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Acute and chronic hyponatremia: A narrative review

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Abstract

Hyponatremia is an important electrolyte abnormality with the potential for significant morbidity and mortality. Catastrophic complications can occur from severe acute hyponatremia and from inappropriate management of acute and chronic hyponatremia. It is essential to define the hypotonic state associated with hyponatremia in order to plan therapy. Understanding cerebral defence mechanisms to hyponatremia are key factors to its manifestations and classification and subsequently to its management. Hypotonic hyponatremia is differentiated on the basis of urine osmolality, urine electrolytes and volume status and its treatment is decided based on duration and central nervous system symptoms. Proper knowledge of sodium and water homeostasis is essential in individualizing therapeutic plans and avoiding iatrogenic complications while managing this disorder. *[J Assoc Clin Endocrinol Diabetol Bangladesh, July 2023; 2 (2): 58-65]*

Keywords: Hyponatremia, cerebral edema, osmotic demyelination syndrome, vasopressin, syndrome of inappropriate ADH secretion

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Introduction

Overall body fluid concentration is regulated within a narrow range by the concerted action of the hypothalamic-pituitary axis to influence water intake through thirst and water excretion via the effect of vasopressin, or antidiuretic hormone (ADH), on renal collecting duct water permeability. In most cases, it is the result of impaired free water excretion due to the inability to suppress ADH. It can also result from polydipsia when water intake overwhelms the maximum renal diluting capacity. In this review, we are discussing the role of neuronal adaptive responses to the hypotonic state that accompanies hypoosmolar hyponatremia focusing on the role played by the organic osmolytes. We are also reviewing the pathogenesis and manifestations of hyponatremia as well as treatment options and guidelines developed by professional organizations, and highlighting recent developments. While managing patients with hyponatremia, it is very important to keep in mind their risks for complications from the acute state as well as risks of demyelination in the chronic state. This should aid in individualizing treatment plans and avoid iatrogenic complications.

Diagnostically, the initial step is to differentiate hypotonic from non-hypotonic hyponatremia. Hypotonic hyponatremia is further differentiated on the basis of urine osmolality, urine sodium level, and volume status.[1] Recently identified parameters, including fractional uric acid excretion and plasma copeptin concentration, may further improve the diagnostic approach. The treatment for hyponatremia is chosen on the basis of duration and symptoms. For acute or severely symptomatic hyponatremia, guidelines adopted the approach of giving a bolus of hypertonic saline. Although fluid restriction remains the first-line treatment for most forms of chronic hyponatremia, therapy to increase renal free water excretion is often necessary. Vasopressin receptor antagonists, urea, and loop diuretics serve this purpose but received different recommendations in different guidelines.[2]

Definition of hyponatremia

Hyponatremia is defined as a serum sodium concentration <135 mmol/L and represents an excess of water in the extracellular compartment relative to the amount of sodium.[3]

Classification

Pseudohyponatremia is a low sodium level (falsely low) due to hyperproteinaemia, hyperlipidemia, or hyperglycemia. True hyponatremia can be classified in different ways:

1. Based on fluid status: hypovolemic (commonly due to fluid loss), hypervolemic (commonly due to fluid retention from heart failure, cirrhosis, or renal failure), and euvolemic (most often because of the syndrome of inappropriate secretion of ADH).
2. Based on duration: acute <48 hours and chronic >48 hours; and
3. Based on severity: mild (130-134 mmol/L), moderate (125-129 mmol/L) and severe (<125 mmol/L).[3]

Etiology of true hyponatremia

1. Hypovolemic (a) (urinary Na>20 mmol/L) Diuretics, salt-losing nephropathy, mineralocorticoid insufficiency, cerebral salt wasting (b) (urinary Na<20 mmol/L), gastrointestinal and third space loss
2. Euvolemic (a) (urinary Na>20 mmol/L) syndrome of inappropriate ADH secretion (SIADH), hypothyroidism, glucocorticoid deficiency (b) (urinary Na<20 mmol/L) primary polydipsia, strenuous exercise
3. Hypervolemic (a) (urinary Na>20 mmol/L) congestive heart failure, cirrhosis, nephroticsyndrome (b) (urinary Na<20 mmol/L) renal failure

