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Disorders of Body Water Homeostasis in Critical Illness

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Disorders of sodium and water homeostasis are among the most commonly encountered disturbances in the critical care setting, because many disease states cause defects in the complex mechanisms that control the intake and output of water and solute. Because body water is the primary determinant of extracellular fluid osmolality, disorders of body water balance can be categorized into hypoosmolar and hyperosmolar disorders depending on the presence of an excess or a deficiency of body water relative to body solute. Because the main constituent of plasma osmolality is sodium, hypoosmolar and hyperosmolar disease states are generally characterized by hyponatremia and hypernatremia, respectively. Both of these disturbances, as well as their overly rapid correction, can cause considerable morbidity and mortality [1–4]. After a brief review of normal water metabolism, this article focuses on the diagnosis and treatment of hyponatremia and hypernatremia in the critical care setting.

Overview of normal water metabolism

Whereas sodium metabolism is predominately regulated by the renin-angiotensin-aldosterone system (RAAS), water metabolism is controlled primarily by arginine vasopressin (AVP). AVP is a nine-amino acid peptide produced by the cell bodies of magnocellular neurons located in the hypothalamic supraoptic and paraventricular nuclei and secreted into the bloodstream from axon terminals located in the posterior pituitary. The primary inputs to these hypothalamic neurons are via hypothalamic osmoreceptors

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and brainstem cardiovascular centers [5]. Osmoreceptors located in the anterior hypothalamus stimulate AVP secretion in response to increased plasma osmolality and inhibit AVP secretion when decreased plasma osmolality is detected. Baroreceptors located in the carotid arteries and aortic arch also stimulate AVP secretion in response to decreases in mean arterial pressure or blood volume. AVP controls water permeability at the level of the nephron by binding to AVP V_2 receptors, causing aquaporin-2 (AQP2) water channel insertion into the luminal surface of collecting duct cells, thereby stimulating free water reabsorption and antidiuresis [6]. Chronically, AVP also increases the synthesis of AQP2 in principal cells of the collecting duct, resulting in enhanced water permeability and maximal antidiuresis [7].

Many different substances can stimulate AVP release, including acetylcholine, histamine, dopamine, prostaglandins, bradykinin, neuropeptide Y, and angiotensin II. Many others inhibit AVP release, including nitric oxide, atrial natriuretic peptide, and opioids [8–10]. Norepinephrine stimulates AVP release via α1-adrenoreceptors but also inhibits AVP release via α2-adrenoreceptors and β-adrenoreceptors [11,12]. Because AVP secretion is influenced by so many different factors, any one of which can predominate in a given clinical circumstance, dysregulated AVP secretion is often the cause of impaired water homeostasis in critical illness.

Hyponatremia

Hyponatremia is a common electrolyte abnormality that varies greatly in its clinical presentation. It has been estimated that approximately 1% of patients have acute symptomatic hyponatremia, 4% acute asymptomatic hyponatremia, 15% to 20% chronic symptomatic hyponatremia, and 75% to 80% chronic asymptomatic hyponatremia [13]. The incidence of hyponatremia (serum $[Na^+] \leq 134$ mmol/L) in the intensive care unit was prospectively found to be approximately 30% [14]. The in-hospital mortality rate for critical care patients with hyponatremia approaches 40%, and hyponatremia has been shown to be an independent predictor of mortality in the intensive care unit [15]. Hyponatremia is generally categorized based on serum tonicity as isotonic, hypotonic, or hypertonic. Although most instances of hyponatremia in critical illness are associated with hypotonicity, isotonic and hypertonic hyponatremia are also well documented and are discussed briefly first herein.

Isotonic hyponatremia

Isotonic hyponatremia is usually synonymous with so-called ''pseudohyponatremia'' and must be distinguished from true hypoosmolality. Plasma osmolality can be measured directly in the laboratory by osmometry or calculated based on the following formula:

$$\text{Posm (mOsm/kg } H_2O) = 2 \times \text{serum } [Na^+] \text{ (mmol/L)} + \text{glucose (mg/dL)}/18 + \text{BUN (mg/dL)}/2.8$$

Normal serum is typically comprised of 93% water and 7% nonaqueous factors, including lipids and proteins [16]. Although the nonaqueous components do not affect serum tonicity, in states of marked hyperproteinemia or hyperlipidemia (typically, elevated chylomicrons or triglycerides), the nonaqueous proportion of serum is relatively increased with respect to the aqueous portion, artifactually decreasing the concentration of Na^+/L of serum although the concentration of Na^+/L of serum water is unchanged. Because isotonic hyponatremia does not cause movement of water between the intracellular fluid (ICF) and extracellular fluid (ECF) compartments, it is not a meaningful cause of disturbed body fluid homeostasis in the critical care setting but must be distinguished from more pathologic disorders.

Hypertonic hyponatremia

Hypertonic hyponatremia has also been termed *translocational hyponatremia* because the presence of osmotically active particles in the plasma induces an osmotic movement of water from the ICF to the ECF, decreasing serum [Na^+] even though serum osmolality remains elevated. Solutes such as glucose, mannitol, sorbitol, or radiocontrast agents all exert this effect. The generally accepted calculation to correct serum [Na^+] for hyperglycemia is a decrease in serum [Na^+] of 1.6 mmol/L for every 100 mg/dL increase in glucose concentration; however, some investigators have found a serum [Na^+] correction factor of 2.4 mmol/L to be more accurate, especially at higher plasma glucose concentrations (eg, >400 mg/dL) [17].

