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Review

Etiology, Clinical Approach, and Therapeutic Consequences of Hyponatremia

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Abstract: A perturbation in the water balance rather than any change in salt content is the main cause of hyponatremia, the most frequent electrolyte abnormality, defined as a serum sodium concentration <135 mEq/L. Hyponatremia may be divided between mild (Na > 120 mEq/L) or severe (Na < 120 mEq/L) hyponatremia, and is most frequently observed in elderly ICU hospitalized patients. Based on tonicity, hyponatremia may be hypotonic (a decreased concentration of the solute), isotonic, and hypertonic (falsely low sodium). According to the volume of extracellular fluid (ECF), hyponatremia is further divided among hypovolemic, euvolemic, or hypervolemic hyponatremia. Finally, hyponatremia may develop rapidly as acute (<48 h), usually with severe symptoms, or slowly as chronic hyponatremia, usually being asymptomatic or with mild symptoms. Acute severe hyponatremia presents with severe CNS problems, increased hospitalization rates, and mortality. The treatment with 3% sodium chloride and a 100 mL IV bolus based on severity and persistence of symptoms needs careful monitoring. A non-severe hyponatremia may be treated with oral urea. In asymptomatic mild hyponatremia, an adequate solute intake with an initial fluid restriction of 500 mL/d adjusted according to the serum sodium levels is preferred. Vaptans could be considered in patients with high ADH activity regardless of whether they are euvolemic or hypervolemic. In general, the treatment of hyponatremia should be based on the underlying cause, the duration and degree of hyponatremia, the observed symptoms, and volume status of patient.

Keywords: hyponatremia; tonicity; volemia; acute; chronic

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1. Introduction

Water and salt metabolism are crucial for the vast majority of dysnatremias, including hyponatremia, that arise from a primary imbalance in electrolyte-free water intake and loss, and, less frequently, from changes in the salt content of the body. Thus, a perturbation in the water balance rather than any change in salt content is the main problem.

Hyponatremia is the most frequent electrolyte abnormality and is defined as a serum sodium concentration of less than 135 mEq/L [1]. A disproportion between total body water (TBW) and a sodium content [2] below 120 mEq/L is considered as severe hyponatremia [3]. The highest prevalence may be found among elderly ICU hospitalized patients (20–35%) with an increased mortality risk due to multiple comorbidities and medications [4], and in around 10% of marathon runners [3,5].

The causes of hyponatremia can be divided based on tonicity as hypotonic (a decreased concentration of the solute), isotonic, or hypertonic (falsely low sodium) [6]; and according to the volume of the extracellular fluid (ECF) as hypovolemic, euvolemic, or hypervolemic hyponatremia [7]. In addition, hyponatremia may develop rapidly as acute (<48 h), usually with severe symptoms, or slowly as chronic hyponatremia, usually asymptomatic or with mild symptoms.

Nephrologists are very familiar with hyperosmolality in their uremic patients due to their elevated blood urea levels. However, urea is a non-effective osmole since it freely diffuses between the intra and extracellular compartment due to the constitutive

presence of aquaporins. Tonicity, which is potentially confused with osmolality, denotes the concentration of osmoles—also known as effective osmoles—that do not freely cross cell membranes. Hypotonic plasma causes an intracellular movement of water, leading to cellular swelling (an example being dialysis disequilibrium syndrome, where urea behaves as an effective osmole due to the blood-brain barrier). Conversely, hypertonic plasma causes cellular shrinkage. Sodium and glucose (in the presence of an insulin deficiency) as obligate extracellular solutes are thus effective osmoles and contribute to both osmolality and tonicity, whereas membrane-permeable urea contributes to osmolality without affecting tonicity. In fact, osmolality deals with the number of effective or non-effective osmoles in a fluid, while the tonicity deals solely with effective osmoles. Hence, urine osmolality, along with the assessment of the sodium and other solutes' concentration (effective osmoles), is a preferred method of hyponatremia evaluation in comparison with urine tonicity.

