Treatment of Hyponatremic Encephalopathy in the Critically Ill

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Objectives: Hyponatremic encephalopathy, symptomatic cerebral edema due to a low osmolar state, is a medical emergency and often encountered in the ICU setting. This article provides a critical appraisal and review of the literature on identification of high-risk patients and the treatment of this life-threatening disorder.

Data Sources, Study Selection, and Data Extraction: Online search of the PubMed database and manual review of articles involving risk factors for hyponatremic encephalopathy and treatment of hyponatremic encephalopathy in critical illness.

Data Synthesis: Hyponatremic encephalopathy is a frequently encountered problem in the ICU. Prompt recognition of hyponatremic encephalopathy and early treatment with hypertonic saline are critical for successful outcomes. Manifestations are varied, depending on the extent of CNS's adaptation to the hypoosmolar state. The absolute change in serum sodium alone is a poor predictor of clinical symptoms. However, certain patient specific risks factors are predictive of a poor outcome and are important to identify. Gender (premenopausal and postmenopausal females), age (prepubertal children), and the presence of hypoxia are the three main clinical risk factors and are more predictive of poor outcomes than the rate of development of hyponatremia or the absolute decrease in the serum sodium.

Conclusions: In patients with hyponatremic encephalopathy exhibiting neurologic manifestations, a bolus of 100 mL of 3% saline, given over 10 minutes, should be promptly administered. The goal of this initial bolus is to quickly treat cerebral edema. If signs persist, the bolus should be repeated in order to achieve clinical remission. However, the total change in serum sodium should not exceed 5 mEq/L in the initial 1–2 hours and 15–20 mEq/L in the first 48 hours of treatment. It has recently been demonstrated in a prospective fashion that 500 mL of 3% saline at an infusion rate of 100 mL per hour can be given safely. It is critical to recognize the early signs of cerebral edema (nausea, vomiting, and headache) and intervene with IV 3% sodium chloride as this is the time to intervene rather than waiting until more severe symptoms develop. Cerebral demyelination is a rare complication of overly rapid correction of hyponatremia. The principal risk factors for cerebral demyelination are correction of the serum sodium more than 25 mEq/L in the first 48 hours of therapy, correction past the point of 140 mEq/L, chronic liver disease, and hypoxic/anoxic episode. (*Crit Care Med* 2017; XX:00–00)

Key Words: central pontine myelinolysis; DDAVP; hypertonic saline; hyponatremia

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Hyponatremia is a frequently encountered problem in the ICU. Hyponatremic encephalopathy, which can occur in either acute or chronic hyponatremia, is defined as neurologic symptoms due to hypoosmolar-induced cerebral edema (1, 2). The presenting symptoms may range from minimal to severe. This is a medical emergency that must be recognized promptly, and treatment initiated expeditiously to avoid devastating neurologic complications, which may ultimately result in death (3). Although the chronicity of the illness (the duration of time between a normal serum sodium and the presentation to the ICU) can affect the clinical presentation and the risks of treatment-related injury due to overcorrection, the decision to treat with hypertonic saline is determined by clinical symptoms not the duration of hyponatremia or the absolute decrease in the serum sodium (1, 2). This is in recognition that chronic hyponatremia of even modest degrees can lead to poor outcomes (2). This review will focus on the treatment of hyponatremic encephalopathy in the ICU setting and not on hyponatremia without symptoms of cerebral edema.

PATHOGENESIS OF HYPONATREMIA

Hyponatremia, a serum sodium of less than 135 mEq/L, is a reflection of a systemic hypoosmolar state and develops when water intake exceeds water excretion. This typically occurs in the setting of impaired free water excretion by the kidneys or less commonly psychogenic polydipsia resulting in an excess of

total body water relative to total body sodium and potassium (**Fig. 1**). Conditions that impair free water excretion are associated with both physiologic and pathologic release of antidiuretic hormone (ADH) (4) and have been well established (5) (**Table 1**). These conditions impair the kidneys' primary defense against the development of hyponatremia, the urinary diluting capacity.

During hyponatremic states, an osmotic gradient develops between the circulation and the brain, resulting in water movement into the brain through aquaporin-4 channels located in astrocytes, one of the types of neuroglial cells (6). Astrocytes, located on the brain side of the microcirculation, help to regulate the movement of fluids and molecules across the blood brain barrier by the cells' foot processes that contact brain capillaries. This fluid movement results in cell expansion and an increase in brain volume. The resultant increase in intraparenchymal brain volume is immediately offset by the shunting of cerebrospinal fluid from the intracranial vault, which accommodates some of the volume perturbation, but this mechanism has limited capacitance (7). The main accommodation comes through energy-dependent extrusion of

Figure 1. Mechanisms for the maintenance of water balance. ADH = antidiuretic hormone.

solutes from the neuroglial cell via the Na^+/K^+ ATPase pump (8). By reducing the neuroglial cell's intracellular osmolality, water leaves the cell down the osmotic gradient resulting in an overall reduction in brain volume, a process known as "regulatory brain volume decrease" (9). Neurologic injury occurs when these mechanisms are unable to fully compensate for the increased intracranial pressure due to the cerebral edema (10). Several clinical factors have been shown to impair the neuroglial cell's adaptive responses, and these clinical factors predict poor patient outcomes (1).