Hypotonic hyponatremia

Of most relevance in the critical care setting is hypotonic hyponatremia, a condition indicative of an excess of water relative to solute in the ECF. Hypotonic hyponatremia can occur as a result of solute *depletion*, a primary decrease in total body solute (often with secondary water retention), or solute *dilution*, a primary increase in total body water (often with secondary solute depletion) (Box 1) [4]. Hypotonic or hypoosmolar hyponatremia is generally subdivided according to the clinical ECF volume status. A recent retrospective analysis found the relative distributions of the types of hypotonic hyponatremia in the intensive care setting to be 24% hypervolemic, 26% hypovolemic, and 50% euvolemic [15].

Box 1. Pathogenesis of hypoosmolar disorders

*Solute depletion (primary decreases in total body solute plus secondary water retention)**

1. Renal solute loss
   - Diuretic use
   - Solute diuresis (glucose, mannitol)
   - Salt-wasting nephropathy
   - Mineralocorticoid deficiency
2. Nonrenal solute loss
   - Gastrointestinal (diarrhea, vomiting, pancreatitis, bowel obstruction)
   - Cutaneous (sweating, burns)
   - Blood loss

*Solute dilution (primary increases in total body water plus secondary solute depletion)**

1. Impaired renal free water excretion
   - A. Increased proximal nephron reabsorption
     - Congestive heart failure
     - Cirrhosis
     - Nephrotic syndrome
     - Hypothyroidism
   - B. Impaired distal nephron dilution
     - Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
     - Glucocorticoid deficiency
2. Excess water intake
   - Primary polydipsia

* Virtually all disorders of solute depletion are accompanied by some degree of secondary retention of water by the kidneys in response to the resulting intravascular hypovolemia. This mechanism can lead to hypoosmolality even when the solute depletion occurs via hypotonic or isotonic body fluid losses. Disorders of water retention can cause hypoosmolality in the absence of any solute losses, but, often, some secondary solute losses occur in response to the resulting intravascular hypervolemia, which can further aggravate the dilutional hypoosmolality.

Hypovolemic hypoosmolar hyponatremia

Simultaneous water and sodium loss results in ECF volume depletion, with secondary AVP secretion and decreased free water excretion. Retention of water from ingested or infused fluids can then lead to the development of hyponatremia. Primary solute depletion can occur via renal or extrarenal sodium losses, each of which can have multiple etiologies.

Extrarenal solute losses

Vomiting, diarrhea, hemorrhage, and excessive sweating all cause extrarenal losses of sodium and potassium, and the fluid loss that accompanies the solute losses is a potent stimulus to AVP secretion. Hyponatremia in hypovolemic shock secondary to volume loss (from hemorrhage or gastrointestinal free water losses) or distributive shock (secondary to sepsis in which there is a relative hypovolemia from vasodilatation) is characterized by a urine sodium concentration (U_{Na}) generally less than 10 mmol/L, reflecting appropriate nephron function to maximize sodium reabsorption and to conserve body solute and ECF volume.

Renal solute losses

Diuretics, mineralocorticoid deficiency, and nephropathies are all important etiologies of renal sodium loss that can lead to the development of hypovolemic hyponatremia. In patients on diuretics, hypokalemia from kaliuresis can worsen hyponatremia by causing a net movement of sodium intracellularly. Thiazides are more commonly associated with severe hyponatremia than are loop diuretics such as furosemide [18]. Renal solute loss is characterized by high urine sodium excretion, typically $U_{Na} > 20$ mmol/L, despite the existence of degrees of volume depletion that would normally activate mechanisms causing renal sodium conservation.

Patients with mineralocorticoid deficiency from primary adrenal insufficiency, or Addison's disease, can present in the critical care setting with new onset adrenal insufficiency or following a period of inadequate steroid replacement and are typically profoundly volume depleted. Aldosterone secreted from the adrenal zona glomerulosa acts at the distal collecting duct to stimulate sodium reabsorption and hydrogen ion and potassium secretion. Conversely, aldosterone deficiency leads to excessive urinary sodium loss, intravascular volume depletion, and a decreased glomeruler filtration rate (GFR), which, in turn, stimulates baroreceptor-mediated AVP secretion and reduced water clearance with secondary water retention and hyponatremia [19].

A unique form of hyponatremia due to primary renal sodium losses sometimes seen in critically ill patients with neurologic lesions is cerebral salt wasting. This syndrome occurs following head injury or neurosurgical procedures. The initiating event is loss of sodium in the urine, which results in a decrease in intravascular volume leading to water retention and hyponatremia because of a hypovolemic stimulus to AVP secretion. Superficially, cerebral salt wasting resembles syndrome of inappropriate antidiuretic hormone secretion (SIADH); both are hyponatremic disorders often seen after head injury with relatively high urine sodium excretion rates and urine osmolality along with plasma AVP levels that are inappropriately high in relation to serum osmolality. In patients who have cerebral salt wasting, the increase in AVP is secondary to volume depletion, whereas a high AVP level is the primary etiologic event in patients with SIADH, who are euvolemic or have a modest increase in plasma volume from water retention. The relative

distribution of cerebral salt wasting and SIADH among hyponatremic neurosurgery patients is unknown, and the etiology of cerebral salt wasting has not been definitively established. Abnormal sympathetic outflow to the kidney with a pressure natriuresis as well as abnormal secretion of atrial or brain natriuretic peptide have been proposed as potential causes [20,21]. Differentiation of cerebral salt wasting from SIADH hinges upon establishing that a period of urinary sodium loss and volume depletion preceded the development of hyponatremia. Because infusion of isotonic NaCl into a euvolemic patient with SIADH results in a rapid excretion of the salt and fluid load to maintain body fluid homeostasis, a high urine sodium concentration and urine flow rate alone do not establish that cerebral salt wasting is present. The patient's vital signs, weight, and input/output records should be reviewed carefully to determine what the patient's volume status and net fluid balance were just before and during the development of hyponatremia, and current physical findings and hemodynamic measures should also be taken into account [22].