2. Etiology of Hyponatremia

2.1. Hypertonic Hyponatremia

An increased serum tonicity (>290 mOsm/kg) in hypertonic hyponatremia may be caused by hyperglycemia and the use of mannitol. In the case of hyperglycemia, a conversion factor for the serum sodium correction [plasma sodium (PNa) increased by 1.6 mEq/L (1.6 mmol/L) for every 100 mg/dL (5.6 mmol/L) of plasma glucose elevation over 100 mg/dL (5.6 mmol/L) level] should be used [8].

2.2. Isotonic Hyponatremia

This type of hyponatremia (275–290 mOsm/kg) is also known as pseudo-hyponatremia and is associated with hypertriglyceridemia and hyperproteinemia. It could create a laboratory misinterpretation since plasma consists of 93% of water and 7% of lipids and proteins, while the sodium distribution belongs to the aqueous fraction. The measurement of PNa with an indirect ion-selective electrode (ISE) always requires a dilutional step. The increased levels of plasma triglycerides and/or proteins are associated with an increased volume of the nonaqueous fraction that displaces the water fraction and thus the whole plasma contains less water and sodium per unit volume, respectively. Hence, the PNa^+ measurement may cause a dilutional error with a falsely low plasma sodium. To avoid such an error, PNa should be measured by direct ISE, i.e., with a blood gas analyzer. Additionally, an isotonic hyponatremia may be also found when irrigant solutions, like mannitol, sorbitol, or glycine, are used in urology (a transurethral resection of the prostate), gastroenterology (colonoscopy), and some gynecological procedures [9].

2.3. Hypotonic Hyponatremia

As explained in the physiology introduction, a normal plasma sodium (135–145 mmol/L) and plasma osmolality/tonicity (275–290 mOsm/kg) is maintained by an interplay between thirst and ADH secretion, balancing the water intake with urinary water excretion.

Hypotonic hyponatremia or true hyponatremia (serum osmolality <275 mOsm/kg) is the most common type of hyponatremia and may be found in cases of: (a) a free-water excess caused by either the intake of a large volume exceeding the kidney diluting capacity or in cases of reduced kidney water excretion with an inappropriately high non-osmotically stimulated ADH level. The latter can be caused by a decreased effective arterial blood volume (because of diarrhea, vomiting, heart failure with low cardiac output, or vasodilation in sepsis or cirrhosis), a syndrome of an inappropriate antidiuresis hormone (SIADH) with autonomous ADH secretion (a brain or lung disorder, certain classes of drugs, and other conditions like nausea and pain), and a decreased cortisol release and a lack of the inhibitory effect on ADH secretion [10]; (b) a reduced glomerular filtration rate (GFR) and thus the kidneys' ultrafiltration capacity (acute/chronic and end-stage kidney disease); (c) a decreased solute daily consumption (<600 mOsm) and, hence, a reduced solute excretion and urine volume (beer potomania or an excessive tea consumption without a sufficient nutritional osmolar intake). The beer potomania is considered as an uncommon etiology of

hyponatremia, with variable urinary osmolality < or >100 mOsm/kg if the urine volume is also small. Hence, it should be recommended to measure the urine osmolality via daily urine collection, rather than solely through spot urine. The mechanism of water retention by the kidney in the presence of a broad range of urine osmolality seems to involve a dynamic course of vasopressin secretion during the development of hyponatremia, though the status of the vasopressin release is rarely investigated. Thus, detailed fluid balance studies and sequential observations of changes in urine and plasma osmolality would advance the understanding of its pathophysiology [11].

Based on the Edelman equation, a decreased ratio between the sum of the total body exchangeable sodium (NaE) and potassium (KE) and the total body water (TBW) points out an ensuing hypotonic hyponatremia. In this regard, there are various clinical scenarios leading to hypotonic hyponatremia: (1) in primary polydipsia, there are normal levels of NaE and KE with an increased TBW; (2) cirrhosis and heart failure are represented by an increased NaE and KE with a proportionally higher increase in TBW; (3) a hypovolemic situation with a proportionally greater decrease in NaE + KE compared to the decrease in TBW; and (4) SIADH being represented by a decreased NaE and KE in the presence of an increased TBW.

