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Approach to the Management of Sodium Disorders in the Neuro Critical Care Unit

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Abstract

Purpose of Review To present an overview of the current diagnostic and therapeutic approaches for patients with hyponatremia and hypernatremia in the neurocritical care unit (NCCU).

Recent Findings Dysnatremias are associated with poor neurological outcomes and mortality in neurocritically ill patients. Volume status determination, although challenging, is critical in differentiating between the two most common etiologies of hyponatremia in the NCCU: SIADH and salt wasting. Central diabetes insipidus (CDI) is common in post transsphenoidal surgery patients and in severe brain injuries where it portends a poor prognosis.

Summary Treatment of dysnatremia should take into account severity of symptoms, rapidity of onset, and presence and extent of underlying brain injury. Severe acute hyponatremia is an emergency that should be treated with intravenous hypertonic saline. Controlled

speed of correction is crucial in preventing osmotic demyelination syndrome in the most vulnerable patients in patients with chronic hyponatremia. SIADH is the most common cause of hyponatremia in the NCCU and is usually treated with fluid restriction, vaptans, oral salt, urea, and occasionally saline and loop diuretics. Salt wasting is a common cause of hypovolemic hyponatremia in severe brain injuries and should be managed with fluid and salt repletion ± fludrocortisone. Hypernatremia is treated with hypotonic solutions after correcting volume status as needed with isotonic solution, with the addition of desmopressin or vasopressin in cases of CDI.

Introduction

Disturbances of sodium and water balance are common in intensive care units (ICUs) [1]. The incidence of dysnatremias is even higher in the neurocritical care unit (NCCU), encountered in 38% of neurocritically ill [2] and roughly half of neurosurgical patients [3]. Brain injury can both induce and result in dysnatremias. Exquisite sodium and water balance between intracellular and extracellular compartments is required to regulate neuronal and glial physiology, and cell volume. This balance relies on the intricate interplay between thirst mechanism, autonomic and cardiovascular systems, hypothalamic–pituitary–adrenal (HPA) axis, and renin–angiotensin–aldosterone system (RAAS) [4••]. Failure of one or more of these mechanisms to regulate natremia leads to a plethora of nervous system complications such as encephalopathy, disorders of consciousness, seizures, cerebral edema, osmotic demyelination, and death [5]. Understanding the pathophysiology behind the various causes of hyponatremia and hypernatremia is therefore crucial in guiding the approach to prevent or safely reverse these electrolyte disturbances. In this review, we delve into the major causes of hyponatremia and hypernatremia encountered in the NCCU. We provide an overview of their respective etiologies, and present approaches to diagnosing and managing them in the neurocritical care context.

Approach to Hyponatremia in the Neurocritical Care Unit

Epidemiology and Pathophysiology

Commonly defined as a serum sodium (SNa) of less than 135 mEq/L, hyponatremia affects 3% of hospitalized patients and complicates about 30% of ICU cases [6, 7]. Virtually, any acute brain injury can be associated with hyponatremia, with conditions as diverse as ischemic and hemorrhagic strokes, brain tumors, or traumatic brain injury (TBI). The highest incidence of hyponatremia among neurocritical care illnesses is in subarachnoid hemorrhage (SAH) where it occurs in 40–57% of patients, depending on the series [8, 9]. Several neurotropic medications commonly used in neurosurgical or neurocritically ill patients such as anti-seizure and psychiatric medications can also cause or contribute to hyponatremia. Regardless of the etiology, hyponatremia has been found to correlate with prolonged ICU stay, mechanical ventilation, and increased mortality among ICU patients [1].

Severity of symptoms caused by hyponatremia depends on the degree and acuity of development of the electrolyte disturbance. Chronic hyponatremia, defined as hyponatremia that develops over a period of > 48 h, causes mild

symptoms and may even be asymptomatic. However, acute hyponatremia especially when severe (i.e., < 120 mEq/L) can lead to a variety of symptoms including headaches, nausea, vomiting, drowsiness, and confusion, and can rapidly progress to seizures, respiratory depression, and fatal cerebral edema. The reason for this difference in temporal response to hyponatremia lies in the protective cerebral mechanisms against hypotonicity. Through aquaporin-4 water channels located on glial membranes, water molecules move up the sodium gradient from extracellular to intracellular compartment, resulting in astrocytic swelling to spare the neurons [10, 11]. In order to counteract this increase in water volume, brain cells adapt by extruding osmotically active solutes into the extracellular compartment. The first solutes to be channeled out of the cells are the inorganic Na+, K+, and Cl- ions. This initial mechanism occurs in the first 4 h of the adaptive response and accounts for 65% of the regulatory volume decrease [12, 13]. If hyponatremia persists beyond 48 h, a second mechanism goes into action with the efflux of organic osmoles, namely glutamate, glycine, taurine, betaine, and myo-inositol. This process accounts for the remaining 35% of the volume decrease [12, 13]. At 48 h from hyponatremia onset, the efflux of inorganic solutes still results in a 40% gain in brain water volume, but after 4 days, the additional extrusion of organic osmoles reestablishes near normal brain water volume [14, 15].

