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REVIEW

Hyponatraemia—treatment standard 2024

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ABSTRACT

Hyponatraemia is the most common electrolyte disorder in hospital patients associated with increased morbidity, mortality, hospital stay and financial burden. The speed of a correction with 3% sodium chloride as a 100- to 150-ml intravenous bolus or continuous infusion 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 hyponatraemia. In asymptomatic mild hyponatraemia, an adequate solute intake with an initial fluid restriction (FR) of 500 ml/day adjusted according to the serum sodium (sNa) levels is preferred. Almost half of the syndrome of inappropriate antidiuretic hormone (SIADH) patients do not respond to FR as first-line therapy. At present, urea and tolvaptan are considered the most effective second-line therapies in SIADH. However, the evidence for guidance on the choice of second-line therapy of hypotonic hyponatraemia is lacking. Oral urea is considered to be a very effective and safe treatment. Mild and asymptomatic hyponatraemia is treated with adequate solute intake (salt and protein) and initial FR with adjustments based on sNa levels. Specific treatment with vaptans may be considered in either euvolaemic or hypervolaemic patients with high ADH activity. In order to ensure optimal patient outcome, close monitoring and readiness for administration of either hypotonic fluids or desmopressin may be crucial in the decision-making process for specific treatment and eventual overcorrection consequences. According to the guidelines, gradual correction and clinical evaluation is preferable over rapid normalization of sNa towards the laboratory reference ranges.

Keywords: diuretics, fluid restriction, hyponatremia, urea, vaptans

Box 1. IN A NUTSHELL

- The treatment of hyponatraemia is based on the aetiological diagnosis of hyponatraemia, and the evaluation should be continuously repeated in each stage of the patient assessment with the actual level of sodium (Na), the severity of hyponatraemia, classification of the volume, measurement of tonicity and identification of the predisposing and aggravating factors.
- Severe or profound hyponatraemia needs immediate treatment with 3% hypertonic saline solution in terms of bolus therapy or continuous infusion. The duration and magnitude of treatment depends on the increase of the desired serum sodium (sNa) level and improvement of the symptoms.
- Chronic hyponatraemia usually has less severe symptoms, classified as mild to moderate according to the Na levels, and the treatment is based on the fluid volume. In hypovolaemic hyponatraemia the volume is replaced with either intravenous physiological saline or by oral intake of Na and water.
- Hypervolaemic hyponatraemia caused by decompensated heart or liver disease and nephrotic syndrome have increased extracellular but reduced intravascular volume that stimulates inappropriate antidiuretic hormone (ADH) secretion. Hence, fluid restriction (FR) is the first line of treatment, except in patients with advanced liver or heart disease. The second choice is the use of loop diuretics. Here, the V2 receptor antagonist tolvaptan is an established drug of choice, with almost no risk of overcorrection if not used simultaneously with loop diuretics. The use of albumin has been justified in advanced liver disease patients. Finally, patients with heart failure and hypervolaemic hyponatraemia may be successfully treated with oral urea administration. The treatment of last resort is sodium–glucose cotransporter 2 (SGLT2) inhibitors.
- The most common cause of mild to moderate euvolaemic hyponatraemia is the syndrome of inappropriate antidiuretic hormone (SIADH). The treatment should be initially causal, since it differs in case of diagnosed SIADH. According to the European and American guidelines, FR is the first-line option for treatment, although the efficacy is not high. Nevertheless, the advice ‘drink when thirsty or eating’ may be useful. Before initiation of FR, preserved renal function with a capacity to excrete free water should be considered. Loop diuretics are the second-line treatment, although evidence is lacking. Vaptans are considered evidence-based drugs of choice. For urea supplementation, there is no evidence of its efficacy and safety. SGLT2 inhibitors may be considered as an effective treatment compared with placebo.

INTRODUCTION

Hyponatraemia arises from a primary imbalance in electrolyte-free water intake and loss and, less frequently, from changes in the salt content of the body. It is the most frequent

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electrolyte abnormality, defined as a serum sodium (sNa) concentration <135 mmol/l [1]. A disproportion between total body water and a Na content <120 mmol/l is considered as severe hyponatremia [2].

Epidemiology

The highest prevalence may be found among elderly intensive care unit (ICU) hospitalized patients (20–35%) with an increased mortality risk due to multiple comorbidities and medications [3]. Hyponatraemia was also reported in 50% of patients with subarachnoid haemorrhage in neurosurgical units [4] and in 20% of hospital patients with heart failure (HF) [5]. Moreover, inappropriate prescribing practices and the limited knowledge of many physicians show the need for interventions to minimize the risks of hospital-acquired hyponatraemia [6]. There is little available hyponatraemia data and clinical practice guidelines to support appropriate diagnosis and treatment decisions for standardization of patient care [7]. In addition, the existing guidance documents vary in methodological rigor and the recommendations are not always consistent [8]. Moreover, it seems that the currently available European [9] and American guidelines [10] do not sufficiently consider the holistic and individual aspects of each patient, with regular follow-up and variations in the measurement of sNa, rather than the isolated single values of Na in serum or urine [11].

