculated as

$$\text{V (L / day)} = \frac{\text{OER (mOsm / day)}}{\text{UOsm (mOsm / L)}}$$

$$\text{V (L / day)} = \frac{\text{200 mOsm / day}}{\text{50 mOsm / L}} = \text{4 L / day}$$

Not counting insensible losses, if a patient ingests >4 L of water, hyponatremia will occur. Examples of this include beer potomania and tea-and-toast diet.

The final step in excreting electrolyte-free water involves maintaining impermeability to water in the collecting duct, which occurs when there is an absence of AVP. Under normal conditions, AVP is released due to two factors: hypertonicity and a decrease in effective arterial blood volume (EABV), which refers to the volume of arterial blood that perfuses tissues. EABV depends on 3 variables: extracellular fluid volume, myocardial function, and peripheral resistance. Consequently, reduced EABV can result from conditions such as hypovolemia, heart failure, or cirrhosis (vasodilation).[32] This decrease in EABV is detected by baroreceptors, which are mechanoreceptors located in the carotid sinus and aortic arch. They stretch in response to increased arterial blood pressure and send signals to the brainstem to inhibit sympathetic nervous system activity and the synthesis/release of AVP in the hypothalamus/posterior pituitary. A decrease in EABV reduces the stretch of the baroreceptors, reducing the inhibitory effect on the sympathetic nervous system (which activates the renin–angiotensin–aldosterone system [RAAS]) and the synthesis/release of AVP. Activation of the RAAS leads to the retention of sodium by the kidneys and low urine sodium (a marker of reduced EABV). AVP circulates in the blood and stimulates vasopressin 2 (V2) receptors present in the basolateral membrane of the collecting duct cells. This results in the insertion of aquaporin 2 water channels in the apical membrane, facilitating the reabsorption of electrolyte-free water. AVP can also be released inappropriately without any physiological stimulus, as seen in the SIAD and cortisol deficiency. It is important to note that SIAD, which was previously referred to as the syndrome of inappropriate antidiuretic hormone secretion (SIADH), underwent a name change due to the identification of a rare genetic disorder known as nephrogenic SIAD (NSIAD). NSIAD is characterized by activating mutations of the V2 receptor, leading to an SIADH-like condition with plasma AVP levels that are undetectable.[33]

Both corticotropin-releasing hormone (CRH) and AVP are produced in the hypothalamus. In the absence of cortisol, CRH secretion is stimulated, along with the release of AVP.[34] Furthermore, in patients with primary adrenal insufficiency, the simultaneous lack of aldosterone leads to renal salt wasting, hypovolemia, decreased EABV, and subsequent release of AVP.[35]

It is important to note that more commonly than not, more than one mechanism described above is responsible for hyponatremia.

Although patients with severe hyponatremia can experience any etiology of hyponatremia, some etiologies are more common in this group. The most common etiologies of hyponatremia in patients with PNa <120 mmol/L are thiazide diuretics, SIAD, and hypovolemia,[36] with thiazide diuretics representing the most common etiology in patients with PNa < 110 mmol/L.[8,37]

Clinical Manifestations

Brain Adaptation to Hypotonicity

During hypotonicity, water moves into brain cells along osmotic gradients leading to cerebral edema. The brain is encased in a rigid skull which limits its expansion. An increase in brain volume of >10% leads to brain herniation and a sure demise without emergent treatment.[38] The first line of defense is the reduction of extracellular water loss which is accomplished by cerebral edema-induced increased hydrostatic pressure which shifts fluid from the brain interstitial space into the cerebrospinal fluid and later into the systemic circulation.[39] Ultimately, protection against lethal cerebral edema lies in the brain ability to lose intracellular water. Astrocytes selectively swell, sparing neurons which lack aquaporin 4 water channels.[40] Astrocytes adapt to hypotonic conditions and reduce their cell volume by extruding solutes together with osmotically obligated water, a process called regulatory volume decrease (RVD). During early adaptation to hypotonicity, astrocytes extrude electrolytes, mainly sodium, potassium, and chloride which is maximal at 3 h which account for 60%-70% of observed brain volume regulation. Late adaptation involves the extrusion of organic osmolytes such as glutamate, creatine, taurine, myoinositol, and glutamine which is largely completed by 48 h and accounts for roughly one-third of total brain solute losses.[41]

Hyponatremia Severity

Hyponatremia severity can be assessed by either biochemical or symptom parameters. Biochemical severity of hyponatremia can be classified as mild (130-134 mmol/L), moderate (120-129 mmol/L), or severe (<120 mmol/L).

Similarly, symptom severity can be classified as apparently asymptomatic, mild, moderate, or severe. Symptom severity correlates with the degree of cerebral edema. During acute hyponatremia (duration <48 h), astrocytes are not able to fully adapt, cerebral edema is prominent, and patients tend to develop severe symptoms. In contrast, in chronic hyponatremia (duration ≥48 h), full adaptation occurs, and astrocytes can restore their cell volume almost back to normal with minimal cerebral edema. These patients tend to have mild symptoms or appear asymptomatic. However, when patients with chronic and apparently asymptomatic hyponatremia are probed, subtle neurocognitive deficits are found.[42] One of the hypotheses to explain this is that the loss of glutamate (a major excitatory neurotransmitter) during RVD leads to glutamate accumulation in the extracellular space and excitotoxicity which could explain some of these symptoms.[43]

Although there is an agreement that seizures and coma constitute severe symptoms, controversy remains regarding what constitutes moderate and mild symptoms. Some consider nausea without vomiting and headaches as moderate symptoms and vomiting as a severe symptom.[44] This is probably true for patients with self-induced water intoxication (eg, primary polydipsia, ecstasy, and marathon runners). However, several studies have shown that nausea and headaches commonly occur in patients with chronic hyponatremia and do not portend a poor prognosis.[45–47]

Diagnostic Approach

The diagnostic approach to hyponatremia in the intensive care unit aims to answer 3 questions: is this a hypotonic hyponatremia? Is it mediated by AVP secretion? Is the secretion of AVP in response to a physiological stimulus?[25]

Is it Hypotonic?