Although many conditions can lead to hyponatremia, two etiologies are more frequently encountered in the NCCU: the syndrome of inappropriate antidiuretic hormone (SIADH) and salt wasting (SW). Both conditions can be difficult to distinguish on clinical grounds given the similarities in laboratory and urine studies, but they fundamentally differ in the volume status of the extracellular fluid (ECF) [8]. In SIADH, the more common condition, there is a dysregulated release of ADH from the neurohypophysis as a result of brain injury. This hypersecretion leads to enhanced water retention at the collecting duct level, leading to a euvolemic or mildly hypervolemic water expansion state, a hypotonic plasma, and a high urine Na concentration. In SW, on the other hand, natriuresis occurs in the setting of brain injury, although a renal origin for this disorder is also posited and proposed as renal salt wasting in the literature [16•]. For this purpose, we are using the term salt wasting in this article rather than what it is commonly referred to as "Cerebral Salt Wasting." While renal salt wasting in possible in the absence of brain injury, it is very rare to diagnose salt wasting in the absence of cerebral injuries.

Two main hypotheses for its pathogenesis are entertained: a disturbance in the sympathetic-driven renal sodium reabsorption, and an enhanced renal sodium excretion, stimulated by the release of brain (BNP) and atrial (ANP) natriuretic peptides in response to brain injury. Regardless of the exact mechanism, the outcome in SW is enhanced natriuresis, polyuria, and hypovolemia. The latter stimulates the appropriate release of ADH, further contributing to the hyponatremia.

Hyponatremia in Selected Brain Injuries

Subarachnoid Hemorrhage

Hyponatremia occurs in up to 57% of patients with aneurysmal SAH (aSAH) [17]. Seventy percent cases are deemed to be SIADH-related, while SW accounts for 6.5% of cases [17]. SIADH can occur any time and is often associated with hydrocephalus and anterior circulation aneurysms [17–19], whereas SW tends to have an early onset and occur in high-grade SAH [20]. SW also tends to precede and parallel the course of vasospasm [21•, 22•, 23], contrary to previous thoughts that hypernatremia, rather than hyponatremia, was linked with poor outcomes and mortality in aSAH [24, 25].

Traumatic Brain Injury

Hyponatremia occurs variably in TBI, but can approach 50% of cases in some studies. It is associated with higher Rotterdam CT score and cranial fractures [26]. The incidence of SIADH is higher with subdural hematomas and contusions but can also be a part of the triphasic response observed after pituitary stalk injury; initial phase consists of central DI, second phase consists of SIADH due to unregulated release of vasopressin, and the third phase is DI as the damaged hypothalamic neurons can no longer produce ADH.

SW can occur in up to 40% of severe TBI (sTBI) cases and is usually associated with higher morbidity and mortality [27]. Regardless of the etiology, wide variability in SNa levels may be an independent predictor of mortality in sTBI [28••].

Stroke

Both acute ischemic stroke (AIS) and spontaneous ICH have been associated with hyponatremia with an incidence ranging between 11 and 40% [29, 30]. The data about the incidence of SIADH vs. SW in acute stroke is conflicting. Some reports show that SW accounts for the vast majority of cases, especially in cases of spontaneous ICH (44 vs. 7%) [30]. Nonetheless, hyponatremia on admission has been correlated with higher mortality rates at discharge, 3 months, 12 months, and 3 years [29, 31, 32].

Diagnostic Evaluation

The diagnostic approach to hyponatremia and its treatment are important tools in a neurointensivist's armamentarium. Once hyponatremia is detected, a structured approach can be helpful in determining the correct diagnosis and therefore the appropriate treatment.

Serum Osmolality

The first step in the diagnostic evaluation of hyponatremia is measurement of serum osmolality to rule out confounders of true hyponatremia. As noted in Fig. 1, hyponatremia can exist in hypotonic, isotonic, or hypertonic conditions. Hypotonic and hypertonic plasma are defined by osmolality values <280 and >295 mOsm/kg, respectively. Isotonic hyponatremia specifically pseudo hyponatremia is seldom seen since the introduction of ion-selective electrodes that eliminate the effects of paraproteinemia, hypertriglyceridemia, and other confounders. Hypertonic hyponatremia occurs in hyperglycemic states but can also be found with unmeasured osmoles such as mannitol, an important therapy in the NCCU, especially when it is dosed frequently. Calculating the osmolar gap, i.e., the difference between measured and calculated osmolality, can lead to the detection of unmeasured osmoles and be useful in guiding administration of mannitol in cerebral edema management.