CLINICAL MANIFESTATIONS

Manifestations are varied, depending on the extent of CNS's adaptation to the hypoosmolar state. The absolute change in serum sodium alone is a poor predictor of clinical symptoms (11). On a practical level, clinical presentations can be classified as acute (where the duration of hyponatremia is known to be < 48 hr). When this occurs, it is often hospital acquired (postoperative or due to inappropriate use of hypotonic fluids in other settings). Acute hyponatremia does also occur in settings such as exercise-induced hyponatremia or methylenedioxymethamphetamine-associated hyponatremia. Chronicity uncertain is the most common presentation and includes most ICU hyponatremia admissions where the time development is uncertain (diuretic related, antidepressant related, hypovolemia, syndrome of inappropriate ADH (SIADH), adrenal insufficiency, etc,). Chronic hyponatremia occurs where the duration of hyponatremia is known to be greater than 48 hours (e.g., a patient with recurrent congestive heart failure admissions and documented laboratory studies showing hyponatremia). Although the chronicity can affect the degree of symptoms (a patient who develops a serum sodium of 122 in 48 hr following surgery is far more likely to develop hyponatremic encephalopathy than a patient who develops a serum sodium of 122 3 wk after initiation of a thiazide diuretic), it is important to understand that all patients with hyponatremia,
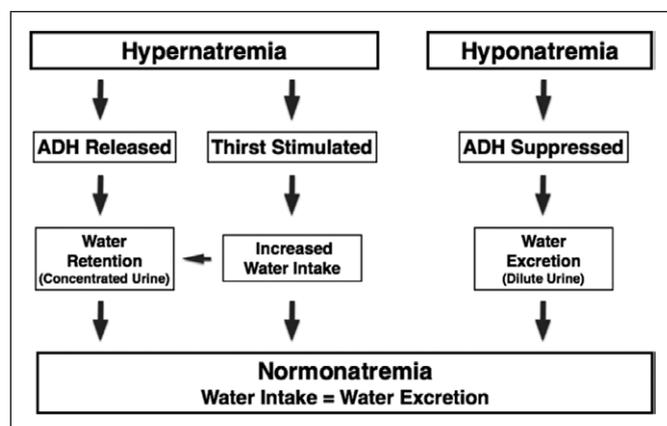
TABLE 1. Major Etiologies of Hyponatremia in the ICU

Hypovolemic Hyponatremia	Euvolemic Hyponatremia	Hypervolemic Hyponatremia
Renal losses	Postoperative state	Congestive heart failure
Diuretics (especially thiazide type)	Exercise-induced hyponatremia	Cirrhosis
Mineralocorticoid deficiency	Drugs	Acute and chronic renal failure
Renal tubular acidosis	Ecstasy (methylenedioxymethamphetamine)	
Cerebral salt wasting	Anticonvulsants	
	Polydipsia	
Extrarenal losses	Syndrome of inappropriate antidiuretic hormone secretion	
Vomiting	Hypothyroidism	
Diarrhea	Glucocorticoid deficiency	
Pancreatitis		
Burns		

regardless of the chronicity of the development of hyponatremia, can develop hyponatremic encephalopathy, especially in high-risk groups such as premenopausal and postmenopausal females and when hypoxia is present (1, 2). Early signs of cerebral edema such as nausea, vomiting, and headaches often go unrecognized (12). As intracranial pressure continues to increase, brain dysfunction, exhibited as altered mentation and seizures, occurs. If left uncorrected, hypercapnic respiratory failure, a sign of brainstem involvement with the possibility of herniation, and death may follow (1, 2, 12, 13).

Although there are many causes of hyponatremia in the ICU, there are two entities that deserve special attention, noncardiogenic pulmonary edema and hyponatremia as well as cerebral/renal salt wasting. Noncardiogenic pulmonary edema associated with the presence of cerebral edema (also known as "the Ayus-Arieff syndrome") (**Fig. 2**) could be the initial presentation of a patient with hyponatremic encephalopathy (14). The two most common causes of hyponatremia and pulmonary edema are exercise-induced hyponatremia and hyponatremia due to ingestion of the recreational drug methylenedioxymethamphetamine, commonly known as "ecstasy" (14, 15) but can be seen in any cause of hyponatremia. The main mechanism for hyponatremic encephalopathy to produce neurogenic pulmonary edema is the increase in intracranial pressure due to hyponatremia (16). The patients described in these reports

Figure 2. A depiction of the Ayus–Arieff syndrome (used with permission from Moritz et al [15]). Hyponatremia produces cytotoxic cerebral edema, which in turn leads to neurogenic pulmonary edema. Pulmonary edema leads to hypoxia, which impairs brain cell volume regulation resulting in a vicious cycle of worsening cerebral edema and pulmonary edema. This syndrome can be reversed by the prompt administration of 3% NaCl.

had normal troponin levels, normal echocardiograms, and normal pulmonary artery occlusion pressures demonstrating that the pulmonary edema seen in these cases was not due to a cardiogenic etiology (14, 16). Hyponatremia produces cerebral edema, which in turn leads to neurogenic pulmonary edema (14). Pulmonary edema then leads to hypoxia which impairs brain volume regulation (6, 17, 18), resulting in a vicious cycle of worsening cerebral edema and hypoxia. This syndrome is treated with a bolus of hypertonic saline (14).