An important concept based on this equation is thus that hypotonic hyponatremia is always caused by an electrolyte-free water (EFW) excess, i.e., TBW is proportionally higher than the sum of the NaE and KE.

A clinical history and physical examination provide essential information for the diagnosis of hypotonic hyponatremia and should allow the classification of patients with hypovolemic, euvolemic, or hypervolemic hyponatremia. It should be noted in Figure 1 that the assessment of the urinary sodium excretion is important to differentiate the hypo- and hypervolemic forms associated with hyponatremia, while, to diagnose the different causes of euvolemic hyponatremia, measuring the urinary osmolality should be helpful.

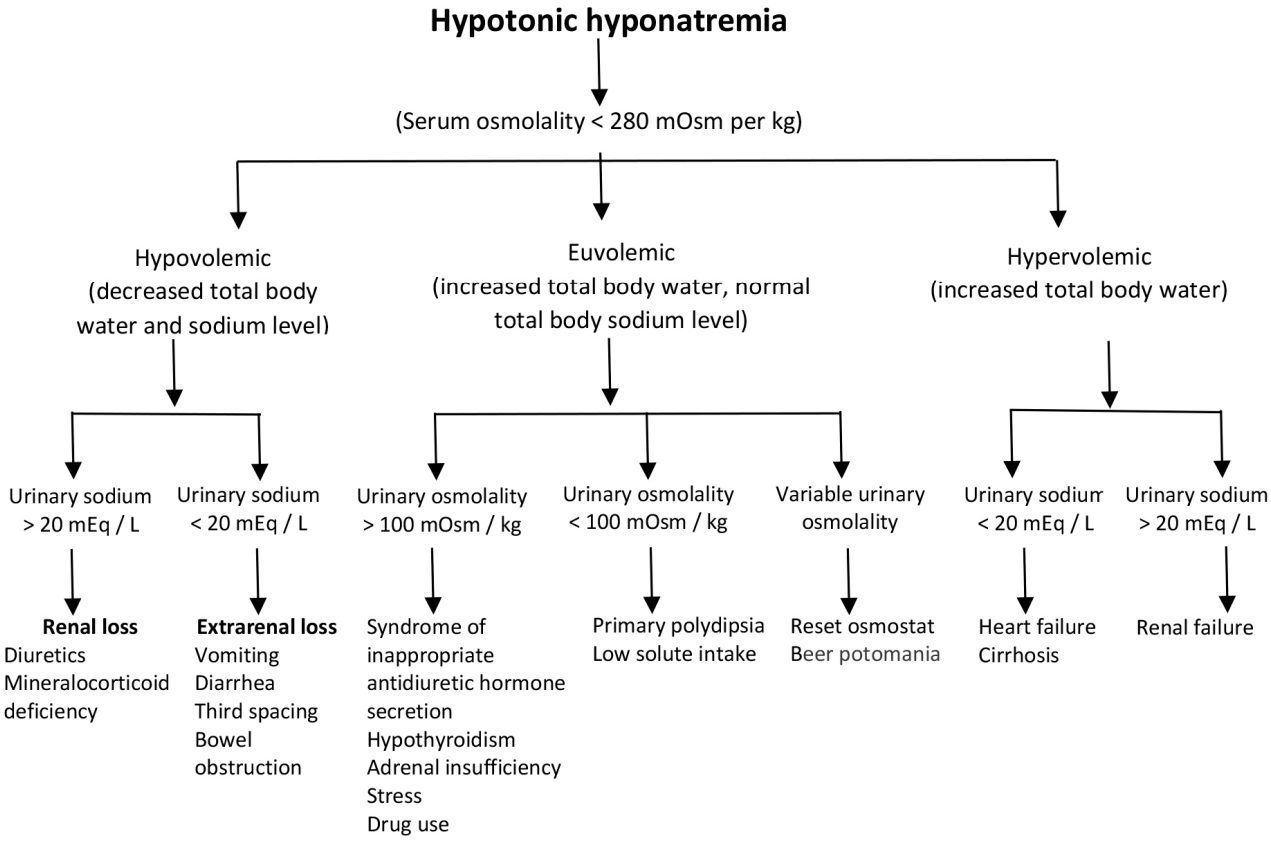

Figure 1. Summary of the clinical approach to hypotonic hyponatremia.