Hyponatremia associated with plasma osmolality ≥275 mOsm/kg can be hypertonic, isotonic, or hypotonic (Figure 2A). In contrast, hyponatremia associated with a plasma osmolality <275 mOsm/kg is always hypotonic (Figure 2B).

Is it Mediated by AVP?

Hypotonic hyponatremia with a urine osmolality <100 mOsm/kg suggests the absence of AVP (AVP independent). The differential diagnosis for AVP-independent hypotonic hyponatremia includes primary polydipsia, low solute intake ,and conditions associated with low GFR with the caveat that in patients with reduced GFR, urine osmolality is less than plasma osmolality but not lower than 100 mOsm/kg. Hypotonic hyponatremia with urine osmolality ≥100 mOsm/kg indicates the presence of AVP (AVP dependent). The differential diagnosis for AVP-dependent hypotonic hyponatremia includes low EABV states, SIAD, and cortisol deficiency.

Is AVP Secretion Physiologically Appropriate?

Urine sodium <20 mmol/L suggests kidney sodium avidity because of increased activity of the renin–angiotensin–aldosterone systems as it occurs in low EABV states such as hypovolemia, heart failure, and cirrhosis (physiologically appropriate AVP). Distinguishing hypovolemia from other etiologies is difficult as the clinical assessment of volume status has poor sensitivity and specificity.[48] Point-of-care ultrasound (POCUS) has emerged as a useful diagnostic tool in this regard.[49] Urine sodium ≥20 mmol/L suggests that kidneys are not sodium avid, inactivity of the RAAS system, and a normal-to-increased EABV. The latter suggests that the secretion of AVP is physiologically inappropriate as it occurs in SIAD and cortisol deficiency.

Syndrome of Inappropriate Antidiuresis

SIAD constitutes the most common etiology of hyponatremia overall, and its diagnostic workup deserves special mention. The diagnostic criteria follow the original criteria described by Bartter and Schwartz in 1967[50]: (1) hypotonic hyponatremia, (2) urine osmolality >100 mOsm/kg, (3) urine sodium > 30 mmol/L, (4) clinical euvolemia, (5) normal kidney, thyroid, and adrenal function, and (6) absence of diuretics within 1 week. A few observations can be derived from these criteria. First, even though patients with SIAD look clinically euvolemic, they are in fact mildly volume expanded due to water retention which eventually leads to compensatory natriuresis (elevated urine sodium). Second, additional tests are required for the diagnosis of SIAD including creatinine and BUN, thyroid-stimulating hormone (TSH), and 8 am plasma cortisol. Unfortunately, these tests required for SIAD diagnosis are infrequently obtained.[51] Third, the literature does not support hypothyroidism as a clinically important cause of hyponatremia. Hammami et al performed a prospective study of 212 patients with thyroid cancer whose thyroid hormone was withheld in preparation for radioiodine therapy allowing them to become hypothyroid. The investigators observed that there was no correlation between post-isolation PNa and TSH levels, and the few patients who developed hyponatremia were more likely to have pre-existing hyponatremia before stopping the thyroid hormone, had kidney dysfunction, were on diuretics, or have lung metastases.[52] In contrast, ruling out adrenal insufficiency is very important as secondary adrenal insufficiency can mimic SIAD. In a prospective, single-center study of 1323 admissions with hyponatremia, Cuesta et al observed that 573 (43.4%) patients were initially classified as SIAD, but after cortisol measurements, 22 (3.8%) of patients were reclassified as secondary adrenal insufficiency.[53] Finally, although not part of the original criteria, hypouricemia (plasma uric acid <4 mg/dL) is usually found in patients with SIAD and can be used as an aid in the diagnosis.[54] It is thought that volume expansion and vasopressin 1 (V1) receptor stimulation leads to a net decrease in tubular reabsorption of urate in this disorder.[55]