Epidemiology

In hospitals, especially in intensive care units, hyponatremia is present in 15–30% of patients.[4]

Pathogenesis of hyponatremia

The plasma osmolality is one of the main factors that contribute to water regulation as it must remain constant (between 280-295 mOsm/kg) and equal to the intracellular osmolality. If low sodium concentration in the extracellular fluid, water will freely move intracellularly to maintain osmotic equilibrium, resulting in cellular swelling.

Hyponatremia results from the inability of the kidney to excrete a water load or excess water intake. Water intake depends upon the thirst mechanism. Thirst is stimulated by an increase in osmolality. Thirst is sensed by osmoreceptors located in the hypothalamus and leads to the release of ADH from the posterior pituitary. ADH acts on the V2 receptors located at the basolateral aspect of the collecting duct cells and leads to increased aquaporin expression on the luminal aspect of the collecting duct cells which increases water absorption and abolishes thirst. In certain states, ADH can be released inappropriately or ectopically, meaning that ADH is released without an osmotic or hemodynamic stimulus. When ADH is suppressed, water is excreted through the kidney.[3]

Hyponatremia results from persistent ADH stimulation, as seen in the following situations:

- In volume depletion state: True volume depletion and in edematous patients with heart failure or cirrhosis in whom tissue perfusion is reduced because of low cardiac output
- Abnormal ADH secretion e.g. SIADH

Symptoms

Patients with acute hyponatremia develop neurologic symptoms resulting from cerebral edema induced by water movement into the brain. These may include seizures, impaired mental status or coma and death. Chronic hyponatremia is more common and may be asymptomatic. Mild hyponatremia is characterized by gastrointestinal tract symptoms of nausea, vomiting, and loss of appetite. Hyponatremia in the elderly may

Table-I: Diagnostic criteria of SIADH

Schwartz diagnostic criteria of SIADH[2]
• Decreased measured serum osmolality (<275 mOsm/ kg of H2O) (normal 280-295)
• Clinical euvolemia
• Urinary osmolality >100 mOsm/kg of H2O (normal 100-1200)
• Urinary Na >40 mmol/L (20 mEq/L in a spot urine sample and 40 to 220 mEq/day)
• Normal thyroid, adrenal and renal functions exclude diuretics and hypokalemia
• Supportive diagnostic criteria:
o Blood urea nitrogen < 10 mg/dl (5 to 20 mg/dl, or 1.8 to 7.1 mmol urea per liter)
o Serum uric acid < 4 mg/dl (normal 3.5 and 7.2 mg/dL)
o Fractional sodium excretion > 1%
o Fractional urea excretion >55%
o Failure to improve or worsening of hyponatremia of 0.9% saline infusion
o Improvement of hyponatremia with fluid restriction

manifest with frequent falls and gait disturbances.[5]

SIADH

The commonest cause of euvolemic hyponatremia is SIADH. The SIADH involves the continued secretion or action of ADH or arginine vasopressin (AVP) despite normal or increased plasma volume, causing more water retention from distal convoluted tubule that leads to hyponatremia with concomitant hypo-osmolality and high urine osmolality which are the hallmark of SIADH.[6]

The criteria, necessary for a diagnosis of SIADH were defined by Bartter and Schwartz in 1967.[7] The essential and supporting diagnostic criteria are shown in table-I. The final criterion emphasizes that SIADH remains a diagnosis of exclusion and the absence of other potential causes of hypo-osmolality must always be verified.