In the critical care setting, depletional hyponatremia from decreased sodium ingestion rather than increased sodium loss can occur in patients on chronic enteral feedings because many tube feed preparations are relatively low in sodium content [23]. Elderly patients are at greater risk for hypovolemic hyponatremia from a variety of causes than are younger individuals [24].

Euvolemic hypoosmolar hyponatremia

Virtually any disease state causing hypoosmolality can present with what appears to be a normal hydration status based on the usual methods of ECF volume assessment. Clinical evaluation of volume status is not sensitive, whereas laboratory measures such as normal or low blood urea nitrogen (BUN) and uric acid concentrations and an elevated U_{Na} are useful correlates of normal ECF volume [4,25]. Many different disease states can present with euvolemic hyponatremia, and the largest subgroup of patients has presented with hypoosmolar hyponatremia in multiple studies over many years [1,15,26].

Syndrome of inappropriate antidiuretic hormone secretion

SIADH is the most common cause of euvolemic hyponatremia in critical illness. It is essential to recognize that hypoosmolality does not always imply that AVP secretion is inappropriate, especially in the hypovolemic patient. Diagnostic criteria for SIADH remain as defined in 1967 by Bartter and Schwartz (Box 2) [27]. First, ECF hypoosmolality must be present, and hyponatremia secondary to pseudohyponatremia or hyperglycemia must be excluded. Second, urinary osmolality must be greater than maximally dilute urine (ie, >100 mOsm/kg H_2O); however, urine osmolality must only be inappropriate at some plasma osmolality (ie, <275 mOsm/kg H_2O) and not for all levels of plasma osmolality, as is frequently found in patients with the *reset osmostat* variant of SIADH [28]. Third, clinical euvolemia must

Box 2. Criteria for the diagnosis of syndrome of inappropriate antidiuretic hormone secretion

Essential

1. Decreased effective osmolality of the extracellular fluid (P_{osm} <275 mOsm/kg H_2O)
2. Inappropriate urinary concentration (U_{osm} >100 mOsm/kg H_2O with normal renal function) at some level of hypoosmolality
3. Clinical euvolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites)
4. Elevated urinary sodium excretion while on a normal salt and water intake
5. Absence of other potential causes of euvolemic hypoosmolality: hypothyroidism, hypocortisolism (Addison's disease or pituitary corticotropin [ACTH] insufficiency) and diuretic use

Supplemental

6. Abnormal water load test (inability to excrete at least 80% of a 20 mL/kg water load in 4 hours or failure to dilute U_{osm} to less than 100 mOsm/kg H_2O)
7. Plasma AVP level inappropriately elevated relative to plasma osmolality
8. No significant correction of plasma [Na^+] with volume expansion but improvement after fluid restriction

be present, because hypo- and hypervolemic states imply other etiologies of hyponatremia, as described elsewhere in this article. A patient with SIADH may experience hyper- or hypovolemia for other reasons, but a diagnosis of SIADH cannot be made until euvolemia is restored. An increased U_{Na} (>30 mmol/L [25]) is the fourth essential criterion, but patients with SIADH can have low U_{Na} if hypovolemia or solute depletion is present. Although increased natriuresis is primarily a manifestation of free water retention [29], there may also be co-existing true sodium depletion secondarily [30]. SIADH is a diagnosis of exclusion and can only be made in the setting of normal renal, thyroid, and adrenal function. Because as many as 20% of patients who meet these criteria for SIADH do not have elevated AVP levels [31], some have proposed renaming this entity the syndrome of inappropriate antidiuresis (SIAD) [32].

It is always important to diagnose the underlying etiology of SIADH, because successful long-term correction of hyponatremia will also require treating the underlying disorder. The most common causes of SIADH in

the critical care setting can be divided into five main categories: pulmonary disease, central nervous system disease, drug induced, tumors, and other etiologies (Box 3) [4]. Pulmonary infections common in the critical care setting, such as viral, bacterial, and tuberculous pneumonia, aspergillosis, and empyema can all cause hyponatremia, as can noninfectious pulmonary diseases such as asthma, atelectasis, pneumothorax, and acute respiratory failure. Some bacterial infections seem to be associated with a higher incidence of hyponatremia, particularly Legionella pneumonia [33,34]. Animal and human studies have demonstrated that hypoxia impairs free water diuresis via increased AVP secretion in the absence of decreased cardiac output, mean arterial pressure, or GFR [35]. Evidence suggests that hypercapnia also impairs free water excretion independent of the effect from hypoxia. In one prospective study of ventilated patients in the intensive care unit, plasma AVP levels were significantly elevated in hypercapneic patients ($PaCO_2 > 45$ mmHg) in comparison with the nonhypercapneic state [36].