Cerebral/renal salt wasting occurs most commonly in neurosurgical patients (19). This condition is characterized by a neurogenic natriuresis by an unknown mechanism that leads to volume depletion and secondary ADH secretion from the pituitary that results in hyponatremia. In this way, the cardinal distinguishing factor between the SIADH, where nonosmotic ADH secretion is the key pathologic feature, and cerebral salt wasting is the presence or absence of a low circulating effective arterial blood volume (**Table 2**). In the past, this differentiation was difficult as the effective arterial blood volume could not be measured directly; however, pulmonary artery occlusion pressure (20, 21) (in the absence of diastolic cardiac dysfunction) or right atrial pressure (22) (in the absence of pulmonary hypertension) could be used to estimate this. Natriuretic peptides (23) hold promise as a tool to estimate effective arterial blood volume as they are directly related to vascular blood volume and can help in determining the vascular status of patient. An additional tool in differentiating SIADH and cerebral/renal salt wasting is the fractional excretion of urate as the excretion of urate is usually reduced in patients with hypovolemia (24). In many cases, patients who have SIADH due to the cerebral trauma during neurosurgery are misclassified as having cerebral salt wasting. This distinction is important to make as the treatment of cerebral salt wasting, when hyponatremic encephalopathy is not present, is volume expanded with 0.9% saline, whereas in a patient with SIADH, 0.9% saline is futile therapy and can lead to iatrogenic fluid overload. When a patient with cerebral salt wasting is aggressively volume expanded with 0.9% saline and there is no improvement in the condition, the diagnosis of needs to be revisited. Following serum sodium, urine osmolality, and serum brain, natriuretic peptide can be helpful in assessing such patients.
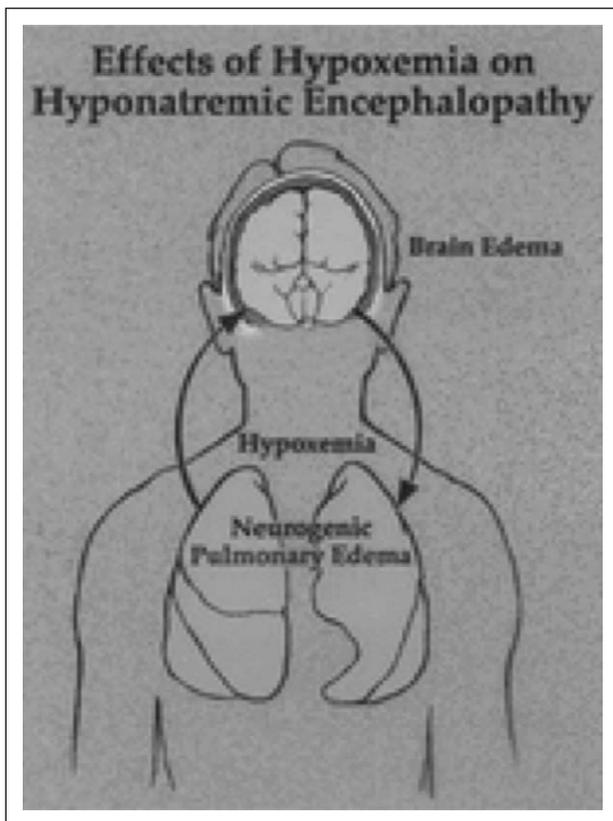
RISK FACTORS FOR HYPONATREMIC ENCEPHALOPATHY

Gender (1), age (25), and the presence of hypoxia (1, 14, 16) are the three main clinical risk factors and are more predictive of poor outcomes than the rate of development of hyponatremia or the absolute decrease in the serum sodium (13) (**Table 3**). These are equivalent risk factors with summative effects (except that in children where gender does not play a role). Children are at increased risk due to a high brain-to-cranial vault size ratio as there is less space for accommodation as brain volume increases (25). Among postsurgical patients who develop hyponatremia, females of premenopausal age are also at increased risk for development of cerebral edema (1).

TABLE 2. Comparison of Syndrome of Inappropriate Antidiuretic Hormone and Cerebral Salt Wasting

Attribute	Syndrome of Inappropriate Antidiuretic Hormone	Cerebral Salt Wasting
Osmolality		
Urine	High	High
Serum	Low	Low
Urine sodium level	> 40 mEq/L	> 40 mEq/L
Volume status	Euvolemia to mild hypervolemia	Hypovolemia
Central venous pressure	Normal to high	Low
Pulmonary artery occlusion pressure	Normal to high	Low
Brain natriuretic peptide level	Normal	High
Blood urea nitrogen/creatinine ratio	Low to normal	High
Serum uric acid level	Low	Low
Serum potassium level	Normal	Normal to high
Fractional excretion of urate		
During hyponatremic phase	High	High
Following correction of hyponatremia	Normal	High

TABLE 3. Risk Factors for Hyponatremic Encephalopathy

Risk Factors	Mechanism
Postsurgical females of premenopausal age[a] (1)	Impaired regulatory brain volume decrease[b]: Estrogens decrease the catalytic activity of astrocyte Na^+/K^+, ATPase preventing solute extrusion
Age < 16 (25)	High brain volume-to-cranial vault size ratio resulting in less space to accommodate brain volume increases
Hypoxia (1, 14, 16)	Impaired regulatory brain volume decrease: Hypoxia decreases the catalytic activity of astrocyte Na^+/K^+, ATPase preventing solute extrusion
Brain injury	Vasogenic cerebral edema Cytotoxic cerebral edema
Acute hyponatremia	Decreased time for brain adaptation

[a]When compared with postsurgical males, this subgroup is 25 times more likely to develop permanent brain damage or death (1).
[b]Regulatory brain volume decrease is the extrusion of solutes out of the neuroglia cell via the Na^+/K^+ ATPase resulting in a reduction in brain volume (6).

This increased risk of premenopausal females has been seen in several clinical scenarios associated with hyponatremia: the use of ecstasy (15, 26), use of diuretics (13), exercise (14), and use of desmopressin (DDAVP; Ferring Pharmaceuticals, Saint-Prex, Switzerland) (27). Estrogens are believed to inhibit the catalytic activity of the astrocyte's Na^+/K^+ ATPase resulting in impairment of regulatory volume decrease. This has been demonstrated in rat astrocytes treated in vitro (28). Finally, hypoxia has been shown to predict poor outcomes in patients with hyponatremic encephalopathy (1), as it also impairs the Na^+/K^+ ATPase from extruding solutes (17, 18). Hypoxia can develop in encephalopathic hyponatremic patients through two mechanisms: hypercapnic respiratory failure (16) and neurogenic pulmonary edema (14).