This article reviews the current hyponatraemia treatment standards, mainly focusing on the treatment of hypotonic or true hyponatraemia, and novel developments based on the pathophysiology through available guidance towards diagnosis, optimized treatment and prevention of overcorrection complications (Box 1).

TREATMENT STANDARDS

Hyponatraemia is presented as a complex condition associated with a variety of symptoms and caused by various aetiological factors requiring a multidisciplinary diagnostic approach. However, a couple of parameters should be determined before the initiation of treatment.

Duration

The hyponatraemia developed over a period of <48 h is called acute, usually found in postoperative patients with excessive fluid administration or self-induced water intoxication and with severe symptoms. If the duration of hyponatraemia is not known or is ≥48 h, it is called chronic and is usually asymptomatic or with mild symptoms.

The degree of hyponatraemia may be severe (sNa <120 mmol/l), moderate (sNa 120–129 mmol/l) or mild (sNa 130–134 mmol/l).

The severity of symptoms may be severe (seizures, coma, respiratory arrest), mild to moderate—non-specific (headache, lethargy, fatigue, dizziness, nausea, vomiting, confusion, forgetfulness, gait disturbances, muscle cramps) or asymptomatic.

Hospitalization is frequently needed in patients with acute, severe and symptomatic hyponatraemia at risk for complications from either untreated or aggressively treated (overcorrected) hyponatraemia. This allows for frequent monitoring and evaluation of the sNa concentration, urine output and neurologic condition.

Tonicity in hyponatraemia is sometimes required to assess free water movement and determine hypotonic (a decreased concentration of the solute <275 mOsm/kg), isotonic (275–290 mOsm/kg) or hypertonic hyponatraemia (>290 mOsm/kg), with falsely low sNa [12, 13]. Such pseudohyponatraemia may be found in the presence of hyperglycaemia and/or hypertriglyceridaemia that raise the serum tonicity and pull water out of cells. Consequently, the extracellular water space is expanded and thereby sNa levels are decreased. Rapid correction of hyperglycaemia without an appropriate increase in sNa may decrease serum osmolality and cause brain oedema, especially in young adults with ketoacidosis [14]. Pseudohyponatraemia observed in the presence of hypertriglyceridaemia can be found in patients with pancreatitis and diabetic ketoacidosis [15].

The volume of extracellular fluid (ECF) may further divide hyponatraemia as hypovolaemic, euvolaemic or hypervolaemic [16]. Determining a patient's volume status is often difficult, but it can be very helpful in defining the aetiology of fluid losses and reduction of ECF volume, worsened tissue perfusion and missing normal response to release and/or suppress ADH secretion. Inadequately suppressed ADH may be found in hypovolaemic patients and patients with HF or cirrhosis that might be also oedematous (hypervolaemic hyponatraemia). In both cases there is decreased effective arterial blood volume, impaired Na excretion and low urine Na concentration, i.e. osmolality. Here, the most common treatment of hyponatraemia is with 3% hypertonic saline. It should be managed under continuous monitoring coupled with simultaneous intravenous (IV) furosemide administration (10–20 mg once a day) in order to promote water extraction via forced natriuresis. In addition, if the cause of acute hyponatraemia is parenteral fluid administration in patients with postoperatively induced syndrome of inappropriate antidiuretic hormone (SIADH), large volumes of isotonic saline will expand the ECF and worsen the cerebral oedema. In the presence of high levels of ADH, a further decrease in sNa through its excretion in a concentrated urine will aggravate hyponatraemia, a phenomenon known as 'desalination' [17]. Hence, administration of an isotonic saline or glucose solution with the addition of sodium chloride (NaCl) 10- or 20-mEq ampules should be discouraged as ineffective and hardly relevant to a disorder of water overload rather than total body Na depletion.

The rate of correction basically depends on the severity of the symptoms [13]. The type of fluid and the speed of administration as the cornerstone of the initial management are calculated based on the equation for Na deficits, (140 − sNa) × total body water, where total body water = body weight (in kg) × 0.6 [13, 18]. In patients with acute or severe hyponatraemia with symptoms, the goal of sNa correction is 4–6 mmol/l in the first 6 h or less, and should be maintained at the same level over the first 24-h period to avoid development of osmotic demyelination syndrome (ODS). In any case, the rate of sNa correction should not exceed 8 mmol/l in any subsequent 24-h period [19]. The underlying rationale for such treatment is that a 4–6 mmol/l increase in sNa reverses the majority of symptoms of hyponatraemia and larger increases do not offer any therapeutic advantage [19, 20]. Conversely, ODS has occurred most frequently in patients whose sNa was raised by >10 mmol/l within the first 24 h or >18 mmol/l within 48 h [21].

It is important to have hourly monitoring in the treatment of acutely developed severe hyponatraemia, with initial boluses of at least 100 ml of 3% saline that may be repeated after each sNa biochemical evaluation until the therapeutic goal of a 4–6 mmol/l increase in sNa is reached. The frequency of monitoring may be decreased to 6–12 h after the desired increase in sNa is achieved.