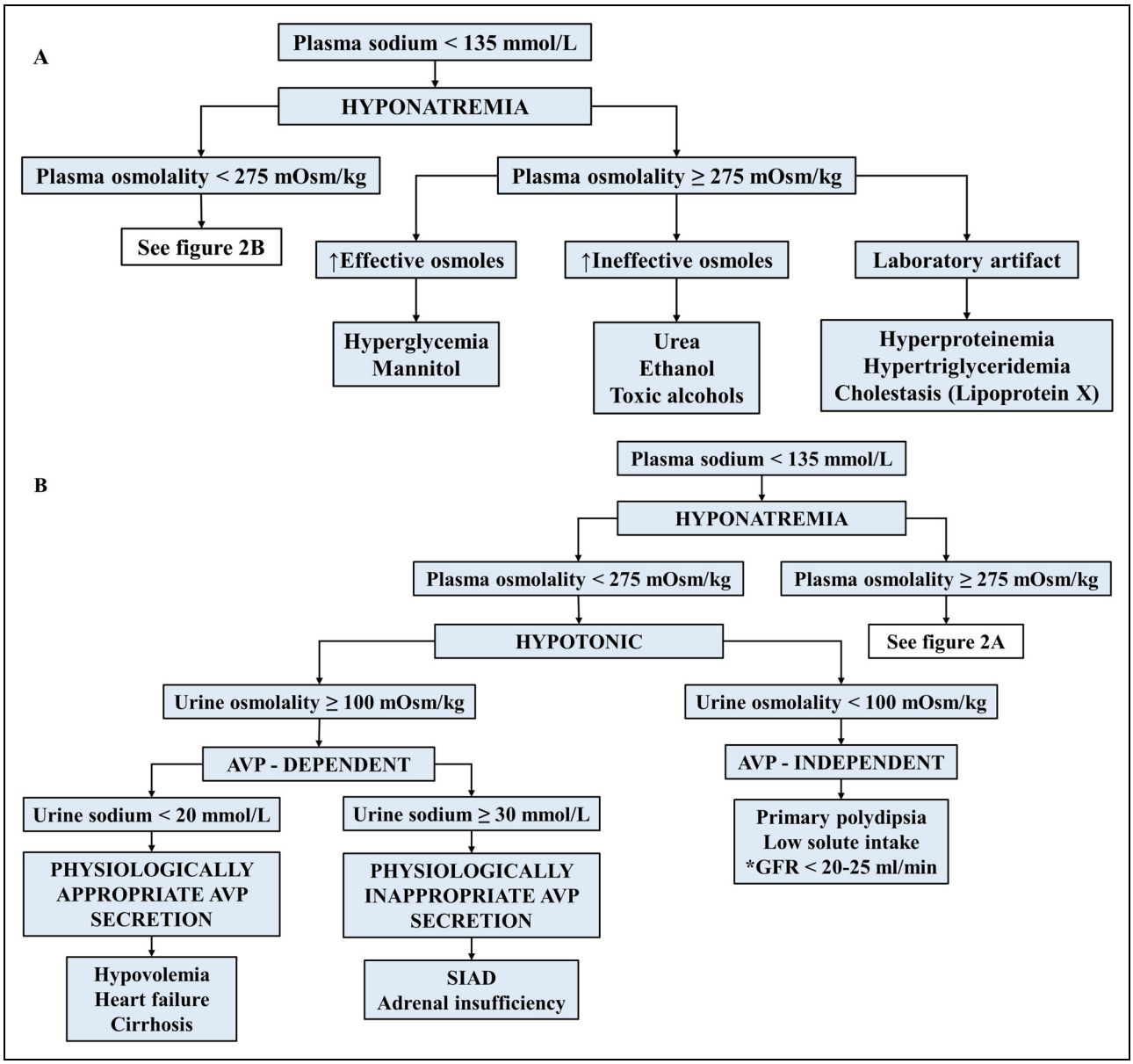

Figure 2. (A) Physiological approach to hyponatremia with plasma osmolality ≥ 275 mOsm/kg. ↑ = increased. (B) Physiological approach to hyponatremia with plasma osmolality < 275 mOsm/kg.
Abbreviations: AVP, arginine vasopressin; SIAD, syndrome of inappropriate antidiuresis; GFR, glomerular filtration rate.

SIAD is a syndrome with multiple etiologies which can be grouped into categories: malignancy, drugs (commonly antidepressants, antiepileptics, and antipsychotic drugs), pulmonary disorders, central nervous system disorders, nausea, and pain. Once the diagnosis of SIAD is established, a cause can usually be elucidated from the clinical presentation. In some cases, especially in the elderly, an obvious cause is never found (idiopathic).[56] An extensive routine diagnostic workup for all patients with SIAD looking for a specific etiology is low yield except perhaps in patients with age ≤70 years old, new onset hyponatremia, or urine osmolality >340 mOsm/kg.[57]

It has been suggested that cerebral salt wasting syndrome (CSW) is a common differential diagnosis of hyponatremia in patients with intracranial pathology (eg, subarachnoid hemorrhage) which must be differentiated from SIAD as their treatments diametrically oppose. The proposed pathogenesis of CSW involves an intracranial process causing primary kidney sodium wasting via an unknown mechanism, leading to decreased EABV and physiologically appropriate secretion of AVP resulting in hyponatremia. Proof that hyponatremia in patients with intracranial pathology is due to CSW would require the presence of natriuresis without a physiologic or non-cerebral etiology and a decreased EABV. Unfortunately, the literature on CSW does not provide convincing evidence of such criteria.[58] For instance, high urine sodium observed in patients with subarachnoid hemorrhage and attributed to CSW can be

explained by antecedent volume expansion with isotonic fluids given to prevent vasospasm while hyponatremia can be attributed to desalination in the setting of SIAD.[58,59] Moreover, EABV is a concept and not something that can be directly measured. Without a gold standard, assessment of EABV relies on volume surrogates (eg, direct measurement of red blood cell mass and plasma volume, central venous pressure, plasma renin and aldosterone, and sodium balance), none of which meet the mark.[58] Recently, Hanon et al prospectively studied 100 patients with nontraumatic subarachnoid hemorrhage and observed that 49 patients developed hyponatremia of which 71.4% was due to SIAD and 8.2% was due to secondary adrenal insufficiency without a single case of CSW.[60] We believe CSW is a rare cause of hyponatremia, and its distinction from SIAD is not only difficult but also unnecessary as the therapeutic approach to patients with symptomatic hyponatremia and intracranial pathology (at risk of brain herniation) from either cause should be the same, hypertonic saline.[61]