PREVENTION OF ICU-ACQUIRED HYPONATREMIA

Until proven otherwise, a patient in a critical care setting should be assumed to have an impairment in free water excretion. In patients with intact kidney function, ADH levels are likely to be high. In patients with renal failure, free water excretion is also impaired. Common situations where water balance is impaired include the following: cases of effective circulating volume depletion (cirrhosis, heart failure, and third spacing of fluid), gastrointestinal fluid losses, diuretic use (especially thiazides), renal failure (acute and chronic), SIADH, cortisol deficiency, and hypothyroidism (**Fig. 3**). As noted above, hypotonic IV fluids should not be used except in the setting of replacement of a water deficit (i.e., hypernatremia). Isotonic
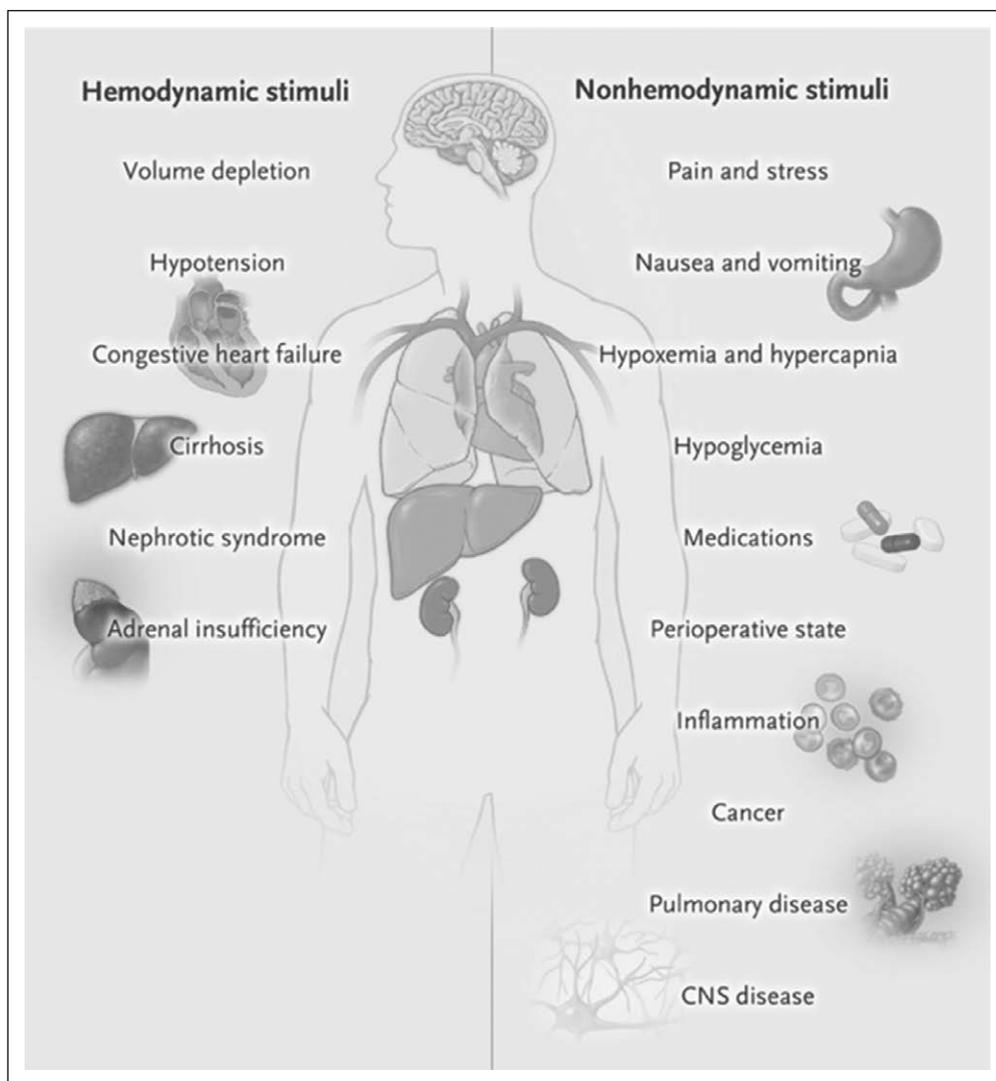
Figure 3. Nonosmotic and osmotic causes of hyponatremia in the ICU. Used with permission from Moritz and Ayus (29).

clinical settings characterized by impaired free water excretion (29) can have disastrous consequences (1). The use of hypotonic fluids is reserved for treatment of a free water deficit, such as exists in the setting of hypernatremia (29).

THE HYPERTONIC SALINE BOLUS: A SAFE AND EFFECTIVE APPROACH TO TREAT HYPONATREMIC ENCEPHALOPATHY

Hypertonic saline is the treatment of choice for hyponatremic encephalopathy (2, 11, 30). Our group has used hypertonic saline to treat over 150 patients (2, 11, 14, 25, 27, 30–33) with hyponatremic encephalopathy. We have used this in both children and adults, in patients with acute and chronic hyponatremia, in patients presenting at a medical tent or emergency department, and in patients with hospital-acquired hyponatremia. In these groups of patients, brain imaging and long-term neurologic follow-up was performed, and we have not encountered cerebral demyelination as a complication of hypertonic saline in any of these cases. Our findings of the efficacy of hypertonic saline in the treatment of hyponatremic encephalopathy have been confirmed by other investigators (34–36).