Glucocorticoid deficiency

Secondary adrenal insufficiency, or hypopituitarism, can also lead to hyponatremia but via a different mechanism than primary adrenal insufficiency. Secondary adrenal insufficiency causes a solute dilution via an increase in total body water rather than the solute depletion that characterizes primary adrenal insufficiency. The glucocorticoid deficiency that defines secondary adrenal insufficiency causes impaired free water clearance through AVP-dependent and AVP-independent mechanisms [37]. Because the main regulator of aldosterone secretion is the RAAS and not ACTH secretion by the pituitary, hyponatremia is not a result of renal salt wasting from mineralocorticoid deficiency in either secondary adrenal insufficiency or relative adrenal insufficiency in septic shock. Nevertheless, glucocorticoid deficiency can result in a clinical presentation almost identical to SIADH, because there is loss of hypoosmolar inhibition of osmoreceptor-mediated AVP release resulting in persistent nonosmotic AVP secretion [38]. This effect is further exacerbated in acute glucocorticoid deficiency by concomitant nausea, hypotension, and a decreased GFR that all further decrease free water clearance [39] and is particularly more marked in elderly patients [40]. With chronic glucocorticoid deficiency, impaired free water excretion also results from AVP-independent decreased cardiac output and renal perfusion, reducing volume delivery to the distal diluting tubules of the nephron [41].

Hypothyroidism

Hyponatremia can develop in hypothyroidism and in particular myxedematous states, although the mechanism by which hypothyroidism induces hyponatremia is not entirely understood. Patients with primary hypothyroidism have impaired free water excretion, which can be reversed by thyroid hormone replacement. It is well known that hypothyroidism is associated with low cardiac output, bradycardia, decreased cardiac contractility,

Box 3. Common etiologies of syndrome of inappropriate antidiuretic hormone secretion

Tumors
Pulmonary/mediastinal (bronchogenic carcinoma, mesothelioma, thymoma)
Nonchest (duodenal carcinoma, pancreatic carcinoma, ureteral/prostate carcinoma, uterine carcinoma, nasopharyngeal carcinoma, leukemia)

Central nervous system disorders
Mass lesions (tumors, brain abscesses, subdural hematoma)
Inflammatory diseases (encephalitis, meningitis, systemic lupus, acute intermittent porphyria, multiple sclerosis)
Degenerative/demyelinative diseases (Guillan-Barré, spinal cord lesions)
Miscellaneous (subarachnoid hemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk section, transphenoidal adenomectomy, hydrocephalus)

Drug induced
Stimulated AVP release (nicotine, phenothiazines, tricyclics)
Direct renal effects or potentiation of AVP antidiuretic effects (desmopressin [DDAVP], oxytocin, prostaglandin synthesis inhibitors)
Mixed or uncertain actions (angiotensin-converting enzyme [ACE] inhibitors, carbamazepine and oxcarbazepine, chlorpropamide, clofibrate, clozapine, cyclophosphamide, 3,4-methylenedioxymethamphetamine [Ecstasy], omeprazole, serotonin reuptake inhibitors, vincristine)

Pulmonary diseases
Infections (tuberculosis, acute bacterial and viral pneumonia, aspergillosis, empyema)
Mechanical/ventilatory (acute respiratory failure, chronic obstructive pulmonary disease, positive pressure ventilation)

Other
Acquired immunodeficiency syndrome and AIDS-related complex
Prolonged strenuous exercise (marathon, triathalon, ultramarathon, hot-weather hiking)
Senile atrophy
Idiopathic

and reduced ventricular filling [42–44]. Low cardiac output stimulates baroreceptor-mediated activation of AVP secretion. It has been postulated that AVP secretion is inappropriately high in severe hypothyroidism causing free water retention [45], but recent studies have demonstrated that hyponatremia is more likely to be mediated by AVP-independent mechanisms. In a series of patients with untreated myxedema due to primary hypothyroidism, all of whom underwent hypertonic saline infusion and a subpopulation who subsequently underwent water loading, there was a significantly lower basal plasma AVP level in the study group (0.5 ± 0.1 pmol/L) when compared with normal controls (2.5 ± 0.5 pmol/L). In addition, the subsequent rise in plasma AVP levels following hypertonic saline infusion was not exaggerated in any patients and was reported to be normal or even below normal in all patients. Plasma AVP was appropriately suppressed in the hyponatremic myxedema patients who demonstrated a degree of impaired urinary dilution during water loading, providing convincing evidence that decreased free water excretion in myxedema is not due to inappropriate plasma AVP elevation [46].

Severe hypothyroidism is also associated with decreased renal function and GFR. A study of patients with severe iatrogenic hypothyroidism demonstrated that approximately 90% had a significantly greater creatinine value in the hypothyroid as compared with the prior euthyroid state. Moreover, once thyroid hormone replacement was given and thyroid function normalized, creatinine values returned to their baseline euthyroid levels before the iatrogenically induced hypothyroid state [47]. Based on this combined evidence, the major cause of impaired water excretion in hypothyroidism appears to be an alteration in renal perfusion and GFR secondary to systemic effects of thyroid hormone deficiency on cardiac output and peripheral vascular resistance [48–50].