Treatment

Therapeutic Principles

The treatment of hyponatremia is based on the presence and severity of symptoms. The presence of moderate or severe symptoms which are common in patients with acute hyponatremia suggest a significant degree of cerebral edema, and it constitutes a medical emergency requiring prompt therapy with hypertonic saline, while the occurrence of mild or no apparent symptoms reflect minimal cerebral edema which does not require emergent treatment, and clinicians should rather address the underlying pathogenesis (eg, volume expansion in hypovolemia, glucocorticoid therapy in adrenal insufficiency, and discontinuation of offending agent in drug-induced SIAD). In this review, we will focus on the treatment of severe hyponatremia (PNa < 120 mmol/L) in the intensive care unit. For a comprehensive review of the therapy of less severe forms of hyponatremia, we refer the readers to a recent publication.[25]

Goals and Limits of Correction

It is important to differentiate between goals and limits of correction. Goals are correction rates that we aim for. Based on several case series, a correction rate of 4-6 mmol/L in any 24 h period is enough to stop even the most severe symptoms of hyponatremia.[62] Furthermore, an increase in PNa of ≥5 mmol/L has been associated with reversal of transtentorial herniation in normonatremic neurosurgical patients.[63] Guidelines published in both sides of the Atlantic have issued similar recommendations in this regard (Table 1).[44,64] For patients with severe symptoms (ie, seizures and coma), the American expert panel recommends increasing PNa by 4-6 mmol/L in the first hour while the European clinical practice guidelines recommend increasing PNa by 5 mmol/L also in the first hour. After the goals of correction are achieved, further correction can be postponed for the next day.

In contrast, limits are correction rates that when exceeded could lead to neurological sequelae in patients with chronic hyponatremia. Because of the lack of complete brain adaptation, patients with acute hyponatremia tolerate rapid rates of correction without post-treatment sequelae.

The American expert panel recommends to correct PNa by ≤10-12 mmol/L in any 24-h period and ≤18 mmol/L in any 48-h period in patients at normal risk for osmotic demyelination syndrome (ODS) and by ≤8 mmol/L in any 24-h period in patients with risk factors for ODS (see *Central pontine and extrapontine myelinolysis and osmotic demyelination syndrome*).[64] A stricter limit of 8 mmol/L per day for patients at higher risk of ODS was proposed not because patients exceeding this limit frequently develop ODS but because they can.[66] In addition, adhering to the limit of 8 mmol/L per day will allow these patients to steer clear of a dangerous rate of correction that could lead to neurologic sequelae since there is always a chance of surpassing the recommended limits. The European clinical practice guidelines recommend avoiding an increase in PNa of >10 mmol/L during the first 24 h and >8 every 24 h thereafter.[44] However, contrary to what published guidelines state, there is no evidence to support a different limit of correction between the first day and subsequent days. We recommend a limit of 8 mmol/L in any 24-h period for patients with severe hyponatremia.

Complications of Therapy

Overcorrection of Hyponatremia. Overcorrection of hyponatremia is defined as an increase in PNa that exceeds the suggested limits of correction. Overcorrection of hyponatremia usually results from spontaneous water diuresis that develops when factors limiting electrolyte-free water excretion vanish (Table 2) such as when AVP is turned off by volume expansion in hypovolemia, glucocorticoid treatment in adrenal insufficiency, or resolution of transient SIAD; solute is provided by diet or electrolyte-containing intravenous fluids in low solute intake states; or the kidney diluting ability is restored by discontinuation of thiazide diuretics.[62] Hence, overcorrection of hyponatremia is usually preceded by a large urine output of diluted urine. George et al retrospectively studied a cohort of 1490 patients with PNa < 120 mmol/L admitted to 7 hospitals and found that younger age, being a woman, schizophrenia, lower comorbidity burden, lower initial PNa, and urine sodium <30 mmol/L were independent predictors for rapid correction of hyponatremia defined as an increase in PNa > 8 mmol/L at 24 h.[67]

Central Pontine and Extrapontine Myelinolysis and ODS. The first official description of central pontine myelinolysis (CPM) is attributed to Adams et al in 1959.[68] The authors identified 4 cases: 2 patients from their own experience who initially presented with symptoms of rapidly evolving flaccid quadriparesis, weakness of face and tongue, dysarthria, and dysphagia and 2

Table 1. Indications, Dosing, and Goals of Correction for Bolus Injection of Hypertonic Saline per Current Guidelines.