Hyperglycemia and other causes of non-hypotonic hyponatremia must be excluded to confirm hypotonic hyponatremia. Initial laboratory tests and imaging studies combined with a history and physical examination are usually sufficient to arrive at the cause of hyponatremia. However, it is often very difficult to assess the volume status in patients with hyponatremia [12], except in cases with an apparent volume depletion with hemodynamic instability or an apparent volume excess with a significant edema/pleural effusion. Since most hypotonic hyponatremic patients present with appetite loss/nausea, many young physicians assume that the patients are hypovolemic. Nevertheless, most frequently, after ADH suppression, a significantly large hypotonic urine output ensues (which is retained in the intracellular space). Hence, the limitation of an extracellular volume assessment in hyponatremia should be always considered.

An extensive list of causes of hypotonic hyponatremia can be consulted in the review by Adrogue et al. [13].

2.4. Hypovolemic Hypotonic Hyponatremia

The most frequent category, hypotonic hypovolemic hyponatremia (a greater decrease in TBW relative to the total body sodium and potassium decrease), may be caused by the use of diuretics with volume depletion and a stimulated antidiuretic hormone (ADH) release [6], fluid loss (vomiting, diarrhea, or sweating) [2], the loss of fluids in the third space most frequently associated with hypoalbuminemia, a cerebral salt-wasting (CSW) condition (increased brain natriuretic peptide), a combined glucocorticoid and mineralocorticoid deficiency [6], and an exercise-associated hyponatremia (EAH) [14]. A clinically important, although relatively rare, cause of hyponatremia is treatment with diuretics, known as thiazide-induced hyponatremia (TIH). Besides the increased sodium excretion, there is a complex mechanism of thiazide-induced hyponatremia interfering with the diluting mechanisms of the urine through their action on the cortical-diluting nephron segments (see the physiology introduction), via stimulation of a non-osmotic antidiuretic hormone release, and through their induction of a chronic potassium depletion [15]. Here, the hypokalemia shifts the sodium intracellularly and enhances vasopressin release, worsening hyponatremia. The role of the hypokalemia-induced hyponatremia is important for understanding the adequate treatment of diuretic-induced hyponatremia (see the discussion below on the therapy of hyponatremia). Hypertensive old women that have a low body mass and are hypokalemic are especially susceptible to thiazide-induced hyponatremia, particularly when they have a pre-existing defect in their renal capacity to excrete free water. However, they rarely develop severe hyponatremia and the TIH resolves itself two weeks after drug withdrawal [16].

2.5. Euvolemic Hyponatremia

It is considered as a stable total body sodium with increased TBW in the presence of excessive (nausea, severe pain), or inappropriate, ADH secretion, known as SIADH [17]. It may be divided into cases with diluted urine (adrenal insufficiency, hypothyroidism, and an excessive intake of water; polydipsia or beer potomania) or concentrated urine—true SIADH [18]. SIADH has been characterized by inappropriate ADH secretion regardless of an increased plasma volume, reducing urine output and leading to hyponatremia [19]. The diagnosis is based on the exclusion of other causes since any unique test or sign is unavailable [20]. It may be caused by any central nervous system (CNS) disorder, ectopic ADH production (small cell carcinoma of the lung), pneumonia or tuberculosis, and in patients on various postoperative anti-pain medications. The treatment of the underlying causes of SIADH [13], together with a reduction in fluid intake and the use of vasopressin 2 receptor inhibitors, may be helpful for the treatment of hyponatremia [21].