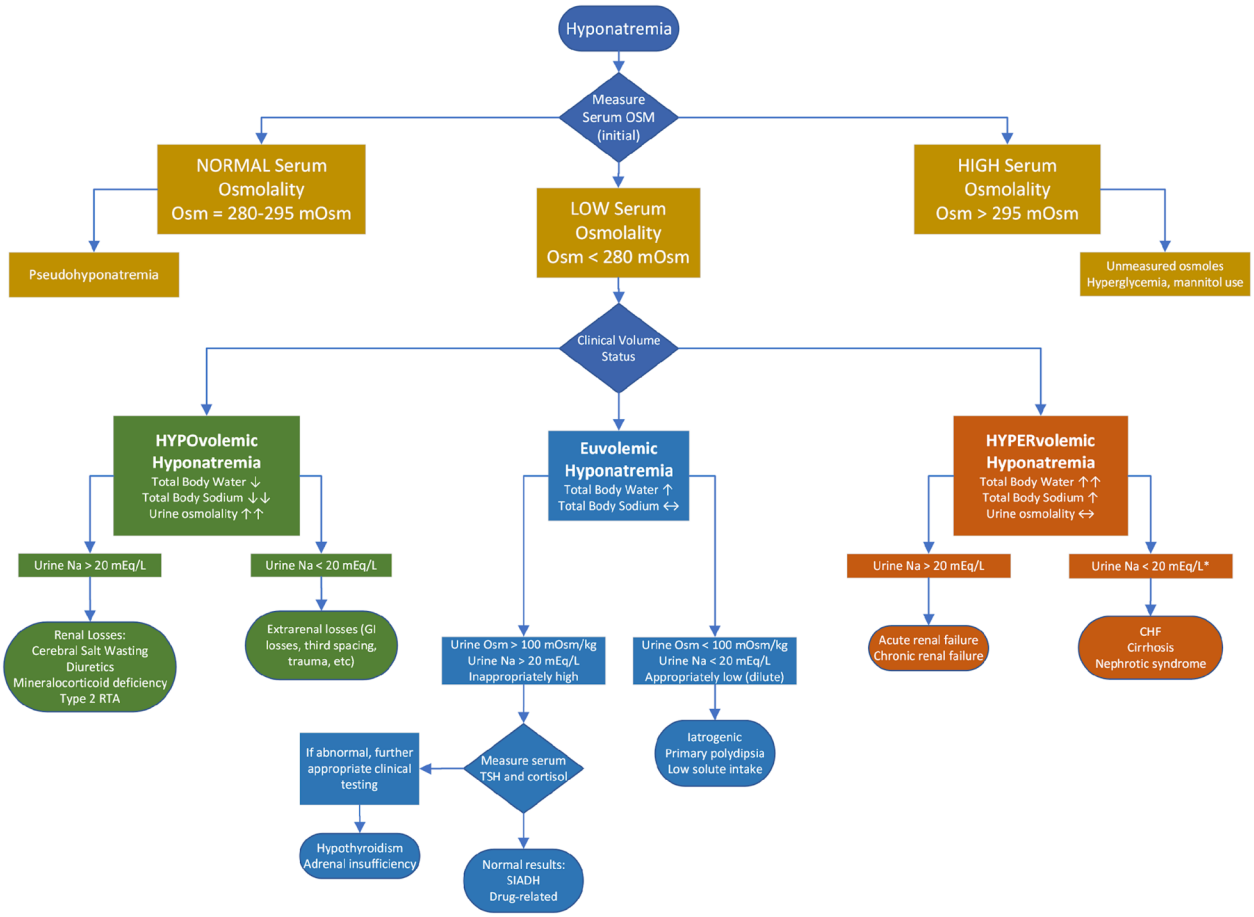

Fig. 1. Diagnostic approach of hyponatremia. *Diuretic use alters the urinary excretion of sodium. In the setting of hypervolemic hyponatremia, urine sodium checked after diuretic use may be higher than expected.

Volume Status Determination

In the predominant case of hypotonic hyponatremia, volume status assessment is the next step in the workup. Though a bedside evaluation can be helpful, with incorporating clinical history, examination of vital signs, jugular veins, mucous membranes, skin turgor, fluid balance, and blood tests such as hematocrit, BUN, and bicarbonate, accuracy of this type of evaluation has proven low in various patient populations [33–35]. In recent years, the use of point-of-care ultrasound (POCUS) as a non-invasive method to determine volume status at the bedside has expanded, with measurement of the inferior vena cava being an effective tool to assess initial fluid status, though less so fluid responsiveness [36]. Formal echocardiography is more time- and resource-consuming but can give better insight into a patient's overall fluid status [35]. Pulmonary artery catheters used to be the gold standard of hemodynamic monitoring but, in light of their invasiveness and inaccuracies [37], they have largely been supplanted by advanced hemodynamic monitors that connect to peripheral arterial and/or central venous catheters which provide a set of dynamic and static hemodynamic measurements with variable performances [38, 39]. No standalone technique has been shown effective in determining fluid status or responsiveness, and a comprehensive evaluation taking into consideration multiple parameters is necessary.

Urine Sodium and Urine Osmolality

As seen in Fig. 1, urine sodium (UNa) and urine osmolality (UOsm) should then be assessed. In hypervolemic hyponatremia, UNa levels can help differentiate renal failure from other edematous diseases such as cirrhosis, congestive heart failure, and nephrotic syndrome. In hypovolemic hyponatremia, urine osmolality is high, but UNa can help differentiate renal losses (high) from extrarenal losses (low). In the euvolemic patient, low UNa and UOsm point to a diagnosis of polydipsia or low solute intake with relative excess water ingestion such as beer potomania, while high levels point to SIADH, hypothyroidism, or adrenal insufficiency. These last two conditions should always be ruled out as hyponatremia will be resistant to treatment without adequate hormonal replacement.