2013 American expert panel recommendations[64]			2014 European clinical practice guidelines[44]		
Indication	Dose	Goal	Indication	Dose	Goal
Seizures or coma, regardless of known chronicity	NaCl 3% 100 mL IV bolus (over 10 min) up to 3 times as needed	Correct PNa by 4 to 6 mmol/L within first hour	Severe symptoms of hyponatremia (ie, vomiting, cardiorespiratory distress, abnormal and deep somnolence, seizures, or coma)	NaCl 3% 150 mL IV bolus (over 20 min) 2 times and then repeat twice or until PNa goal is achieved	Correct PNa by 5 mmol/L within first hour
High risk of herniation: • Intracranial pathology or increased intracranial pressure • Acute hyponatremia[a] with headache, vomiting, or confusion	NaCl 3% 100 mL IV bolus (over 10 min) up to 3 times as needed	Correct PNa by 4 to 6 mmol/L within first hour	Moderate symptoms of hyponatremia (ie, nausea without vomiting, confusion, or headaches)	NaCl 3% 150 mL IV bolus (over 20 min) once	Correct PNa by 5 mmol/L within first 24 h
Acute hyponatremia with mild to moderate symptoms[b]	NaCl 3% in a continuous IV infusion at a rate of 0.5 to 2 mL/kg/h	Correct PNa by 4 to 6 mmol/L within 6 h			

Reproduced with permission from Rondon-Berrios and Sterns.[65]
Abbreviations: IV, intravenous; PNa, serum sodium.
[a]The American expert panel defined acute hyponatremia as known duration <24-48 h (eg, postoperative hyponatremia) or self-induced water intoxication (eg, due to schizophrenia, endurance exercise, or use of ecstasy).
[b]The American expert panel did not specifically define "mild to moderate symptoms" but implied these to be symptoms attributed to hyponatremia that are less severe than those mandating urgent correction within 1 h.

Table 2. Risk Factors for Overcorrection of Hyponatremia.

Risk factor	Mechanism of water diuresis
Volume expansion in hypovolemia	Inhibition of AVP secretion
Glucocorticoid replacement in adrenal insufficiency	Inhibition of AVP secretion
Resolution of transient SIAD	Inhibition of AVP secretion
Discontinuation of desmopressin	Decreased V2 receptor stimulation
Initiation of vasopressin antagonists	Decreased kidney responsiveness to AVP
Discontinuation of thiazide diuretics	Restoring DCT diluting capacity
Administration of solutes in low solute intake	Increasing osmolar excretion rate

Abbreviations: AVP, arginine vasopressin; SIAD, syndrome of inappropriate antidiuresis; V2, vasopressin 2 receptor; DCT, distal convoluted tubule.

asymptomatic patients from an autopsy series. All the cases had in common a single, sharply outlined focus of myelin destruction in the rostral part of the pons. Lesions were small in the asymptomatic cases. Interestingly, axons were largely spared, and there were no inflammatory changes. In their discussion, Adams et al mentioned, "We have been unable to discover any reference to a disease of this type in the medical literature of the past 75 years." Three of the cases suffered from alcohol use disorder, and 1 had malnutrition. The authors' conclusion was "the nature and location of the disease favor either an exogenous or an endogenous intoxication or a deficiency of some essential substance." No link to hyponatremia or its correction was suggested as PNa was not routinely measured until the mid-1960s when the flame photometer became widely available.[69] Since the majority of cases reported by Adams et al suffered from alcohol use disorder but alcohol use preceded the first report of CPM for centuries, then this suggested that a new etiology was at work from 1950s onwards. Interestingly, the description of this new entity coincided with the beginning of "the plastic revolution" and the widespread use of intravenous fluids in medical practice suggesting a iatrogenic origin.[70] From then on, multiple reports of CPM appeared in the literature in association with different underlying conditions. Within a few years, it became apparent that CPM lesions could occur outside the pons (extrapontine myelinolysis [EPM]). In 1961, Adams first mentioned hyponatremia in the context of CPM,[71] and in 1973, Finlayson et al,[72] followed by Tomlinson et al in 1976,[73] were the first ones to suggest that CPM could be associated with the correction of an electrolyte abnormality. In the early 1980s, studies conducted in dogs by Laureno[74] and in rats by Noremberg[75] conclusively demonstrated that rapid correction of chronic hyponatremia leads to

CPM while uncorrected hyponatremia or slow correction of hyponatremia does not. Furthermore, animal studies[76] and case reports[77] demonstrated that relowering of PNa after overcorrection of hyponatremia reverses imminent neurological manifestations of CPM and consolidated the relationship between rapid correction of PNa and neurological complications. In 1986, Sterns et al described 8 patients with an initial PNa <115 mmol/L whose PNa was corrected by ≥12 mmol/L per day and developed clinical features of CPM.[78] Patients often had a biphasic course with an initial phase reflecting an improvement of hyponatremic symptoms followed 3-6 days later by the onset of neurological deficits including seizures, dysphagia, dysarthria, and paralysis. The diagnosis was established on clinical grounds only as lesions on initial brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) might not be evident until up to 4 weeks after the initial insult, and in mild cases, lesions might never appear. Lesions found in brain imaging represent severe clinical disease. Sterns et al additionally performed a literature review and found 80 cases with PNa ≤105 mmol/L; in 51 of them, enough data was provided to estimate rates of PNa correction.[78] Over 50% of the cases that corrected ≥12 mmol/L per day experienced neurological deficits while 13 patients in whom the correction rate was <12 mmol/L per day recovered without complications. Sterns et al proposed the term ODS to describe the neurologic findings that appear after rapid correction of chronic hyponatremia.[78]

Although not systemically studied, other risk factors have been associated with ODS (Table 3). These risk factors either increase hypertonic stress or lead to a suboptimal intracellular response. Hypertonic stress depends not only on the rate of correction but also on the biochemical severity of hyponatremia, with patients with PNa ≤105 mmol/L being at the highest risk. Additionally, other forms of hypertonic stress such as hypernatremia[79] and severe hyperglycemia[80] can also lead to ODS. Other factors such as alcohol use disorder, advance liver disease, and malnutrition are associated with organic osmolyte depletion leading to a suboptimal intracellular response.[81]

It is important to recognize that ODS and CPM/EPM are not synonymous. ODS should be considered a particular subtype of CPM/EPM associated with osmotic challenges. CPM/EPM can actually develop in the absence of osmotic insults (eg, thiamine deficiency,[82] hyperammonemia,[83] and malignancy[84]).