However, despite the efficacy of this therapeutic approach, we recognize that the indiscriminate use of prolonged infusions of hypertonic saline without appropriate monitoring can produce neurologic injury from an excessive correction of hyponatremia. Because of this concern, and to minimize the risk of hypertonic saline therapy, in 2005, we introduced a simple approach of using small repeated intermittent boluses of hypertonic saline (37) in order to achieve a rapid and controlled increase in serum sodium to treat hyponatremic encephalopathy, that conformed to the various opinions on the safe limits of correcting hyponatremia (38).

Our approach is to treat any patient with suspected hyponatremic encephalopathy (whether acute or chronic), with either early (nausea, vomiting, headache) or advanced symptoms (seizures, respiratory arrest), child or adult, and with a

normal saline (0.9% NaCl) containing 154 mEq/L of Na$^+$ and Cl$^-$ is the most appropriate parenteral fluid when IV fluids are indicated for the maintenance of intravascular volume in the postoperative period (29). Also, in the ICU setting, it is the most appropriate fluid choice in almost all circumstances unless replacing a water deficit and hypotonic fluids are clearly needed (29). Also, any patient receiving fluid therapy should have the serum sodium measured at least daily (29).

Hospital-acquired hyponatremic encephalopathy occurs most commonly when hypotonic fluids are administered to a patient with an impairment of free water excretion (29). A clinical setting that merits specific discussion is the postoperative state (1). Approximately 1% of patients develop a serum sodium of less than 130 mEq/L following surgery, and clinically important hyponatremia complicates 20% of these cases (1). The postoperative state commonly includes multiple stimuli for ADH release including pain, stress, nausea, vomiting, narcotic medications, and volume depletion (29). Administration of a hypotonic IV fluid in the postoperative state or in other

2 mL/kg bolus of 3% NaCl. The time course over which the hyponatremia has developed is not a determinant of who should receive therapy for suspected hyponatremic encephalopathy, this is because chronicity is not always known and hypertonic saline therapy is known to be safe, even when the duration of hyponatremia is clearly chronic (known to be > 48 hr in duration). Early symptoms (nausea, vomiting, headache, and ataxia) while they are milder in severity should still be treated with hypertonic saline as they may be a precursor to more severe manifestations (such as seizures and respiratory arrest). Even though the risk of imminent decompensation may be low in many cases (e.g., a patient with cirrhosis, ataxia, and a serum sodium of 115), given the safety of hypertonic saline when used appropriately (30) and the superiority of hypertonic saline over fluid restriction alone in management of chronic hyponatremic encephalopathy (2), we feel that the use of hypertonic saline, especially in an ICU setting, rather than fluid restriction alone is warranted. Early IV saline therapy in symptomatic patients with chronic hyponatremic encephalopathy is associated with 0% morbidity and mortality, whereas delay of therapy with IV saline until respiratory insufficiency develops is associated with 64% morbidity and mortality (either death or neurologic injury leading to permanent institutionalization) (2). We advocate for earlier intervention, rather than waiting for more catastrophic symptoms to develop prior to initiating therapy. As long as precautions regarding hypertonic saline therapy we discuss elsewhere are adhered to, concerns about osmotic demyelination syndrome should not prevent appropriate treatment of patients with chronic hyponatremic encephalopathy with hypertonic saline. The bolus could be repeated 1–2 times in sequential fashion if symptoms persisted. A single bolus would result in, at most, a 2 mEq/L acute rise in serum sodium, which could quickly reduce brain edema. In most cases, a 4–6 mEq/L acute rise in plasma sodium will begin to reverse the neurologic symptoms, and failure to show some clinical improvement following an acute elevation in serum sodium would suggest that the patient is not suffering from hyponatremic encephalopathy. The bolus approach can be given safely through a peripheral IV and can be used in a non-ICU setting (30). It would be effective regardless of the etiology of hyponatremia, serving as a volume expander in hypovolemic hyponatremia and is sufficiently hypertonic to increase the serum sodium in euvolemic hyponatremia from SIADH. It also does not require the use of complicated formulas, which have been demonstrated to be inaccurate as they assume a closed system and do not account for the renal response to therapy (39). Other therapies such as 0.9% NaCl, 1.8% NaCl, mannitol, urea, oral sodium, and vaptans cannot be recommended as first-line therapies to treat hyponatremic encephalopathy as they do not reliably increase the serum sodium or reverse the neurologic symptoms (38).