SIADH vs. SW

As mentioned earlier, volume status is the only reliable way to differentiate between the euvolemic SIADH and hypovolemic SW and should therefore be diligently assessed in the NCCU patient, as the laboratory profiles are essentially identical (Table 1). In addition to low SNa, both conditions have high UOsm (above 100 mosmol/kg and usually above 300 mosmol/kg), high UNa (above 40 mEq/L), and low serum uric acid. One way to differentiate SIADH and SW by labs, however, is to calculate the fractional excretion of uric acid (FeUA) after correcting the hyponatremia. The FeUA is high in both conditions (i.e., >11%). After correction, FeUA will return to normal values (i.e., 4–11%) in SIADH but remain elevated in SW [40, 41].

Table 1 Comparison of clinical findings, laboratory values, pathomechanisms, and treatment options between syndrome of inappropriate antidiuretic hormone (SIADH), salt wasting (SW), and central diabetes insipidus (CDI). *FeUA*, **fractional excretion of uric acid;** *IV*, **intravenous;** *PO*, **per os**

	SIADH	SW	CDI
Untreated volume status	Euvolemic or Hypervolemic	Hypovolemic	Hypovolemic
Urine output	↓	↑	↑↑
Serum sodium	↓	↓ or ↓↓	↑
Urine sodium	↑	↑↑	↓
Serum osmolality	↓	↓	↑
Urine osmolality	↑	↑	↓↓
Uric acid	↓	↓	↑
FeUA before sodium correction	> 11%	> 11%	4–11%
FeUA after sodium correction	4–11%	> 11%	4–11%
Plasma ADH	↑	↔	↓
Pathomechanism	Free water retention secondary to increased ADH release	Excessive secretion of sodium and water	Free water loss secondary to decreased ADH release
Treatment options	Fluid restriction (if appropriate for clinical setting) IV hypertonic saline Oral salt ± loop diuretics High solute diet Oral urea Vaptans	IV/PO fluid repletion (isotonic or hypertonic) Fludrocortisone	IV/PO fluid repletion (hypotonic) Desmopressin Low solute diet

Management

The following section on the management of hyponatremia is articulated around the careful consideration of the following points: (1) severity of symptoms, (2) acuity of development, (3) SNa level, (4) etiology, (5) volume status, and (6) presence of brain pathology. A management algorithm is presented in Fig. 2.

Is the Hyponatremia Symptomatic?

Moderately to severely symptomatic hyponatremia, whether acute or chronic, should be treated as a neurological emergency due to the potential for rapid development of neurological deterioration and brain herniation. A search for the cause should never delay treatment, and therefore, *regardless of etiology*, symptomatic hyponatremia should be treated with the prompt infusion of 3% NaCl hypertonic saline (HTS). Isotonic saline should be avoided because it is not efficient at rapidly raising sodium and can exacerbate hyponatremia in SIADH, in which the real problem is excess free water.

HTS is available in concentrations ranging from 1.5 to 23.4% and may be given by bolus or continuous infusion. A US expert panel recommends administering 100 mL 3% NaCl bolus over 10 min up to 3 doses for severe