Etiology of SIADH

CNS disorders: meningitis, stroke, brain abscess

Pulmonary: pneumonia, TB, lung abscess

Endocrine: hypothyroidism, adrenal insufficiency, hypopituitarism

Neoplastic: pancreatic or lung cancer

Drugs: antidepressant, antiepileptic, anticancer, antibiotics (azithromycin), vasopressin, desmopressin, opiates, NSAIDS

Organic osmolytes and defence against brain swelling

The major chemical classes of brain organic osmoles are methylamines and amino acids such as taurine, glutamine and glutamate and polyols such as sorbitol.[8] In the mammalian brain, in acute hyponatremia the first defence against brain swelling is believed to involve a hydrostatic shift of fluid from the brain to cerebrospinal fluid (CSF) and ultimately to the systemic circulation.[9] The second defence involves the active depletion of ions within brain cells, namely sodium, potassium, and chloride. The third defence is the depletion of organic osmolytes.[10] In contrast, the slow development of hyponatremia, even to very severe degrees, is not complicated by significant brain swelling. In humans, the region of the brain at greatest risk appears to be the pons.[11] Re-adaptation means the reversal of the previous process (reaccumulation) to maintain equilibrium and requires a longer time. Rapid correction before this time leads to osmotic demyelination syndrome (ODS).

Brain injury with acute hyponatremia

Hypotonic hyponatremia primarily presents with symptoms of CNS dysfunction. The severity of these symptoms depends on the etiology, the degree and the rapidity of hyponatremia. These symptoms are more pronounced and can be life-threatening when the drop in serum sodium concentration is large, <120 mmol/l and within a few hours.[12] As part of the adaptive response of the brain to the hypoosmolar state that is associated with hyponatremia, water will move into the brain tissue, along the osmotic gradient, through the aquaporin-4 channels expressed on the foot processes of the astrocytes, in an attempt to limit osmotic stress injury to the neurons. This will result in swelling of the brain cells (ballooning) and brain edema. Astrocytes utilize energy-dependent mechanisms that require the Na^+ and K^+ ATPase system to expel K^+ and Cl^-, while organic osmolytes like glutamate, glycine, taurine, creatine, myoinositol, and Gamma-aminobutyric acid (GABA) are translocated through leak-pathways, hence decreasing volume and edema.[13]

Brain injury with chronic hyponatremia

In chronic hyponatremia (>48 h), the losses of both electrolytes and organic osmolytes from brain cells are efficient mechanisms that regulate brain volume and thus minimize brain swelling and neurological symptoms.[14]

Consequences of overly rapid correction

As previously stated, since chronic hyponatremia develops slowly, it allows the brain to compensate considerably by the cellular exit of electrolytes and organic solutes that promotes water loss thus ameliorating brain swelling and minimizing symptoms. This adaptive process in chronic hyponatremia predisposes the brain to the development of ODS in the event serum sodium is rapidly corrected while re-accumulation of organic osmolytes is delayed. ODS occurs especially in the pons (central pontine myelinolysis), although extrapontine myelinolysis affecting the basal ganglia, cortex, lateral geniculate body and internal capsule can also occur hence the term central pontine myelinolysis changed to ODS.[15]

Clinically, ODS manifestations may include quadriparesis, dysarthria, dysphagia, and other pseudobulbar symptoms, pseudobulbar palsy, seizures, locked-in syndrome, coma and even death. Usually, the development of these symptoms may occur several days after the correction of hyponatremia and in some cases, as suggested from the autopsy series, ODS may be asymptomatic or mildly symptomatic. These

symptoms may or may not be reversible.[16]

Differential diagnosis of hyponatremia

The initial differentiation in hypotonic and nonhypotonic hyponatremia is important because management is different (Figure-1). Nonhypotonic hyponatremia is usually caused by hyperglycemia, but