Euvolemic hyponatremia may also be caused by various drugs (antidepressants, opioids and antipsychotics [22], thiazides, some anti-cancer drugs, or non-steroidal anti-inflammatory drugs) [23], recreational drugs (ecstasy), excessive fluid use during

transurethral resection (TUR) syndrome, colonoscopy or cardiac catheterization intervention [9], and CSW [24].

Ecstasy-associated hyponatremia is complicated and, due to a large water intake, often secondary to ecstasy-mediated hyperthermia with a loss of water and electrolytes, and non-osmotic ADH-secretion mediated by ecstasy and its metabolites. Women are over-represented (85%) in the population with this complication [25].

Hyponatremia associated with disorders in cerebral pathology, such as contusions, intracranial hemorrhages, CNS tumors, meningitis, and encephalitis, is most commonly due to SIADH or CSW, especially in those with a subarachnoid hemorrhage [26]. CSW may be caused by either a decreased sympathetic nervous system function or the secretion of a circulating factor that decreases renal sodium reabsorption. It is characterized by low serum sodium with low plasma osmolality and high urine osmolality (>100 mOsm/L (mmol/L) and frequently >300). Urine sodium is usually >40 mmol/L and serum uric acid is low. CSW may be improved with isotonic saline administration, unlike SIADH, which is not.

2.6. Hypervolemic Hyponatremia

This type of hyponatremia (a greater increase in TBW compared to the increase in total body sodium) can develop in the presence of acute/chronic renal failure or nephrotic syndrome, or by extrarenal causes such as congestive heart failure, liver cirrhosis, or an excessive fluid intake [27]. In this category, there is a decreased effective circulating volume stimulating a non-osmotically induced antidiuretic hormone (ADH) release, resulting in water retention and generalized edema.

3. Clinical Picture

The patient's medical history is important as it could point to a certain diagnostic direction. Clinical symptoms and signs correspond to the chronicity and degree of hyponatremia. In patients with a gradual decrease in sodium, diagnosed as mild-to-moderate hyponatremia (>120 mEq/L) and developed over more than 48 h, the symptoms may be absent or minimal.

The ensuing hyponatremia leads to cell edema and swelling. The major problem comes from the brain in the non-distensible cranium. Most sensitive to the osmotic stress are the astrocytes, and the cell swelling in hypotonic hyponatremia is somehow mitigated with the decreased intracellular solute content. Thus, the expert opinion on the time course of brain compensation also defines the development of acute hyponatremia as a condition developing over less than 48 h.

Acutely developed severe hyponatremia (<48 h, <120 mEq/L) causes cerebral edema and the symptomatology may vary between either mild (headaches, vomiting, nausea, fatigue, anorexia, muscle cramps [3], impaired cognition, reduced attention, altered posture, and gait with increased falls [28]) or a severe symptomatology due to hyponatremic encephalopathy presenting as confusion, agitation, seizures, or even coma and death [29,30]. Chronic hyponatremia may also interfere with the bone metabolism and be associated with an increased risk of osteoporosis and bone fracture [31]. Nevertheless, an urgent evaluation of the volume and neurological status is essential for the prevention of neurological damage [32].

4. Diagnostic Algorithm

Considering the high variety of diseases that can either cause hyponatremia or be associated with it, it is clear that in view of its complexity, a multi-disciplinary diagnostic approach is needed to solve most cases of hyponatremia. The algorithm presented above in this paper may hopefully be helpful.

In summary, first the differentiation between isotonic, hypotonic, and hypertonic hyponatremia should be made. Once the hypotonicity of the hyponatremia has been established, the patient's volume status (hypovolemic, euvolemic, or hypervolemic) may point towards the underlying cause of the hyponatremia. A differentiation between acute

or chronic hyponatremia development is important for the evaluation of symptoms and treatment. A gradual sodium decrease over days in chronic hyponatremia is associated with only moderate symptoms and rare complications, and thus is often named "asymptomatic". However, "asymptomatic" hyponatremia may not actually and always be really asymptomatic [33]. In cases of rapid sodium loss in acute severe hyponatremia, particular attention to the neurological status should be paid and lifesaving treatment should immediately be started (see below). Such acute and severe hyponatremia is associated with potentially dangerous effects in cases of brain edema that may result in coma or death.