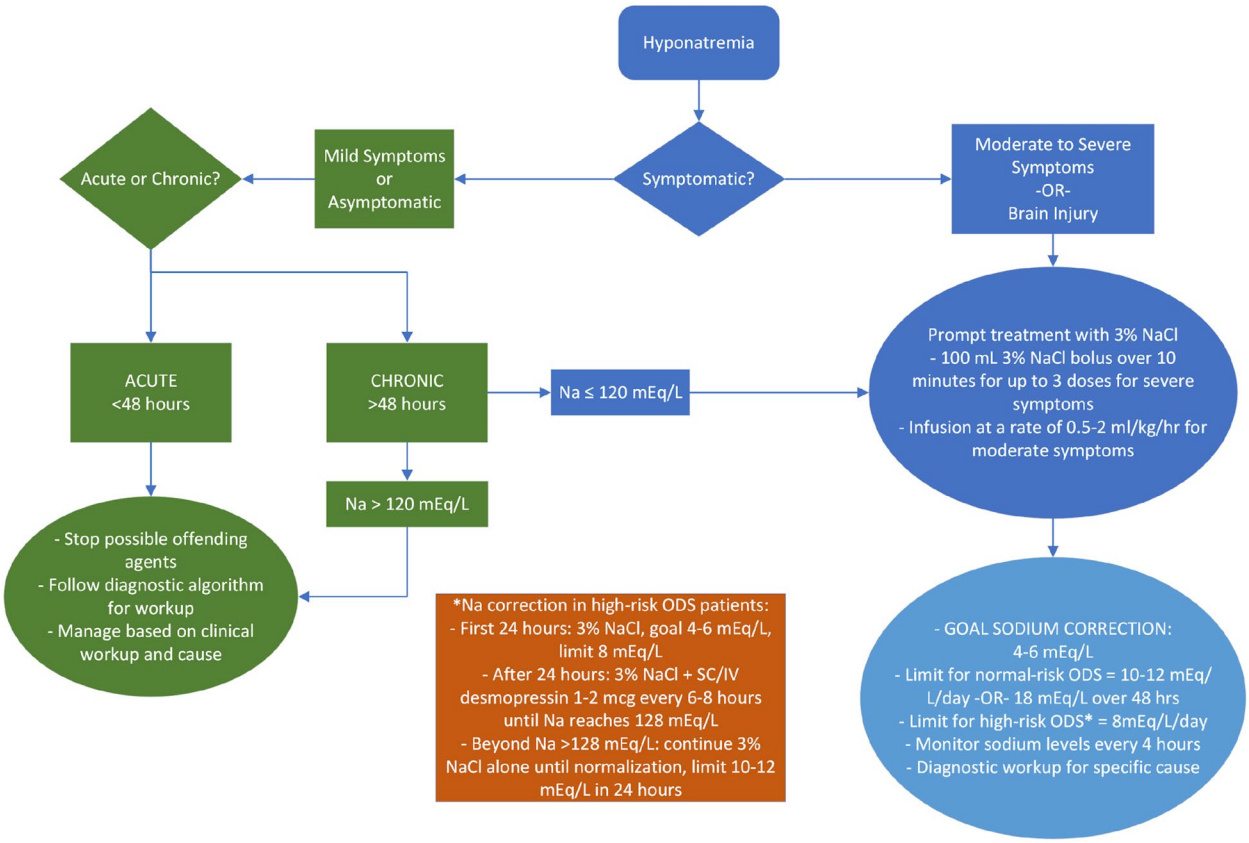

Fig. 2. Approach to the initial management of hyponatremia.

symptoms or start an infusion at a rate of 0.5–2 ml/kg/h for moderate symptoms [42]. The goal is to raise SNa by 4–6 mEq/L, which is usually sufficient in preventing or reversing neurological deterioration [43, 44]. If symptoms related to brain herniation persist, repeat boluses may be needed. Note that symptoms may occur at higher SNa levels in brain-injured patients. During active correction with 3% HTS, SNa should be checked every 4–6 h in order not to overcorrect and precipitate ODS [42, 45]. Once symptoms have resolved, HTS therapy can be stopped while SNa continues to be monitored closely to detect recurrent drops in SNa. A search for etiology should also be started to direct specific treatment. To prevent development of ODS, we do not exceed an increase of 10–12 mEq/L in 24 h or 18 mEq/L in any 48-h period in cases of acute severe hyponatremia [42].

Recent data demonstrated that peripheral administration of HTS in formulations ranging from 3 to 23.4% was as safe and effective as central venous administration, resulting in growing acceptance in NCCU [46••, 47, 48]. Serum K should be concurrently monitored with SNa because correction of hypokalemia with oral potassium can speed up the rise in SNa and also because HTS therapy can worsen hypokalemia. HTS can also cause a hyperchloremic metabolic acidosis that can contribute to renal failure and worsen outcomes. Buffered HTS (50% chloride, 50% acetate) can lower the chloremic load in such instances.

Is the Hyponatremia Acute or Chronic?

If symptoms are neither moderate nor severe, the next step is determining acuity vs. chronicity of the process. If the hyponatremia occurred acutely (< 48 h) but is not severe enough to produce significant symptoms, we recommend discontinuing potential offenders, starting a diagnostic workup and directing treatment at the cause [42, 45].

If the hyponatremia is chronic but the patient is known to have an intracranial pathology associated with cerebral edema, a similar approach to the one detailed above for the symptomatic patient is used. Goal of HTS therapy depends in part on the degree of edema and mass effect, but as mentioned earlier, a 4–6 mEq/L rise in SNa is usually enough to prevent neurological deterioration. Some clinicians, however, aim for normal or even higher SNa levels in these cases, but an optimal target is unclear.

For the non-brain-injured patient with a mild or moderate chronic hyponatremia (SNa > 120–134 mEq/L), we recommend discontinuing any potential offender (medications and hypotonic fluids), limiting water intake, increasing salt intake, and starting cause-directed treatment [45]. The use of hypertonic saline in these cases is usually not recommended unless symptoms develop or worsen.

In chronic severe hyponatremia (SNa < 120 mEq/L), slow HTS administration is recommended while closely monitoring SNa levels every 4 h. These patients are particularly prone to the development of ODS [49]. This condition arises from the rapid correction of hyponatremia. The clinical syndrome usually lags behind the rapid correction by 2–6 days and can produce a multitude of irreversible symptoms including bulbar dysfunction, quadriparesis, confusion, movement disorders, seizures, and coma [50, 51]. Patients at highest risk for ODS are those with SNa < 105 mEq/L for more than 2 days, hypokalemia, alcoholism, malnutrition, advanced hepatic failure, or liver transplant recipients [49, 52, 53•]. The sodium correction goal for these patients is more restrictive than in patients at normal risk of ODS: 4–6 mEq/L/day with a limit of 8 mEq/L in 24 h [42]. To prevent overcorrection in patients with chronic severe hyponatremia, some experts recommend using parenteral desmopressin but only after achieving a SNa rise of 6–8 mmol/L during the first 24 h of HTS therapy. In these cases, desmopressin is usually given at doses of 1–2 mcg either intravenously or subcutaneously, every 6–8 h, until SNa rises above 128 mEq/L [42, 54]. After that, 3% HTS can be continued without desmopressin following the incremental limits given above. This strategy is however not endorsed by international guidelines and some experts prefer to reserve the use of desmopressin for when water diuresis complicates the course of therapy. If overcorrection has occurred, relowering of SNa to the goal of 4–6 mEq/L in 24 h can be achieved by either giving 2–4 mcg desmopressin parenterally every 8 h or replacing water losses with 5% dextrose in water (D5W) at a rate of 3 mL/kg/h or based on noted overcorrection and total body water estimate [42, 55]. Total body water calculation can aid in the management, and may help determine if free water diuresis is needed to correct the sodium in the absence in brain injuries.