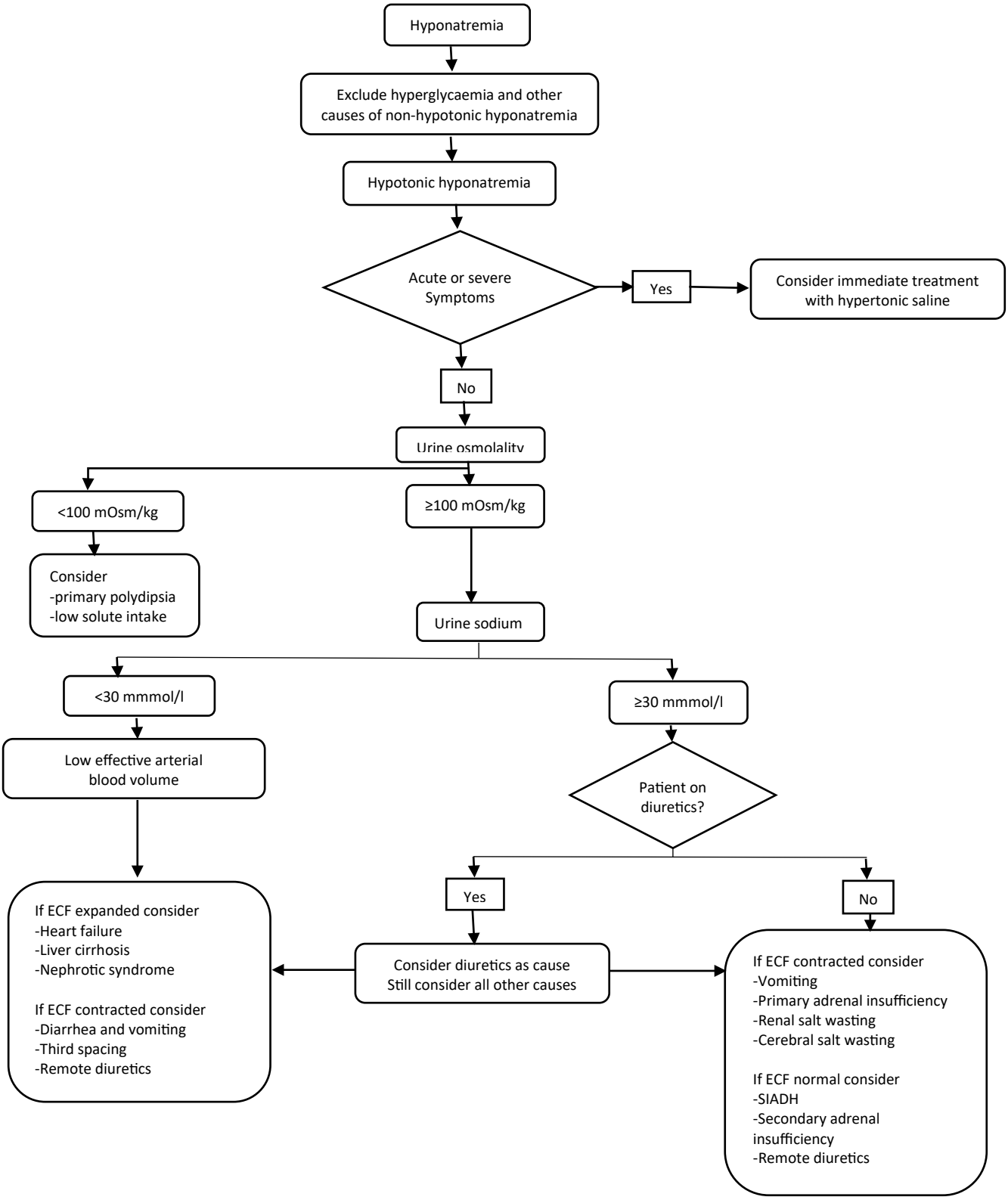

Figure-1: Flow chart for differential diagnosis of hyponatremia[1]