Hypervolemic hypoosmolar hyponatremia

In hypervolemic hyponatremia, there is an excess in total body water and total body sodium, resulting in clinically evident edema or ascites; however, in many cases, the increase in total body water is out of proportion to that of total body sodium, causing hyponatremia. Congestive heart failure, cirrhosis, and nephrotic syndrome all share this common pathophysiology, although the specific mechanisms vary among these different disease states.

Congestive heart failure

Although clearly a condition of total body ECF overload, the decreased cardiac output in congestive heart failure causes a perceived intra-arteriolar volume depletion, best described as a decrease in the effective arterial blood volume at the level of the carotid artery and the renal afferent arteriole baroreceptors [51,52]. Decreased renal perfusion activates the RAAS and the sympathetic nervous system, resulting in increased sodium reabsorption

and secondary free water reabsorption [53]. Decreased renal perfusion and subsequent increased baroreceptor firing activate non-osmotic AVP secretion, resulting in increased free water reabsorption. The goal of these physiologic mechanisms is to restore normal renal perfusion in a perceived state of intra-arteriolar volume depletion, but the net effect is to further exacerbate hypervolemia and progressive hyponatremia in patients with congestive heart failure.

In a study of over 200 patients with severe congestive heart failure, those who were also hyponatremic were found to have a shorter median survival (164 versus 373 days). These patients were found to have elevated plasma renin activity, and there was a significant mortality benefit to treating this subgroup of patients with ACE inhibitors [54]. In addition, hyponatremia during the early phase of acute myocardial infarction has been found to predict long-term mortality independently of left ventricular ejection fraction and other accepted predictors of cardiac outcomes [55].

Cirrhosis

Once ascites develops as a sequelae of chronic liver disease, approximately 30% of affected patients will manifest hyponatremia (serum $[Na^+] < 130$ mmol/L) [56]. Similar to the findings in congestive heart failure, there is impaired free water excretion in cirrhosis owing to non-osmotic release of AVP [57], but, in contrast to congestive heart failure, cirrhosis is characterized by a high cardiac output. Gastrointestinal endotoxin, which is less efficiently cleared due to portal-systemic shunting, stimulates nitric oxide production and vasodilatation [58]. Arterial dilatation, particularly in the splanchnic vasculature, leads to arterial underfilling and non-osmotic secretion of AVP [51,52]. Following disease progression with splanchnic vasodilatation, decreased mean arterial pressure and reduced renal perfusion can lead to the hepatorenal syndrome [59]. The increase in AVP secretion and water retention is proportional to the severity of cirrhosis, such that the extent of hyponatremia reflects hepatic disease progression with a serum $[Na^+]$ less than 125 mmol/L, often indicative of end-stage disease [60]. In addition, the diuretic therapy that is commonly used to treat ascites often worsens hyponatremia by decreasing intravascular volume and renal perfusion, which increase AVP levels and further compromises the kidney's ability to excrete free water [61].

Advanced renal failure

Patients with mild-to-moderate renal dysfunction are generally able to excrete sufficient free water to maintain a normal serum $[Na^+]$, whereas patients who have end-stage renal disease have impaired urinary dilution and free water excretion such that the minimum urine osmolality increases to 200 to 250 mOsm/kg H_2O, even though AVP secretion is appropriately suppressed. As a result, patients with advanced renal disease typically manifest hyponatremia owing to abnormal water retention.

Treatment of hyponatremia

The symptom severity of hyponatremia depends in large part upon the rapidity of the decrease in serum [Na^+]. Most patients are not symptomatic until the serum [Na^+] decreases to less than 125 mmol/L [62]. Symptoms are predominantly neurologic, including nausea, vomiting, headache, fatigue, irritability, and disorientation. Severe hyponatremia can progress to seizures, brainstem herniation, and death. The initial evaluation of patients in the critical care setting with hyponatremia includes a thorough history and physical examination, with particularly careful evaluation of ECF volume status including an assessment of orthostatic blood pressure and pulse. Initial laboratory evaluation should include serum electrolytes, glucose, an evaluation of renal function with BUN, creatinine, and uric acid, serum osmolality, and urine osmolality and sodium. Treatment of hyponatremia must strike a balance between the risks of the hyponatremia and the risks of correction. The magnitude of these risks depends on the degree of brain volume regulation that has transpired as a result of intracranial fluid and solute shifts [37]. The treatment of some hyponatremia-associated disease states involves treating the underlying etiology, such as steroids for adrenal insufficiency and thyroid hormone for hypothyroidism. In most cases, the appropriate treatment of hyponatremia relies on the identification of the underlying ECF volume status, the acuity with which the hyponatremia developed, and the severity of neurologic symptoms present (Fig. 1) [4].

Severe acute symptomatic hyponatremia

Acute hyponatremia (defined as $<$48 hours duration) with very low sodium values ($<$110–115 mmol/L) with seizures or coma is a medical emergency. The risk for neurologic complications is high, because cerebral edema can evolve quickly as a result of osmotic movement of water into the brain. In patients with severe acute hyponatremia, hypertonic (3%) NaCl should be infused at a rate to increase serum [Na^+] approximately 1 to 2 mmol/L/h until a less hyponatremic serum [Na^+] (ie, 125–130 mmol/L) has been achieved. In comatose or seizing patients, a faster rate of sodium correction of 3–5 mmol/L/h for a short period of time (ie, 1–2 hours) may be warranted to avoid imminent brainstem herniation [63].