Special Considerations in the NCCU

The following section focuses on the specific treatment of SIADH and SW, most commonly encountered in the NCCU. Since fluid management strategies in both conditions are diametrically opposed, making an accurate diagnosis is of utmost importance. Hyponatremia in patients with acute brain injuries should be managed with the understanding that the majority of these patients have compromised cerebral autoregulation, cerebral perfusion pressure (CPP), and elevated intracranial pressure (ICP). It is therefore crucial to optimize volume status in these patients while correcting hyponatremia. Patients with high-grade aSAH typify this concept. Because of their increased risk of developing cerebral vasospasm and DCI, high-grade aSAH patients should not be allowed to become hypovolemic. This is important because standard therapies for SIADH, such as fluid restriction, vaptans, and loop diuretics, cause a water deficit and can lead to volume depletion, contributing to cerebral vasospasm and ischemia. Correction of hyponatremia with HTS is therefore the preferred strategy in these cases, the goal being maintenance of a euvolemic state. Similarly, misdiagnosing SW for SIADH can have the unwanted consequences of worsening both hypovolemia and hyponatremia.

Treatment of SIADH

a. Correction of possible reversible causes should be the first step in management. This means identifying and stopping offending drugs, treating pain and nausea (powerful stimulators of ADH release) and correcting adrenal insufficiency and hypothyroidism, if applicable.
b. Fluid restriction is the mainstay treatment for mild to moderate SIADH but rarely raises SNa level by more than 3–4 mEq/L in 3 days [56•]. To be effective, the restriction has to create a negative water balance which, as mentioned above, is not desired in certain neurocritical care patients, such as those with high-grade aSAH or intracranial hypertension. The daily fluid intake typically recommended for fluid restriction is based on calculation of electrolyte-free water clearance (can generally start with 800–1000 mL) which may not be well tolerated by all patients [57].
c. Vasopressin receptor antagonists, or "vaptans," block V1 and V2 receptors located in renal connecting tubules and collecting ducts, causing water diuresis ("aquaresis"). Two vaptans are FDA-approved: conivaptan, an intravenous, non-selective V1a and V2 receptor antagonist, and tolvaptan, an oral selective V2 receptor antagonist. Tolvaptan was shown to be effective in treating hyponatremia in two double-blinded RCTs [58]. Conivaptan was studied in the NCCU and found to be effective and safe in this patient population, with a mean rise of 5.8 mEq/L in 12 h and no overcorrection [59]. A small open-label study in patients with TBI showed that conivaptan raised SNa and lowered ICP more effectively than the usual care arm at 4 h [60]. Vaptans should not be used in volume-deplete states and we discourage its use in aSAH due to the potential for vasospasm and DCI. Vaptans are also contraindicated in hepatic failure due to

hepatotoxicity, and liver enzymes should be monitored during therapy. For this reason, the FDA cautions against their use for longer than 30 days. The starting oral dose for tolvaptan is 15 mg daily which can be doubled every 24 h to a maximum dose of 60 mg daily [61]. Conivaptan is given as an IV bolus of 20 mg over 30 min followed by a continuous infusion of 20–40 mg over 24 h that can be extended to 96 h. Patients should not be fluid-restricted during vaptan use in order not to overcorrect [42].

d. Oral salt tablets are used for their osmotic diuresis property. In SIADH, since sodium handling is intact, the body will excrete the sodium load and, with it, the volume of water needed to maintain a fixed urine osmolality. A typical regimen is 6–9 g daily in 2 or 3 divided doses (1 g oral salt contains 17 mEq of Na and 17 mEq of Cl) [62, 63]. Loop diuretics such as furosemide or torsemide can be added to oral salt tablets to augment water excretion.

e. Seldom used and only recently introduced in the USA, oral urea is an inexpensive, well-tolerated, and effective way to treat SIADH [64–67]. Its mechanism of action is similar to that of oral salt. It is given at doses of 15–60 g daily and is often administered in a powder drink mix to make it more palatable.