may also be caused by the administration of mannitol or hypertonic radiocontrast. In these settings, management is usually conservative. Nonhypotonic hyponatremia can also be caused by pseudohyponatremia, a laboratory artefact that may occur with high concentrations of triglycerides, cholesterol, or protein.[17] The United States guideline subsequently divided hypotonic hyponatremia into hypovolemic, euvolemic, and hypervolemic hyponatremia. Hypovolemic and euvolemic hyponatremia are notoriously difficult to differentiate on the basis of physical examination, whereas hypervolemic hyponatremia is usually clinically obvious (presence of edema or ascites).[18] Two studies that analysed the diagnostic performance of the clinical assessment of volume status in patients with hyponatremia reported low sensitivity (50%–80%) and specificity (30%–50%).[19] It is better when urine osmolality (U_{Osm}) and urine sodium (U_{Na}) concentration are prioritized over the assessment of volume status.[20] Because the kidneys will respond to hypovolemia or a low effective arterial blood volume with sodium retention, U_{Na}<30 mmol/L can be used to identify both hypovolemic and hypervolemic hyponatremia. Three caveats, however, should be emphasized: (1) U_{Na} will also be low in patients consuming a low sodium diet (2) the (recent) use of diuretics will increase U_{Na}, and (3) patients with CKD may be less able to reabsorb sodium.

These considerations prompted the European guideline committee to propose an algorithm that prioritizes UOsm and U_{Na} over volume status. Fenske et al. found that fractional uric acid excretion FEUA>12% had the highest sensitivity and specificity to diagnose SIADH with or without diuretic use.[21] More recently, a larger study confirmed that FEUA>12% had the best sensitivity and specificity for SIADH. FEUA is high in both SIADH and cerebral salt wasting but normalizes in SIADH only during treatment.[22] Of note, in neurosurgical patients with hyponatremia, cerebral salt wasting is a rare but important entity. Cerebral salt wasting is associated with hypovolemia in contrast SIADH (euvolemia), is a good clinical marker for differentiation.[23]

Guidelines for the treatment of hyponatremia

The United States guidelines recommended the use of hypertonic saline in patients with acute (<48h) hyponatremia with moderate to severe symptoms while the European guidelines based its recommendations to use hypertonic saline on the severity of symptoms rather than the duration.[24,25] It is important to point out that the European guidelines recognized vomiting to be a severe symptom along with respiratory arrest, seizure, somnolence, and coma. Both guidelines agreed to use hypertonic saline boluses with comparable doses ranging between 100 and 150 ml over 10-20 min that can be repeated 2-3 times until resolution of the symptoms.[24,25] This approach is expected to increase serum [Na^+] by 4-6 meq/L resulting in the reversal of the cerebral edema.

A recent study found both the slow continuous infusion and the rapid intermittent boluses of hypertonic saline in symptomatic hyponatremia patients to be effective and safe.[26] In patients at higher risks of ODS (serum [Na^+] <105, hypokalemia, alcoholism, advanced liver disease and malnutrition), a minimum daily correction rate of 4-6 meq/L was recommended. Both guidelines reached a consensus that the limit (not the goal) should be around 10 mmol/L per day for both acute and chronic hyponatremia. Both guidelines recommend hypotonic fluids or desmopressin for the re-lowering of serum sodium in case of rapid correction.[27]

Principles of treatment of hyponatremia

The treatment of hyponatremia in hospitalized patients has four important goals: to prevent further declines in the serum sodium concentration, to decrease intracranial pressure in patients at risk for developing brain herniation, to relieve symptoms of hyponatremia, and to avoid excessive correction of hyponatremia in patients at risk for ODS.[28]

Treatment depends on:

- Volume status
- Duration of hyponatremia (whether acute <48 h or chronic >48 h))
- Presence or absence of symptoms
- Etiology of hyponatremia

Euvolemic hyponatremia

General treatment: Acute hyponatremia is generally symptomatic. The risk of brain herniation is high and rapid correction is needed. These patients do not have enough time for brain adaptations to occur. Treatment is recommended with 3% NaCl (1 litre = 513 meq Na^+). Recent guidelines have suggested for giving a bolus of 100 ml 3% NaCl IV over 10 min, repeated up to 3 doses till acute symptoms subside. The goal is to provide an urgent correction by 4 to 6 mmol/L to prevent brain herniation.[29] Chronic hyponatremia is generally asymptomatic or has mild symptoms.