This approach has already been successfully used in critical care patients (36) and has been adopted as the standard of care by the European Societies of Nephrology, Endocrinology and Critical Care (38) and sport medicines societies (40). The goal of this initial bolus is to quickly treat severe cerebral edema. The sodium should not be corrected more than 5 mEq/L in the first 1–2 hours of treatment and not to exceed 15–20 mEq in the first 48 hours of treatment. Prompt recognition of the problem and early initiation of therapy are the most important factors associated with successful intervention
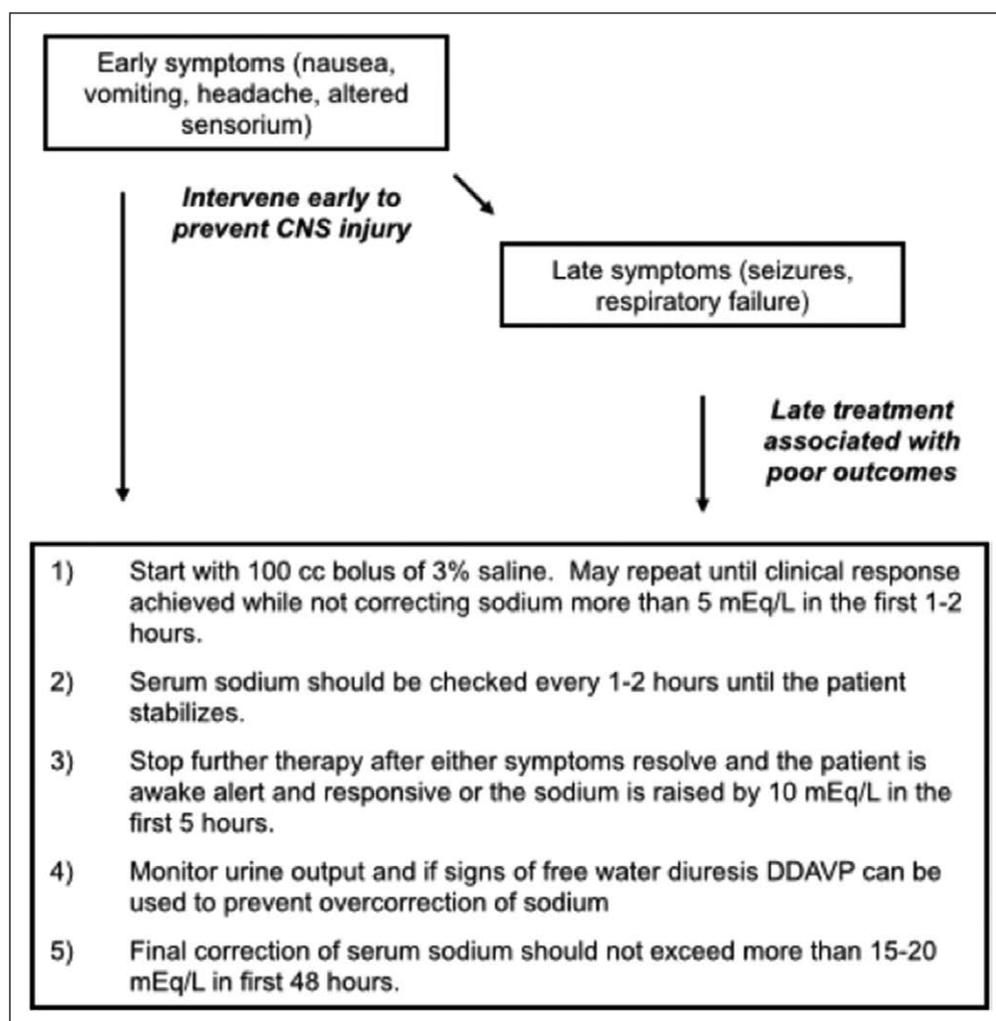

Figure 4. Treatment of hyponatremic encephalopathy. DDAVP by Ferring Pharmaceuticals, Saint-Prex, Switzerland.

and good neurologic outcomes. It is critical to recognize the early signs of cerebral edema (nausea, vomiting, and headache) and intervene with IV 3% sodium chloride as this is the time to intervene rather than waiting until more severe symptoms develop (2, 41). When therapy is delayed until after late symptoms (altered sensorium, seizure, and respiratory arrest) develop, the prognosis is much worse (41). The goals of therapy with hypertonic saline (**Fig. 4**) can be summarized as follows: 1) remove patients with severe manifestations of cerebral edema from immediate danger; 2) correct serum sodium to a mildly hyponatremic levels; and 3) maintain this level of serum sodium to allow for the brain to adapt to the change in serum osmolality.

A recent case series has demonstrated that 500 mL of 3% saline over 6 hours can be given safely (30). Any patient receiving bolus therapy of 3% saline should have the serum sodium checked every 1–2 hours until the patient has clinically stabilized. The rationale for close monitoring is that ongoing water losses cannot always be predicted. Therefore, urine output should be followed closely to assess for a water diuresis that is indicative of free water losses that can cause correction of the sodium in addition to the increase in serum sodium provided by hypertonic saline. Finally, the serum sodium should not be corrected past normonatremic levels during the first 48 hours of therapy as this is a further risk factor for the development of cerebral demyelination (11).