In hypovolemic states, including the majority of patients with a U_{Na} less than 30 mmol/L, fluid resuscitation with isotonic NaCl with or without potassium is appropriate with a goal serum [Na^+] increase of 0.5 mmol/L/h. Accumulated evidence in experimental animals and humans confirms that a slower rate of serum [Na^+] correction minimizes the risk for central pontine myelinolysis [64]. The serum [Na^+] should be measured every 2 to 4 hours during acute corrections of hyponatremia to ensure that the increase in serum [Na^+] is proceeding at the desired rate. Young premenopausal women appear to be at greater risk for neurologic sequelae from hyponatremia, with 75% of cases of brain damage occurring in this subpopulation in some studies [65].

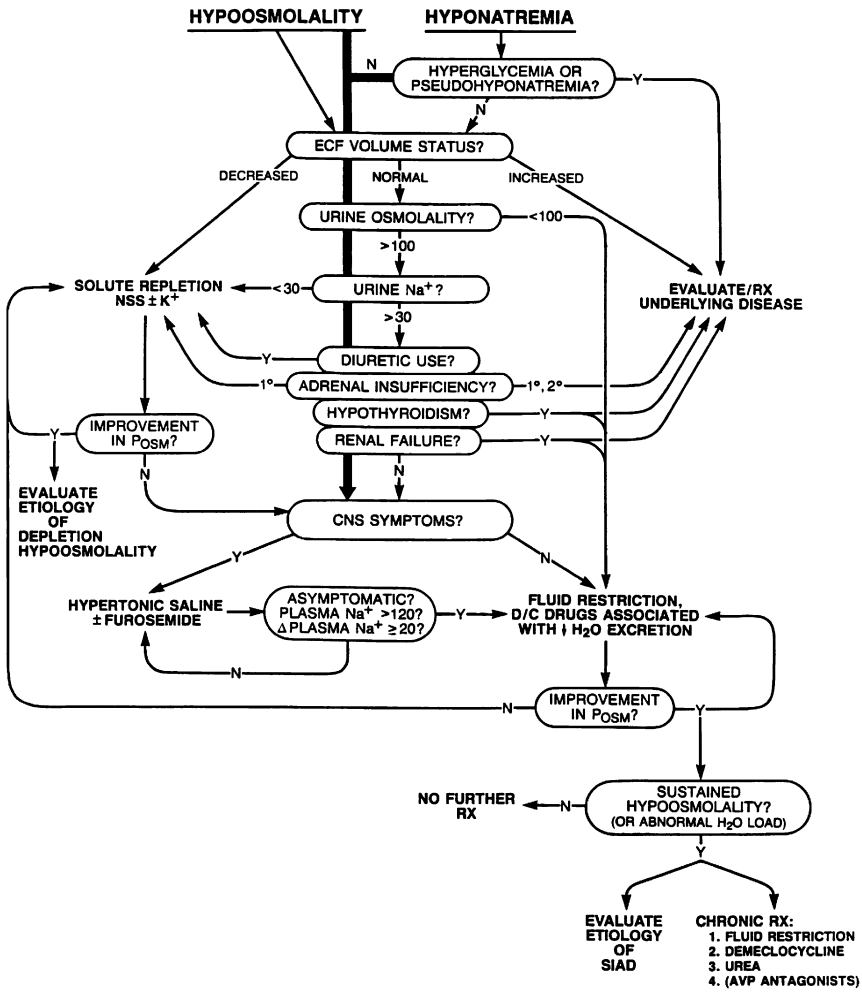

Fig. 1. Schematic summary of the evaluation of hypoosmolar patients. The dark arrow in the center emphasizes that the presence of central nervous system dysfunction due to hyponatremia should always be assessed immediately so that appropriate therapy can be started as soon as possible in symptomatic patients while the outlined diagnostic evaluation is proceeding. d/c, discontinue; ECF, extracellular fluid volume; N, no; NSS, normal (isotonic) saline; P_{osm}, plasma osmolality; Rx, treat; SIADH, syndrome of inappropriate antidiuretic hormone secretion; Y, yes; 1°, primary; 2°, secondary. The numbers referring to osmolality are in mOsm/kg H_2O; the numbers referring to Na^+ concentration are in mmol/L. (*Adapted from* Verbalis JG. SIADH and other hypoosmolar disorders. In: Schrier RW, editor. Diseases of the kidney and urinary tract. 7th edition. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2534; with permission.)

Treatment of hyponatremia in hypervolemic states includes free water restriction, diuresis with loop diuretics, and ACE inhibitors. Current clinical trials are underway investigating the use of AVP V_2 receptor antagonists for the treatment of euvolemic and hypervolemic hyponatremia.

Severe chronic symptomatic hyponatremia

In SIADH, fluid restriction is the mainstay of serum [Na^+] correction, with the goal of maintaining fluid intake 500 mL/d below urine output; however, this degree of fluid restriction is difficult to maintain in an intensive care setting where obligate fluid intakes for various therapies and parenteral nutrition often exceed this level. Furthermore, fluid restriction is not recommended to correct serum [Na^+] in hyponatremic patients with subarachnoid hemorrhage, because this patient subgroup has an increased risk for cerebral infarction that has been shown to be worsened by fluid restriction and lowered blood pressure [66].