Table 3. Risk Factors for Osmotic Demyelination Syndrome.

Risk factor
Overcorrection of chronic hyponatremia
Plasma sodium ≤105 mmol/L
Advanced liver disease
Alcohol use disorder
Malnutrition
Hypokalemia

The treatment of established ODS is supportive although animal studies and case reports have shown success with PNa relowering,[76,77] glucocorticoids,[85–87] intravenous immunoglobulin,[85,87] and plasma exchange.[87]

Early case series observed an excess mortality of up to 90% associated with ODS.[88] However, more recent data published over the last 20 years showed that most patients with ODS survive and recover without significant sequelae.[89–92]

Treatment of Acute Hyponatremia and/or Hyponatremia With Severe Symptoms

Patients with acute hyponatremia or hyponatremia with severe symptoms are at risk for brain herniation and require emergent therapy with hypertonic saline 3%. The first description of this treatment is attributed to Helwig et al who in 1938 reported the case of a 64-year-old woman who developed severe neurological symptoms including seizures and coma as a result of water intoxication produced by the absorption of 8.25 L of water via proctoclysis (a procedure commonly done in the past for resuscitation when intravenous techniques were less advanced) after undergoing a hysterectomy for uterine bleeding.[93] Helwig et al noted that her symptoms slowly resolved after infusion of NaCl 5% solution and recovered uneventfully.

For patients with severe symptoms of hyponatremia, self-induced water intoxication, hyponatremia of known duration <24-48 h, and intracranial pathology/increased intracranial pressure, the American expert panel recommends the administration of hypertonic saline 3% 100 mL IV bolus up to 3 times as needed to control the symptoms.[64] Similarly, for patients with severe symptoms of hyponatremia, the European clinical practice guidelines recommend hypertonic saline 3% 150 mL IV bolus twice and then repeat twice or until the PNa goal is achieved[44] (Table 1).

However, the evidence supporting the use of hypertonic saline as bolus over a slow continuous infusion is limited.

Garrahy et al prospectively studied 22 patients with SIAD (mean PNa 119 mmol/L) with severe symptoms who were treated with bolus of hypertonic saline and compared them with a historical control of 28 similar patients (mean PNa 121 mmol/L) who were treated with slow continuous infusion of hypertonic saline.[94] The investigators observed that compared to the control group, patients in the bolus group had a higher increase in PNa at 6 h (median PNa change 3 [1 to 4] vs 6 [2 to 11], $P < .0001$) with a concomitant greater improvement in the scores of the Glasgow Coma Scale (GCS) (median GCS 1 [−2 to 2] vs 3 [1 to 6], $P < .0001$). However, despite having a similar PNa at 24 h in both groups, the administration of a third bolus of hypertonic saline was associated with a greater need for interventions to prevent overcorrection of hyponatremia (dextrose 5% and/or desmopressin).

Baek et al conducted the 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 (SALSA) trial, a multicenter, open-label, randomized controlled trial across South Korea that compared rates of overcorrection of hyponatremia using hypertonic saline as a rapid intermittent bolus versus slow continuous infusion in 178 patients with symptomatic hyponatremia (PNa < 125 mmol/L, corrected for glucose).[95] The investigators found no difference in overcorrection rates among the bolus group versus the slow continuous infusion group (17.2% vs 24.2%, $P = .26$). No cases of ODS were observed. However, they observed that patients in the bolus group achieved a higher proportion of desired PNa correction rate within 1 h of administration and a lower need for relowering of PNa. They concluded that bolus therapy should be the preferred therapy when treating symptomatic hyponatremia. However, several limitations make the results of this study difficult to generalize.[65]

The administration of hypertonic saline is only permitted via central venous lines in some hospitals. The avoidance of its administration via peripheral intravenous line stems from the concern of phlebitis given its high osmolarity (1026 mOsm/L). However, this is a misconception which originated in a study by Gazitua et al that compared the risk of phlebitis between the use of solutions that contained amino acids versus several crystalloid solutions and found that the risk of phlebitis with solutions containing amino acids with osmolarity >600 mOsm/L was significantly higher than that in the crystalloid group (70.1% vs 43.7%, $P < .05$).[96] These findings were extrapolated to hypertonic saline which was not evaluated in this study. Madieh et al recently performed a systematic review and meta-analysis of 10 studies that included 1200 patients who received hypertonic saline via the peripheral route and observed a low rate of complications including infiltration, phlebitis, edema, erythema, and thrombosis.[97] The incidence of phlebitis was 6.2% which is comparable to accepted standards.[98] Furthermore, over 98% of patients in the SALSA trial received hypertonic saline via peripheral veins with only 2 patients experiencing phlebitis.