No head-to-head studies of continuous IV infusion of 3% saline versus bolus IV infusion have been performed, so this must appropriately temper our conclusions, but given the observation studies demonstrating the efficacy and safety of a bolus approach and the potential for overcorrection with a longer, continuous infusion, we feel that bolus IV infusion therapy is a viable and safer alternative to continuous IV infusion of 3% saline and may be the preferred approach.
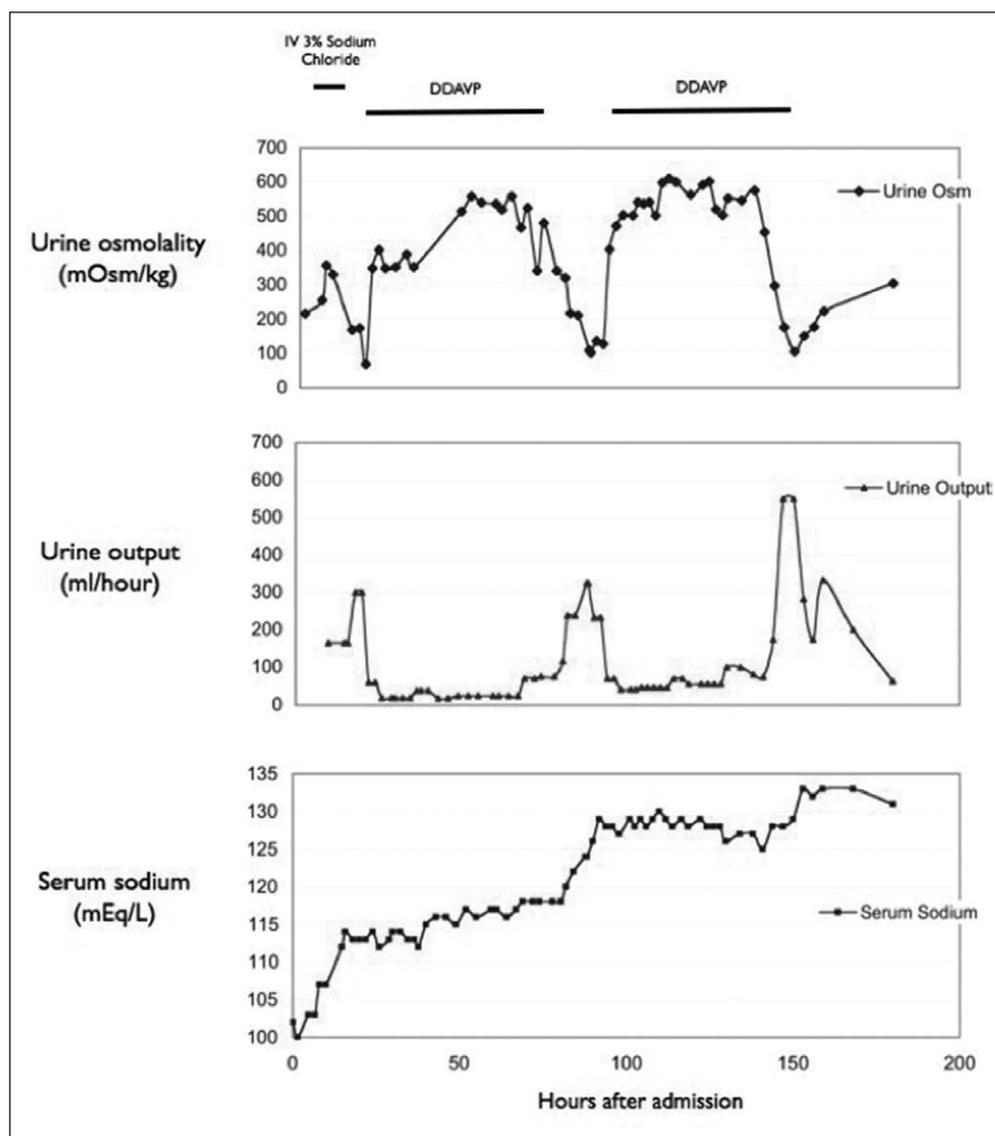

Figure 5. Clinical use of desmopressin to prevent overcorrection of severe hyponatremia in a patient thiazide-associated hyponatremia with 3% IV saline and subsequent use of (DDAVP; Ferring Pharmaceuticals, Saint-Prex, Switzerland) to therapeutically slow the rate of water diuresis and ultimately rate of sodium correction.

RISK FACTORS FOR THE DEVELOPMENT OF CEREBRAL DEMYELINATION

Cerebral demyelination is a potential complication from the overcorrection of severe and chronic hyponatremia. It is primarily seen in patients with hyponatremia of greater than 48 hours duration and a plasma sodium less than 115 mEq/L (38, 42–45). It is infrequently seen in patients with acute hyponatremia or plasma sodium values greater than 120 mEq/L (34, 35, 38, 45, 46). Although there are multiple isolated reports of cerebral demyelination occurring in patients with hyponatremia (38) when examined in large series of patients with severe hyponatremia, cerebral demyelination is extremely rare (46–48). Animal studies and clinical observations in humans have demonstrated that cerebral demyelination is a complication from an excessive magnitude of correction of hyponatremia of greater than 25 mEq/L over a 24–48 hours period (11, 49, 50). Cerebral demyelination does not appear to be related to an excessive hourly rate of correction as long as the overall magnitude is kept less than 20 mEq/L in the first

48 hours of therapy (11). The main risk for an overcorrection of hyponatremia is not from the use of hypertonic saline but rather from renal response to fluid therapy and a spontaneous free water diuresis that occur when the stimulus for arginine vasopressin release abates. The primary conditions where a brisk free water diuresis can occur are thiazide-induced hyponatremia, water intoxication, volume depletion, adrenal insufficiency following replacement therapy, and DDAVP-induced hyponatremia following DDAVP withdrawal (13, 27). Cerebral demyelination can occur with any therapy used to correct severe and chronic hyponatremia, including normal saline and V2 antagonists, if there is an excessive correction of hyponatremia (13).

There are risk factors other than hyponatremia that can place a patient at risk for developing cerebral demyelination such as severe liver disease (11), hypokalemia (44), thiazide diuretic use (13), alcoholism (11, 13), malnutrition (51), hypophosphatemia (13), and hypoxia (13). Most reported patient with cerebral demyelination have had one or more of these risk factors. Patients with these risk factors have been reported to have cerebral demyelination in the absence of hyponatremia (13). When symptoms of cerebral demyelination manifest, it is typically a delayed phenomenon, occurring days to weeks following the correction of hyponatremia (11). Patients may present with a continuum of symptoms, ranging from asymptomatic to those with extremely altered mentation, which may manifest as a pseudocoma with a locked-in stare (11). MRI of the brain, which is sensitive for the detection of demyelinating lesions, is often necessary to establish the diagnosis (11).