Treatment of SW

a. Fluid repletion is the cornerstone of therapy in SW. Isotonic fluids such as 0.9% NaCl are frequently chosen for fluid repletion but HTS may be needed to achieve faster and higher SNa goals, especially in patients with significant cerebral edema. Different methods for fluid replacement, some more nursing-intensive than others, have been used in the setting of ongoing polyuria: continuous infusion, intermittent replacement of cumulated urinary losses ("ml per ml"), or a combination thereof. A detailed assessment of volume status and fluid responsiveness is recommended to guide fluid replacement in SW.

b. Fludrocortisone, a synthetic mineralocorticoid, enhances Na reabsorption at the distal convoluted tubule leading to water retention and expansion of the ECF volume. It has been studied in small trials and cohorts of patients with intracerebral pathology where it was found to improve hyponatremia and volume status [68–70]. Its effects on mortality, functional outcomes in sICH, and rates of DCI in aSAH are unclear due to scant data [71]. One of the only RCT on the effect of fludrocortisone in aSAH showed a statistically non-significant benefit in reducing the rate of DCI [70]. Typical fludrocortisone dosing in SW starts at 0.05–0.1 mg twice daily and goes up by 0.1 mg increments to 0.3 mg twice daily, if needed. Due to its potassium-wasting properties, serum K levels should be monitored closely during administration.

Approach to Hypernatremia in the Neuro Critical Care Unit

Epidemiology and Pathophysiology

Hypernatremia, defined as SNa > 145, is a common electrolyte disorder in critical care, affecting 4–26% of patients [72]. Acute hypernatremia, especially when severe (> 160 mEq/L), can lead to confusion, lethargy, seizures and coma. Glial cells and neurons lose water content as a result of the osmotic gradient. The brain tries to restore its intracellular volume by moving water from the cerebrospinal fluid into the brain interstitium, followed by early intracellular uptake of ions and late accumulation of organic osmoles.

In the NCCU, hypernatremia is often a desired therapeutic goal in some settings, particularly in the management of cerebral edema, usually achieved with osmotherapy. However, hypernatremia can also be unintended, as in diabetes insipidus, dehydration, or after loop diuretic administration, in which case its occurrence has been linked to poor outcome in the NCC patient population [73]. A retrospective review of patients with sTBI at a single US center showed that mild (defined as 151–155 mEq/L), moderate (156–160 mEq/L), and severe (> 160 mEq/L) hypernatremia were independent predictors of in-hospital mortality, with hazard ratios of 3.4, 4.4, and 8.4, respectively ($p < 0.001$) [74]. The pathogenic link between hypernatremia and poor outcome is thought to involve neuronal dysfunction and death, myelinolysis, but also cardiac dysfunction, impaired gluconeogenesis, and acute kidney injury via renal vasoconstriction and reduced glomerular filtration [72, 75]. It is important to remember, however, that hyperchloremia has been extensively recognized as an independent risk factor of poor outcomes in various critically ill patient populations [76–78]. Although it is difficult to separate the confounding effects of these two co-occurring electrolyte disorders, a recent study suggests that hyperchloremia, not hypernatremia, is associated with increased mortality in moderate and sTBI [79•]. The following discusses the management of hypernatremia, focusing primarily on central diabetes insipidus (CDI).

Central Diabetes Insipidus

Diabetes insipidus (DI) is a rare disease process with a prevalence of 1 in 25,000 in which patients have decreased responsiveness to (nephrogenic DI) or release of (CDI) vasopressin. The classic presentation of DI is polydipsia (greater than 3L/day), polyuria (greater than 50 mL/kg/day), and nocturia [80•, 81].

Central DI arises from an impaired synthesis of arginine vasopressin (AVP or ADH) but can also be caused by inadequate secretion alone. It is most commonly acquired, but can be congenital with mutations in either the AVP gene or WFS1 gene (Wolfram syndrome) [82]. There can be many causes of acquired central DI, but the most common causes encountered in the NCCU are post-operative neurosurgical patients and catastrophic brain injuries, specifically in patients with sTBI and cardiac arrest.

Transient CDI following transsphenoidal surgery is a known complication, with incidence reported anywhere from 8 to 30%. The highest risk tumor pathologies include craniopharyngioma, which has reports of pre-procedural central DI as well, Rathke cleft cyst, and pituitary adenomas. In one large retrospective single-center study, permanent DI was most common in tumors originating from Rathke's pouch [82, 83•].

CDI in patients with injuries to the brain is often associated with poorer outcomes. CDI after sTBI occurs in 20–26% of patients, may be transient, and often in a triphasic pattern specifically in deceleration injuries [84, 85]. The initial DI phase is secondary to stunning of hypothalamic AVP neurons and pituitary stalk transection, and usually lasts 5–7 days [86]. The second phase, which lasts 2–14 days, is marked by SIADH secondary to large ADH release from the degenerating posterior pituitary. The third and last phase is a re-emergence of DI when ADH stores are exhausted and can be permanent in a minority of patients (6.9% in one cohort) [82, 84, 87•].

In sTBI, studies have shown that development of DI is associated with higher mortality and worse functional outcomes of survivors [87•]. In cardiac arrest, studies are not as numerous, but one study looking at out of hospital cardiac arrest reported outcomes of persistent vegetative state or death in all post-arrest patients who developed DI [88]. In catastrophic brain injuries, central DI is a poor prognostic sign and can also be seen just prior to or in conjunction with the determination of brain death [87•, 88].