Table 4. Strategies to Prevent and Treat Overly Rapid Correction of Hyponatremia Using Desmopressin.

Strategy	Indications	Description
Proactive	Start immediately when PNa <120 mmol/L AND: • High risk for rapid correction[a], AND/OR • High risk for ODS[b]	• Desmopressin 2-4 mcg IV/SC every 6-8 h, AND • NaCl 3% 100 mL bolus for seizures, coma, or rapidly falling PNa[c], OR • NaCl 3% 1-1.5 mL/kg IV over 6 h (to increase PNa by ≈ 1 mmol/L every 6 h)
Reactive	Worrisome PNa trajectory: • PNa goal of 6 mmol/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 mmol/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 mmol/L)

Reproduced with permission from Rondon-Berrios and Sterns.[65]
Abbreviations: PNa, serum sodium; UOP, urine output; IV, intravenously; SC, subcutaneously.
[a] Low solute intake, hypovolemia, adrenal insufficiency, transient SIAD, thiazide diuretics, desmopressin, and vasopressin antagonists.
[b] Alcohol use disorder, hypokalemia, liver disease, malnutrition, PNa ≤ 105 mmol/L.
[c] 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).

Treatment of Chronic and Severe Hyponatremia With Mild or No Apparent Symptoms

Patients with chronic and severe hyponatremia with mild or no apparent symptoms are at minimal risk for brain herniation. Instead, the main concern in these patients is the neurological sequelae from rapid correction especially in patients with risk factors (Table 3). Since overcorrection is usually the result of large water diuresis, the use of desmopressin, an AVP analog, has been proposed to curtail this undesired occurrence.[99] Three different therapeutic approaches to the use of desmopressin in severe hyponatremia have been described in the literature[100] (Table 4): (1) proactive strategy ("DDAVP clamp"), started along hypertonic saline and at the outset of PNa correction allowing for a gradual correction; (2) reactive strategy, started during PNa correction as a reaction to a worrisome PNa trajectory to prevent PNa from exceeding correction limits; and (3) rescue strategy, started along dextrose 5% and after PNa overcorrection had occurred aiming to relower PNa just below correction limits. Published guidelines endorse the use of the reactive strategy and rescue strategies. The rescue strategy seems to be the least desirable as interventions are administered after overcorrection already occurred. Some disadvantages of the reactive strategy are that it is difficult to know when water diuresis will occur, and once urine water losses are recognized, there are often delays in administering desmopressin. Furthermore, water diuresis washes out the medullary interstitium, and the urine-concentrating ability might be diminished for several hours which could limit the response to desmopressin. Even though there is limited evidence supporting the proactive strategy[101] and the published guidelines do not actively recommend its use, we believe the proactive strategy has a sound physiological rationale and could be effective and safe in experienced hands; therefore, nephrology consultation is highly recommended prior to implementing this strategy. When desmopressin is used, it is important that patients adhere

to strict fluid restriction (eg, ≤800 mL/day) to prevent exacerbation of hyponatremia.

If slow continuous infusion rather than bolus of hypertonic saline is chosen, when considering the volume of hypertonic saline to be administered for a desired change in PNa, several formulas have been proposed. These formulas are mathematical manipulations of the simplified Edelman equation and have been shown to be prone to significant error.[102] Mohmand et al performed a retrospective study of 62 patients with severe hyponatremia (mean PNa 116.9 ± 0.9 mmol/L) treated with hypertonic saline and observed that one of such formulas underestimated the actual PNa change in 74.2% of the cases, sometimes by a factor of 5.[103] The main flaws of formulas is that they estimate PNa changes under the premise of a closed system without accounting for urinary water and electrolyte losses, and when they do consider them, they assume static conditions and cannot account for minute-to-minute variations in urine composition that occur during treatment of hyponatremia.[104] Therefore, we recommend a simply weight-based calculation to estimate the initial volume of hypertonic saline to be administered: 1-1.5 mL/kg to be infused over 6 h.[65] For instance, for a 70-kg person, an estimated volume of $1.5 \times 70 = 105$ mL is to be infused over 6 h at an initial rate of 105/6 = 17.5 mL/h. Based on the simplified Edelman equation, this volume of hypertonic saline is estimated to increase PNa by ≈1 mmol/L. This must be followed by compulsory monitoring of PNa for rate adjustment based on subsequent PNa values. It is also recommended to stick to a single method of PNa determination (direct or indirect) as they commonly provide different results. We prefer to follow whole blood sodium (direct ISE) as the turnaround time tends to be much shorter.

Since potassium and sodium are osmotically equivalent, potassium supplementation can increase PNa. Therefore, the hypertonic saline rate should be reduced or temporarily paused when potassium salts are administered (1 mmol of hypertonic KCl is roughly equivalent to 2 mL of NaCl 3%).[65]

The critically ill patient with severe hyponatremia and concomitant acute kidney injury is a special case as strategies outlined using desmopressin might prove futile given the severely reduced GFR and potential desmopressin tubular unresponsiveness. In these patients, especially the ones in need of dialysis clearance to address hyperkalemia or metabolic acidosis, continuous kidney replacement therapy (CKRT) rather than conventional hemodialysis, using either a customized hyponatremic sodium bath or the infusion of dextrose 5% running post filter can prevent rapid correction of hyponatremia.[105]