However, it may present with seizures if hyponatremia is very severe.

Specific treatment: It is important to rule out hypothyroidism and glucocorticoid deficiency before diagnosis of SIADH. Treatment of the underlying cause of SIADH is always the first therapeutic step. In cases of chronic hyponatremia or mild symptoms and serum sodium above 120 mEq/L water restriction is the main cornerstone of treatment and can be treated with oral salt tablets in addition to fluid restriction (1g of oral salt is equivalent to 35 mL of 3% saline). An alternative or possible addition to fluid restriction and sodium chloride administration in patients with hyponatremia is the use of an ADH receptor antagonist. The vasopressin receptor antagonists produce selective water diuresis (also called aquaresis) without affecting sodium and potassium excretion. The US Food and Drug Administration (FDA) warns that tolvaptan should not be used in any patient for longer than 30 days and should not be given at all to patients with liver disease (including cirrhosis).[30] In some severe, symptomatic or acute cases 3% NaCl is needed. Do not use isotonic saline in SIADH and if ineffective or even lower the Na level, clinically strong suspicion for SIADH.[31]

Urea administered orally or enterally (via a gastric tube) will increase the serum sodium concentration by increasing the excretion of electrolyte-free water. Urea is an alternative to the combination of loop diuretics and oral salt tablets. Favourable short and long-term outcomes with urea therapy for hyponatremia have been reported in patients with SIADH.[32] Concurrent use of a loop diuretic is beneficial in patients with SIADH. Furosemide inhibits the sodium chloride reabsorption in the thick ascending limb of the loop of Henle and causes more water loss than sodium loss. Thiazides should not be used.

Vasopressin receptor antagonists (vaptans) act on vasopressin receptors as antagonists. There are multiple receptors for vasopressin (ADH): The V1a, V1b and V2 receptors. The V2 receptors cause antidiuresis, while V1a and V1b receptors cause vasoconstriction and adrenocorticotropic hormone (ACTH) release, respectively. The vasopressin receptor antagonists produce a water loss (aquaresis) without affecting sodium and potassium excretion. Vaptans are the most appropriate physiological approach to treat hyponatremia in SIADH as they do not deplete electrolytes and restriction of fluids is not needed.

Hypovolemic hyponatremia

Sodium chloride, usually as 0.9% NaCl need to correct the volume deficit, 3% normal saline is not indicated. 0.9% NaCl corrects the hyponatremia by two mechanisms: it slowly raises the serum sodium by approximately 1 meq/L for every litre of fluid infused and by correcting the hypovolemia, it removes the stimulus to ADH release.

Hypervolemic hyponatremia

Water restriction is the mainstay of therapy. Cirrhotics may need severe water restriction (<750 ml/day) which is difficult. Loop diuretics are the cornerstones of therapy in hypervolemic hyponatremia. Salt administration or 3% NaCl is generally contraindicated for chronic therapy in edematous patients, however, may be needed in case of acute symptomatic hyponatremia. Vaptans can be used in CHF and cirrhotic patients for the management of fluid overload and/or hyponatremia after water restriction and diuretics have been tried.[33]

Primary polydipsia

Fluid restriction is warranted in hyponatremic patients with primary polydipsia in whom increased fluid intake is the primary problem. Treatment of adrenal insufficiency and hypothyroidism is needed, if present.

Conclusions

It is critical that acute and chronic hyponatremia be distinguished. Acute hyponatremia with attendant brain swelling must be corrected urgently. Chronic hyponatremia must be corrected at a rate consistent with brain organic osmolyte regulation. Hyponatremia is a frequently encountered problem in clinical practice and is an important cause of morbidity and mortality. The establishment of etiology and appropriate treatment improves outcomes. A knowledge of recent guidelines of treatment and the appropriate use of vaptans is essential for all clinicians for proper diagnosis and management.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

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