5. Therapeutic Approach

The treatment of hyponatremia should be based on the underlying cause [2,6], the duration and degree of hyponatremia, the observed symptoms, and the volume status of the patient. The speed of correction depends on the severity of the symptoms [6]. The type of fluids and the speed of administration as the cornerstone of the initial management are calculated based on the equation for sodium deficits = (140 − serum sodium) × total body water, where total body water = kilograms of body weight × 0.6 [5,6].

Of note, a rapid hyponatremia correction may lead to complications [34]. In severely symptomatic acute hyponatremia, a rapid correction with 100 mL intravenous (IV) bolus with 3% sodium chloride [31] is either repeated based on the persistence of symptoms [27], or given up to a 5 mmol/L sodium increase over 1–4 h is reached [6]. In cases of mild-to-moderate hyponatremia with symptoms, a slow infusion of 3% sodium chloride should be administered after calculation of the sodium deficit and frequently monitored [27].

One of the few recent studies prospectively investigating whether hypertonic saline is best administered as a slow continuous infusion (SCI) therapy or a rapid intermittent bolus (RIB) therapy for symptomatic severe hyponatremia is the SALSA study [35]. The primary outcome was an "overcorrection" at any given period, defined as increase in the serum Na^+ level by >12 or 18 mmol/L within 24 or 48 h, respectively. The results showed that both RIB and SIC therapies of hypertonic saline for treating hyponatremia were effective and safe, with no difference in the need for overcorrection. However, RIB had a lower incidence of therapeutic re-lowering treatment and tended to have a better efficacy in achieving serum Na^+ within 1 h compared to SCI. Overall, the results showed that the rapid intermittent administration of hypertonic saline is the preferred treatment of symptomatic hyponatremia, which is consistent with the current consensus guidelines.

Less aggressive treatment is certainly administered in asymptomatic chronic hyponatremia; if hypovolemic, an isotonic sodium chloride fluid without diuretics should be administered and, if euvolemic, it should be restricted up to 1-L of daily fluid. In hypervolemia, the underlying cause should be treated restricting salt and fluids, and diuretics should be regularly used.

Within therapies for chronic non-severe hyponatremia, oral urea as an oral osmotic diuretic that increases urinary water excretion appears to be a very effective and safe treatment for the prevention of possibly associated morbidity and mortality [36]. Since, it has been tolerated poorly due to its taste, there are newer, proven safe and efficient, oral American formulations enhancing its palatability [37]. The dose of oral urea is 0.25–0.5 g/kg/day and it should be increased in cases of a higher urine osmolality, usually >30 g/day [38].

Although there is still no RCT on the treatment of severe chronic hyponatremia <120 mEq/L, we suggest a slow 3% IV saline (15–30 mL/h) administration, even in asymptomatic patients with a regular follow up to prevent ODS [39].

In specific patients with hypokalemia, alcoholism, malnutrition, liver disease [40], and at high-risk for osmotic demyelination syndrome (ODS), a sodium correction should be limited up to 8 mEq/L, in the averaged-risk patients up to 10 mEq/L, and up to 12 mEq/L for 24 h in others. Serum sodium should be measured every 4–6 h, and if the increase has reached 8 mEq/L (8 mmol/L) in the first 12 h, measures to prevent a further increase should be instituted by matching urine output with 5% dextrose in water. When desmopressin (dDAVP) is used to avoid an overly rapid correction, the recommended dose is 2–4 μg

parenterally every 6 to 8 h. If an inadvertent overcorrection has occurred, there is a window of opportunity to again decrease the serum sodium levels using dDAVP to prevent brain lesions [13].

Particularly in the case of combined hyponatremia and hypokalemia, it should be remembered that the primary mechanism of the hyponatremia in that situation is that potassium depletion results in a shift of sodium into the cell with a commensurate exit of potassium from the cell into the extracellular fluid. The reverse process occurs during potassium repletion. Treating the hyponatremia with saline and the hypokalemia with potassium infusions simultaneously risks an "overshooting" of the plasma sodium increase, with dangerous hypernatremia as a consequence and risk of ODS [41].