PREVENTION OF OVERCORRECTION OF HYPONATREMIA WITH USE OF DESMOPRESSIN (DDAVP)

Our group in 1993 (52) advanced the concept that DDAVP could be used to minimize water excretion during correction of hyponatremia in cases that involve a risk of water diuresis (caused by a drop in urine osmolality termed a "reverse urine osmolality"), for example, compulsive water drinking, cortisol deficiency, thyroid deficiency, and medication-induced hyponatremia (e.g., thiazide diuretics) (52). This concept has been validated by other groups, showing the clinical usage of this therapeutic maneuver (53–58). During the treatment of hyponatremia, the clinician needs to be vigilant to be sure that a free water diuresis does not occur. In order to prevent ongoing water losses in the urine and "autocorrection" of the serum sodium, DDAVP can be given to increase urinary concentration and reduce free water losses. However, this must be done carefully, with the patient strictly fluid restricted or kept with no enteral intake in an ICU setting. If unrestricted fluid intake occurs during DDAVP administration, significant hyponatremia can develop. An increase in urine output is the first sign that a water diuresis is ensuing, and therefore hourly urine output needs to be followed in all patients with hyponatremic encephalopathy, especially those with drug-induced hyponatremia. DDAVP administration leads to a prompt reduction in urine and increase in urine osmolality as seen in (**Fig. 5**), where a representative case is presented of a patient with alcoholism and thiazide-induced hyponatremia presents with seizures and an initial serum sodium of 103 mEq/L who developed a water diuresis following correction of her hyponatremia with IV 3% sodium chloride. Keeping the serum sodium from increasing by more than 15 mEq/L in the first 48 hours is the goal during the treatment of hyponatremic encephalopathy. Use of DDAVP during this initial period may require the patient to stay in the ICU in order to monitor intake and output strictly. After 48 hours, the DDAVP can usually be stopped and the patient observed while the sodium continues to correct. This general approach is outlined in **Figure 6**.
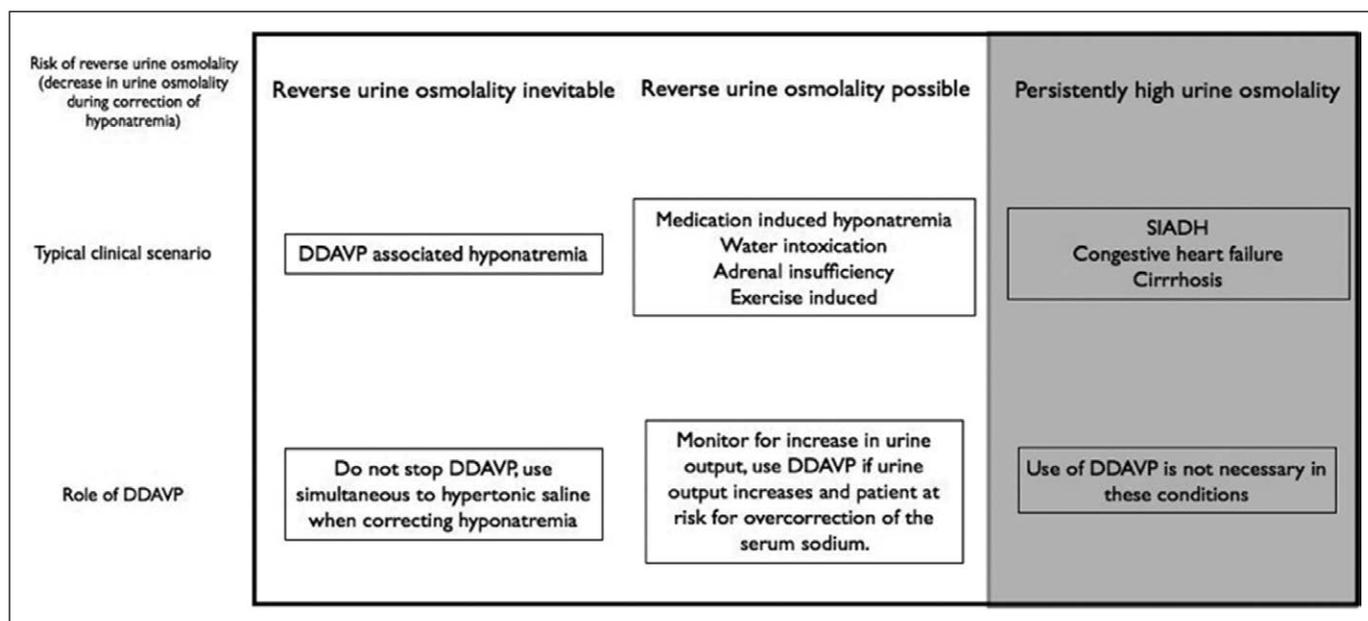

Figure 6. Use of desmopressin to prevent overcorrection of the serum sodium while treating hyponatremic encephalopathy. DDAVP by Ferring Pharmaceuticals, Saint-Prex, Switzerland. SIADH = syndrome of inappropriate antidiuretic hormone.

SUMMARY

Hyponatremia is a common clinical disorder in the ICU setting, and when it is complicated by hyponatremic encephalopathy, it is associated with poor outcomes. Prompt recognition of patients with hyponatremic encephalopathy is critical in order to provide immediate therapy. Treatment with bolus therapy of 3% IV sodium chloride is recommended when early symptoms occur rather than waiting until late symptoms develop as delay in therapy is associated with poor neurologic outcomes. We recommend patients be treated by correcting the serum sodium with hypertonic saline beginning with an IV bolus of 100 mL of 3% saline, which may be repeated if needed. The goal of therapy is to adequately treat cerebral edema while avoiding correction of the serum sodium by more than 15–20 mEq/L in the first 48 hours of therapy, thereby preventing the development of cerebral demyelination.

ACKNOWLEDGMENT

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