Other current therapies for chronic hyponatremia include demeclocycline (600–1200 mg/d), furosemide (20–40 mg/d), NaCl tablets (3–18 g/d), and urea (30 g/d). Although these therapies are effective in some cases, in general they are suboptimal, and some patients, especially those with edema-forming states such as congestive heart failure and cirrhosis, are unable to tolerate the solute loads associated with many of these treatments. AVP receptor antagonists are a novel therapeutic class shown to be effective at preventing AVP-induced AQP2 membrane insertion in the renal collecting duct, causing the excretion of solute-free water, which has been termed *aquaresis* [67]. There are currently four nonpeptide agents in various stages of clinical trials, and the US Food and Drug Administration recently approved the use of conivaptan, the only combined AVP V1aR and V2R antagonist, for the treatment of euvolemic hyponatremia. Conivaptan is given as a 20-mg intravenous loading dose over 30 minutes followed by 20 to 40 mg as a continuous infusion over 24 hours for maximum of 4 days. Multiple studies have demonstrated that AVP V_2R receptor antagonists increase serum [Na^+] by inducing an aquaresis at a dose-dependent rate in patients with euvolemic and hypervolemic hyponatremia [68,69]. Clinical trials have documented that these agents are generally well tolerated and show great promise for the treatment of euvolemic and hypervolemic hyponatremia [68,69].

Hypernatremia

Similar to hyponatremia, hypernatremia can be induced by several illnesses in the critical care setting. Hypernatremia is generally categorized according to the causal factors involved: hypervolemic, hypodipsic, and increased free water losses (Box 4) [4].

Box 4. Pathogenesis of hyperosmolar disorders

Water depletion (decreases in total body water in excess of body solute)

1. Insufficient water intake
   - Unavailability of water
   - Hypodipsia (osmoreceptor dysfunction, age)
   - Neurologic deficits (cognitive dysfunction, motor impairments)
2. Hypotonic fluid loss*
   - A. Renal: diabetes insipidus
     - Insufficient AVP secretion (central diabetes insipidus, osmoreceptor dysfunction)
     - Insufficient AVP effect (nephrogenic diabetes insipidus)
   - B. Renal: other fluid loss
     - Osmotic diuresis (hyperglycemia, mannitol)
     - Diuretic drugs (furosemide, ethacrynic acid, thiazides)
     - Postobstructive diuresis
     - Diuretic phase of acute tubular necrosis
   - C. Nonrenal fluid loss
     - Gastrointestinal (vomiting, diarrhea, nasogastric suction)
     - Cutaneous (sweating, burns)
     - Pulmonary (hyperventilation)
     - Peritoneal dialysis

Solute excess (increases in total body solute in excess of body water)

1. Sodium
   - Excess [Na^+] administration (NaCl, $NaHCO_3$)
   - Sea water drowning
2. Other
   - Hyperalimentation (intravenous, parenteral)

* Most hypotonic fluid losses will not produce hyperosmolality unless insufficient free water is ingested or infused to replace the ongoing losses; therefore, these disorders also usually involve some component of insufficient water intake.

Hypervolemic hypernatremia

Hypervolemic hypernatremia can result from the infusion of hypertonic fluids (ie, $NaHCO_3$ or total parenteral nutrition) or from enteral feedings with inadequate free water administration.

Hypodipsic hypernatremia

Decreased water intake, or hypodipsia, probably represents the leading cause of hyperosmolality encountered in intensive care settings. This etiology is particularly prevalent among the elderly [70] or patients who have altered mental status who do not respond appropriately to physiologic stimuli that signal increased thirst.

Hypernatremia from increased water losses

A variety of diseases can cause increased free water losses in the critical care setting, including gastrointestinal water losses, intrinsic renal disease, hypercalcemia, hypokalemia, and solute diuresis, but the most common cause is hyperglycemia and glucosuria. Although these etiologies represent the most frequent causes of hypernatremia with critical illnesses, they must be differentiated from diabetes insipidus, which represents the quintessential clinical cause of hypernatremia. Generally, a urine osmolality less than 800 mOsm/kg H_2O in the setting of elevated serum osmolality is indicative of a renal concentrating defect. In the absence of glucosuria or other causes of osmotic diuresis, this generally reflects the presence of diabetes insipidus [4]. Diabetes insipidus is generally subdivided into central and nephrogenic disease.

Central diabetes insipidus

Central diabetes insipidus is caused by a deficiency of AVP secretion from the posterior pituitary but does not become fully manifest until more than 85% of the magnocellular AVP-secreting neurons are damaged [71]. Central diabetes insipidus is rare, with a prevalence of 1:25,000. Most cases (40% to 50%) are secondary to a hypothalamic lesion, such as a tumor, or infiltrative diseases such as sarcoidosis and histiocytosis. Approximately 20% to 30% of central diabetes insipidus is categorized as idiopathic, but most of these patients most likely have underlying autoimmune disease. Lymphocytic infundibuloneurohypophysitis is the foremost cause of spontaneous diabetes insipidus without prior head trauma or neurosurgery, potentially accounting for as many as 50% of all cases [72,73]. A small fraction of cases (5%) are genetic, often with a delayed onset. Sellar lesions and pituitary adenomas are not a common cause of diabetes insipidus, because, over time, the secretion of AVP from magnocellular neurons can shift to regions higher in the hypothalamus [5]. Because these lesions are typically slow growing, if a sellar lesion is detected in the setting of new-onset diabetes insipidus, this suggests the presence of a rapidly enlarging sellar mass such as metastatic disease. The absence of the posterior pituitary bright spot on saggital views of precontrast MR imaging can be useful to verify the presence of central diabetes insipidus with two important caveats: (1) there is an age-associated loss of the posterior pituitary bright spot in the absence of diabetes insipidus, and (2) the posterior pituitary bright spot may still be apparent in

a patient with central diabetes insipidus secondary to the persistence of oxytocin, which is also stored in the posterior pituitary [5].

Nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus is caused by end-organ resistance of the kidney to the antidiuretic effects of AVP. Whereas familial or hereditary nephrogenic diabetes insipidus is secondary to mutations of the AVP V_2 receptor or the AQP2 water channel, acquired nephrogenic diabetes insipidus is caused by hypercalcemia (serum $[Ca^{++}] > 13$ mg/dL), hypokalemia (serum $[K^+] < 2.5$ mmol/L), or medications such as lithium and demeclocycline. A plasma AVP level is useful to distinguish central diabetes insipidus from nephrogenic diabetes insipidus; however, to differentiate definitively nephrogenic diabetes insipidus from central diabetes insipidus and from normal individuals with primary polydipsia, performance of a water deprivation test is often necessary (Box 5) [4].

Treatment of hypernatremia

Treatment goals of hypernatremia include correcting the established water deficit and reducing ongoing excessive urine water losses. Patients in the intensive care setting are typically unable to drink in response to thirst, and progressive hypertonicity from untreated diabetes insipidus can be associated with grave consequences unless appropriately treated. The following formula is used to estimate the pre-existing water defecit [74]:

$$\text{Water deficit} = 0.6 \times \text{premorbid weight} \times \left[1 - 140/\left(\text{serum } \left[Na^+\right] \text{ mmol/L}\right)\right]$$

This formula assumes that total body water is 60% of body weight, that no body solute is lost as hypertonicity developed, and that the premorbid serum $[Na^+]$ is 140 mmol/L, but the formula does not take ongoing water losses into account. The serum $[Na^+]$ should be lowered to approximately 330 mOsm/kg H_2O within the first 24 hours of correction to reduce the risk of exposure to the central nervous system of ongoing hypertonicity.

The treatment of central diabetes insipidus with DDAVP is an effective means of improving polyuria and hypernatremia. Initial doses in the acute setting are 1 to 2 μg (intravenous, intramuscular, or subcutaneous). If hypernatremia is present, free water should also be given in an effort to correct serum sodium, with 5% dextrose in water as the preferred intravenous replacement fluid. DDAVP is preferred over AVP, because the former has a longer duration of action, avoids the vasopressor effects of AVP at V_{1a} receptors, and is available in intranasal and oral preparations. Although some cases of nephrogenic diabetes insipidus respond to large doses of DDAVP, traditionally, nephrogenic diabetes insipidus is treated with sodium restriction and thiazide diuretics (any drug in this class may be used with equal

Box 5. Water deprivation test

Procedure

Initiation of the deprivation period depends on the severity of the diabetes insipidus. In routine cases, the patient should be given nothing by mouth after dinner. In cases with more severe polyuria and polydipsia, this may be too long a period without fluids, and the water deprivation should be begun early in the morning of the test (eg, 6 AM).

The test should be stopped when body weight decreases by 3%, the patient has orthostatic blood pressure changes, the urine osmolality reaches a plateau (ie, less than 10% change over three consecutive measurements), or the serum sodium is greater than 145 mmol/L.

Obtain a plasma AVP level at the end of the test when the plasma osmolality is elevated, preferably above 300 mOsm/kg H_2O.

If the serum sodium concentration is less than 146 mmol/L or the plasma osmolality is less than 300 mOsm/kg H_2O, infuse hypertonic saline (3% NaCl at a rate of 0.1 mL/kg/min for 1–2 h) to reach these endpoints.

Administer AVP (5 U) or DDAVP (1 μg) subcutaneously and continue following urine osmolality and volume for an additional 2 hours.

Interpretation

An unequivocal urine concentration after AVP/DDAVP (>50% increase) indicates neurogenic diabetes insipidus, and an unequivocal absence of urine concentration (<10%) strongly suggests nephrogenic diabetes insipidus or primary polydipsia.

Differentiating between nephrogenic diabetes insipidus and primary polydipsia as well as for cases in which the increase in urine osmolality after AVP administration is more equivocal (eg, 10% to 50%) is best done using the plasma AVP levels obtained at the end of the dehydration period or hypertonic saline infusion and the relation between plasma AVP levels and urine osmolality under basal conditions.

potential for benefit), which block sodium absorption and act to decrease renal diluting capacity and free water clearance. Prostaglandins increase renal blood flow and decrease medullary solute concentration, resulting in a small decrease in the interstitial gradient for water reabsorption. Drugs such as prostaglandin synthase inhibitors promote water reabsorption and

impair urinary dilution, reducing free water clearance and urine output. These agents are helpful as adjunctive therapies in the treatment of nephrogenic diabetes insipidus.

Summary

Disorders of sodium and water metabolism are commonly encountered in the intensive care setting predominantly owing to the large number of varied disease states that can disrupt the balanced mechanisms that control the intake and output of water and solute. Disorders of body water homeostasis can be divided into hypoosmolar disorders, in which there is an excess of body water relative to body solute, and hyperosmolar disorders, in which there is a deficit of body water relative to body solute. Prompt identification and appropriate treatment of these disturbances are important to prevent the increased morbidity and mortality that accompany disorders of body fluid homeostasis in patients in critical care settings.

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