In patients with normovolemic hypotonic hyponatremia, fluids should be restricted. Malnourished SIADH patients should be put on a high protein diet, taking into account the needed solute load and consequently more free-water renal removal. SIADH hyponatremia patients usually have sodium levels <135 mEq/L with serum osmolality <280 mOsm/kg, urinary sodium levels >20 mMol/L, and urine osmolality >100 mOsm/L [42]. Here, the underlying cause of SIADH should be corrected and fluids restricted, while in hypervolemic hyponatremia, fluid restriction as well as a low salt diet should be prescribed [43].

Mild and asymptomatic hyponatremia is treated with an adequate solute intake (salt and protein) and an initial fluid restriction of 500 mL/d, with adjustments based on serum sodium levels. A prolonged fluid restriction of 1200–1800 mL/d usually maintains the patient as asymptomatic [44]. Moderate and/or mild symptomatic hyponatremia is treated with hypertonic saline (3%), raising the serum sodium up to 8 mmol/L during the first day and correcting sodium and potassium losses with 0.9% saline and furosemide use. Severe hyponatremia or severe symptoms are treated with hypertonic saline (3%) 1–2 mL/kg IV in 3–4 h. In cases with hypovolemic hyponatremia due to the diuretic use and with low blood potassium levels, the simultaneous correction of potassium can assist the correction of hyponatremia [34].

Concerning the prognosis, it depends on the severity and underlying cause of the hyponatremia, and is poor in acute, severe hyponatremia, particularly in older populations [45]. The consequences of untreated or inadequately treated hyponatremia are an altered cognitive status, seizures, rhabdomyolysis, coma, and death. Rapid correction of chronic hyponatremia may cause ODS, previously recognized as central pontine myelinolysis [46], and should be treated with dDAVP [47].

Specific treatment with selective vasopressin 2 receptor antagonists (vaptans) should be considered in either euvolemic or hypervolemic patients with high ADH activity [48,49]. These drugs increase the renal free-water excretion, while remaining sodium unaffected, thus increasing the serum sodium level. However, American and European guidelines did not reach the same conclusion regarding these medications [50]. In addition to common use in SIADH patients [34], the US, unlike the EU, guidelines recommend their use in patients with cirrhosis or heart failure who fail to limit their fluid intake [49]. The evidence suggests that vaptans may be slightly more effective than fluid restriction in hyper or euvolemic hyponatremia, but should not be used in people with hypovolemia [51].

Finally, hyponatremia frequently presents (~30%) in nursing homes and in approximately 30% of people who are depressed and use selective serotonin reuptake inhibitors [33]. People with hyponatremia require longer hospitalizations, with increased medicare costs and a higher number of readmissions [52].

6. Conclusions

Hyponatremia is the most frequent electrolyte abnormality and, when acutely developed, presents with severe CNS problems associated with increased hospitalizations (falls, seizures, and comas), and mortality. The speed of a correction with 3% sodium chloride and 100 mL IV bolus depends on the severity and persistence of the symptoms, and needs frequent biochemical monitoring. The rapid intermittent administration of hypertonic saline is preferred for treatment of symptomatic hyponatremia. As for the

non-severe hyponatremia, oral urea may be a very effective and safe treatment. Mild and asymptomatic hyponatremia is treated with adequate solute intake (salt and protein) and an initial fluid restriction of 500 mL/d, with adjustments based on serum sodium levels. Specific treatment with vaptans may be considered in either euvolemic or hypervolemic patients with high ADH activity.

The prognosis of hyponatremia depends on the severity and underlying causes, being poor in acute, severe hyponatremia, particularly in older populations. The consequences of untreated or inadequately treated hyponatremia are increased morbidity and mortality. Rapid correction of chronic hyponatremia may cause ODS, and should be treated with dDAVP in a dose of 2–4 μg parenterally every 6 to 8 h according to the sodium levels.

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