Revival of an Old Debate

The results of a recent large retrospective study by MacMillan et al[106] and accompanying editorial[107] have questioned the need for strict adherence to PNa correction limits resurrecting a debate that existed in the early 1980s.[108,109] This has motivated a recent report by 24 experts from 20 institutions around the globe urging clinicians to continue to follow treatment guidelines to minimize the risk of complications.[110]

Using a general internal medicine database, the investigators conducted a retrospective study of patients with an initial PNa < 130 mmol/L admitted to 5 hospitals over the course of ~10.5 years. They excluded patients with plasma glucose ≥450 mg/dL but did not exclude patients with acute hyponatremia. The primary outcome was the proportion of patients with ODS ascertained using radiology reports for admissions and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10) codes for admissions and readmissions within 7 days. The secondary outcome was the proportion of patients who experienced overcorrection of hyponatremia defined as PNa correction >8 mmol/L per day. Because PNa is almost never measured exactly at 24-h intervals, the investigators used the nearest PNa within 6 h to the 24-h time mark to calculate correction rates.

A total of 22 858 admissions (17 254 unique patients) met the inclusion and exclusion criteria. The mean PNa was 125 ± 4.6 mmol/L, and almost 87% had a PNa >120 mmol/L. Only 265 patients (1.2%) had a PNa < 110 mmol/L. ODS was identified in 12 patients in the entire cohort (incidence 12/22 858 = 0.05%). The mean PNa among patients with ODS was 111 ± 10 mmol/L, and 7 out of the 12 patients with ODS had a PNa < 110 mmol/L. Hypokalemia and alcohol use disorder were present in 58% and 50% of patients with ODS, respectively.

Out of 22 858 admissions included in the study, 20 572 (90%) had available PNa data to estimate correction rates. Overcorrection occurred in 3632 admissions (17.7%) in the entire cohort as well as in 184 out of the 265 (69.4%) patients with PNa <110 mmol/L. Seven out of the 12 patients with ODS did not experience overcorrection. In addition, 5 or less patients with ODS with initial PNa of 126-129 mmol/L did not experience overcorrection, but they developed hypernatremia with PNa up to 153-164 mmol/L representing an increase in PNa of 24-38 mmol/L.

Since the incidence of ODS in this cohort was only 0.05%, the authors concluded that ODS is an extremely rare complication. We believe this conclusion to be misleading. Other studies that included patients with mild to moderate hyponatremia have also reported low rates of ODS. However, studies of patients with chronic and severe hyponatremia report different results.[37] The great majority of patients in the study by MacMillan et al had a PNa ≥120 mmol/L, a population at very low risk for ODS. In addition, it is unknown how many of these patients had acute hyponatremia, also a condition at no risk for ODS. The only group of patients with a significant risk for ODS were the patients with PNa <110 mmol/L. Since 7 of the 265 patients with PNa <110 mmol/L developed ODS, then a more appropriate incidence would have been 7/265 = 2.6%, a number too common to ignore.

Because of a high relative frequency of overcorrection of hyponatremia among patients with PNa <110 mmol/L and because most patients with ODS (7 out of 12) did not experience overcorrection, the investigators concluded that ODS is

not related to overcorrection of hyponatremia. We find this conclusion misguided. It has always been clear that overcorrection of hyponatremia does not inevitably lead to ODS; rather, it increases the risk of ODS especially in patients with other risk factors (hypokalemia, malnutrition, alcohol use disorder, and advanced liver disease) which this study did not systematically identify. Furthermore, up to 5 patients with ODS experienced significant hypernatremia. As described before, ODS can occur in the setting of hypernatremia and severe hyperglycemia. These findings support a relationship between osmotic insults and ODS. The ascertainment of ODS was also problematic as the investigators identified ODS by searching radiology reports and ICD-10 codes. ODS is a clinical diagnosis, not a radiological diagnosis. Relying on brain imaging for ODS diagnosis will only capture the minority of patients with severe disease, and often, MRI findings are delayed. For these reasons, the number of cases of ODS could have been easily underestimated. A meticulous manual chart review looking for symptoms/signs of ODS was needed. There were also issues with the methodology used to define overcorrection. The authors used the closest PNa within 6 h of the 24-h time point; however, there could be a considerable change of PNa in 6 h affecting the 24-h PNa estimates. The investigators also included patients with a plasma glucose up to 450 mg/dL which could have considerably reduced the number of patients with PNa < 110 mmol/L (at risk) when correcting for glucose. Similarly, the treatment of hyperglycemia in these patients could have raised the PNa by as much as 6 mmol/L, resulting in an overestimation of the number of patients who overcorrected.

Therefore, because of the population studied and the methodology used to ascertain ODS and PNa correction rates, the study by MacMillan et al cannot provide reliable answers. We believe that therapeutic caution with frequent blood draws, use of desmopressin, and a somewhat longer hospitalization are a small price to pay to prevent the devastating consequences of ODS.

Conclusions

Severe hyponatremia is a prevalent disorder in patients in the intensive care unit, and it is linked to increased morbidity, mortality, and healthcare resource utilization. We need to recognize the significant clinical effects of acute or severely symptomatic hyponatremia, which require immediate treatment with hypertonic saline. On the flip side, it is important to exercise caution when correcting chronic hyponatremia to avoid the development of neurologic sequelae. Some studies support the use of desmopressin to limit the speed of PNa correction.

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