Diagnostic Evaluation

Unintended hypernatremia should be worked up, especially when DI is suspected since it can lead to severe hypernatremia, dehydration, and hypovolemic shock, if left untreated. The main distinguishing factor between CDI and other causes of hypernatremia is the urinary output. Diagnosis is made based on the clinical features of a high hypotonic urinary output of more than 50 mL/kg body weight in a 24-h period (polyuria) that leads to the consumption of more than 3 L/day of water (polydipsia) [80•, 89]. Historically, serologic diagnosis was made using the water deprivation test. Patients with a urinary osmolality of < 300 mOsm/kg during water deprivation with a subsequent increase in osmolality of > 50% after administration of exogenous ADH were diagnosed with CDI [90]. Later studies however proved this test to have an accuracy of up to only 70% due to various factors. Current studies are evaluating copeptin, a precursor of ADH, to diagnose CDI as it is more reliably testable as a surrogate for diagnosis and can be used post operatively to predict the likelihood of a patient developing CDI [91••].

In the NCCU, hypotonic polyuria is often the heralding sign of CDI defined as a urinary output of > 200 mL/h for 3 consecutive hours with a urine specific gravity of < 1.005 or urine osmolality of < 200 mOsm/kg accompanied by serum sodium levels > 145 mEq/L [92]. The development of a hypovolemic hypernatremia is most often due to the patient's impaired cognition, poor thirst, or limited access to free water to regulate their free water deficit. In patients already receiving hypertonic saline to induce hypernatremia to serum

sodium levels > 145 mEq/L due to their primary neurologic injury, the diagnosis relies more on clinical presentation, rate of rise of sodium, and the risk of developing CDI based on the patient's neurologic injury. Close monitoring of vital signs and fluid balance should be instituted in all patients with suspected or known CDI.

Treatment

General Concepts

In any case of hypovolemia, volume resuscitation by administration of isotonic solutions should be performed before efforts to correct hypernatremia take place. If a loss of free water alone is present, it should be treated by the administration of free water in the form of a 5% dextrose solution, safe in terms of hemolysis. If pure sodium gain is the case, natriuresis should be induced through the application of loop diuretics. At the same time, fluid loss during loop diuretic therapy must be restored with the administration of fluid that is hypotonic to the urine [72].

Regardless of the underlying etiology, hypernatremia is treated with hypotonic fluids such as 0.45% NaCl (1/2 NS) or dextrose 5% in water (D5W), the choice being guided by the desired rate of correction and the hypotonicity of the replacement fluid. Free water deficit is calculated to gauge the volume of replacement, using the following equation: 0.5 (females) or 0.6 (males) × weight in kg × (measured SNa/ideal SNa – 1). Importantly, a patient who is hypovolemic or hemodynamically unstable, even if hypernatremic, should be treated with isotonic fluids until adequately resuscitated.

Carefully considering the speed of correction is of utmost importance to prevent rebound cerebral edema, particularly in brain-injured patients. This is determined mostly by the extent and type of brain injury, and the rapidity of hypernatremia onset. In any case, serum sodium and potassium should be monitored every 4–6 h during active correction. In acute hypernatremia (< 48 h in onset), the SNa correction goal is at a rate of 1–2 mEq/L per hour [72]. In the brain-injured patient, however, normalization may not be the goal, and a higher SNa and slower correction may be indicated. In chronic hypernatremia (> 48 h), correction should be slower due to the risk of cerebral edema conferred by the adaptive cerebral mechanisms that take place when hypernatremia develops over more than 48 h. The recommended rate of correction in this case is 0.5 mEq/L per hour, with a limit of 12 mEq/L in 24 h [72]. Of note, the rate of correction is more consequential in children than in adults.

Central Diabetes Insipidus

For central diabetes insipidus, treatment is often guided by the degree of polyuria. Desmopressin (dDAVP), a synthetic vasopressin analogue, is used to prevent further urinary water loss [93]. It has a half-life of 3 h and duration of action of 8 h [94]. Intravenous dDAVP 0.5–1 mcg as a starting dose

is often sufficient to slow urinary output [83•]. This dose may be increased to 2 mcg if ineffective, or repeated every 6 to 24 h based on the need. The smallest dose should be used to prevent water intoxication. In the awake post-transsphenoidal surgery patient, oral replacement with 0.1 to 0.8 mg/day in 2 or 3 divided doses may be used. Other formulations such as intranasal, sublingual, or subcutaneous exist but lead to more erratic absorption and response and are generally not recommended in the neurocritically ill patient. For patients with underlying TBI or post-cardiac arrest, when hemodynamics are also impaired, intravenous vasopressin infusions may be necessary to adequately slow urinary water loss [92].

The awake patient whose thirst mechanism is intact should be allowed access to water and drink to thirst. This helps guide the appropriate desmopressin dosing regimen. In the altered patient who is unable to drink, a clinical assessment of hemodynamic status to guide fluid replacement and desmopressin dosing will be needed.

Conclusion

Dysnatremias are increasingly recognized as independent risk factors of poor outcome in the NCCU. Their diagnostic workup should always include a careful assessment of volume status and laboratory markers to make a correct diagnosis. This is crucial, for instance, in the appropriate management of SIADH and SW for which treatment is opposite. Speed of onset, severity of symptoms, and extent of preexisting brain injury need to be taken into account when correcting hyponatremia and hypernatremia as rapid overcorrection can lead to osmotic demyelination and cerebral edema, respectively.

Compliance with Ethical Standards

Conflict of Interest
All authors declares no conflict of interest.

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•• Of major importance

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