Finally, despite all preventive measures to avoid overcorrection of hyponatraemia, ODS may occur in patients with severe hyponatraemia lasting >2–3 days, with also possible emergence of water diuresis. These patients need a rescue strategy for re-lowering

sNa, with an oral intake of water, administration of 5% glucose solution (2–4 ml/kg/h) over 4 h and/or desmopressin (1–3 μg IV or subcutaneously) at intervals of 8–12 h concomitantly with subsequent sNa monitoring [9]. The therapy may be repeated if the sNa level is not lowered ≈1 mmol/l/h or until it falls within the therapeutic goal [10]. Moreover, the corrective measures for hyponatraemia should be stopped once the lowering strategy is initiated.

A summary of strategies to personalize the treatment of hyponatraemia is presented in Box 2.

Box 2. Strategies on how to personalize the treatment of hyponatraemia.

- An appropriate diagnosis of hyponatraemia is essential for treatment. Usually, severe hyponatraemia, i.e. profound and acutely developed hyponatraemia (sNa <125), with symptoms should be treated immediately. Thereafter, measurement of tonicity and assessment of the volume status should be considered for further causal therapy and prognosis.
- Severe hyponatraemia is urgently treated by repeated boluses of 100–150 ml or 2–4 ml/kg IV administration of 3% HSS in 20–40 min until the desired increase in sNa is reached. Alternatively, a continuous infusion may be administered at doses of 0.5–1 ml/kg/h. The comparison between the two approaches is still under debate.
- Mild to moderate hypovolaemic hyponatraemia needs adequate volume replacement by either IV physiological saline (NaCl 0.9%) 23–30 ml/kg/day or, if possible, by oral intake of 9 g Na (amount equivalent to 1 L NaCl 0.9%) with meals and fluids.
- In hypervolaemic hyponatraemia, FR is the first line of treatment unless caused by an overdose of diuretics (mainly thiazides) or gastrointestinal bleeding in which fluid replacement should also be considered. Certainly, fluid intake and diuresis need careful monitoring. The second choice is the use of loop diuretics that attenuate ADH-mediated water reabsorption, at doses of 20-40 mg every 8–12 h. Recommended salt intake that enhances their action is 3–5 g NaCl/day. Tolvaptan is a treatment of choice in hypervolaemic hyponatraemia, especially in HF patients. The initial dose is 15 mg, which leads to a slow increase in sNa, with no risk of overcorrection and need for monitoring Na levels if not simultaneously used with loop diuretics. Tolvaptan use in refractory hyponatraemia is approved. The use of albumin in advanced liver disease patients is justified as adjuvant therapy that increases oncotic pressure and intravascular volume that decreases ADH stimulus. Treatment with urea is appropriate in HF patients at doses of 15–60 g/day, since it helps free water excretion, most probably through its osmotic effect on the proximal tubule. SGLT2 inhibitors may be helpful as a last treatment option in CHF patients, although still without firm evidence.
- In case of mild to moderate euvolaemic hyponatraemia, aetiological causes should be excluded before initiating treatment for SIADH. Although recommended by the major guidelines as first-line therapy, the efficacy of FR seems questionable. On the other hand, the counselling to drink only when thirsty or eating may be efficient. However, there is a very slow correction of hyponatraemia by FR at a rate of 1–2 mmol/l every 24–48 h, but only for a couple of days. Additionally, a prerequisite for FR initiation is preserved renal function with a capacity to excrete free water, which is usually reduced in the elderly. Loop diuretics are considered as a second choice for euvolaemia treatment, although randomized studies are lacking. Vaptans are definitely efficient drugs with up-to-date best evidence for normalization of Na levels in almost 48 h. The initial dose is 7.5 mg and monitoring of blood and urine parameters for eventual treatment of overcorrection is needed if Na increases >5 mmol/l in 6 h. If the correction of sNa is ≤8 mmol/l at 24 h, the dose is doubled to 15 mg, with the same procedure after 48 h. In case of overcorrection, 2 μg of desmopressin should be administered subcutaneously if the increase is up to 5 mmol/l, while if up to 6–8 mmol/l, IV glucose 5% at a rate of 2–3 ml/kg/h for 2–3 h should be added. There is no evidence for urea's efficacy and safety as a single or combined treatment with vaptans. The initial dose is 15 g and the dose may be omitted if there is Na overcorrection, or doubled in case of insufficient Na correction on the third day. The SGLT2 inhibitor is an effective treatment at a dose of 25 mg/day, especially in patients on a Na- and potassium-rich diet.

In severely symptomatic acute hyponatraemia (Fig. 1), a rapid correction with a 100–150 ml IV bolus or 2–4 ml/kg IV administration of 3% hypertonic saline solution (HSS) in 20–40 min [22] is either repeated based on the persistence of symptoms [9] or given until a 5 mmol/l Na increase over 1–4 h is reached [13]. However, there is a greater possibility for overcorrection with bolus HSS, while the undercorrection may be underestimated. Indeed, it was proven in a large retrospective cohort study that bolus HSS is independently associated with more frequent over- and undercorrection in patients with ≤60 kg and ≥100 kg body weight [23]. An observational study of 62 ICU patients confirmed HSS bolus therapy was able to correct Na more consistently as compared with conventional treatment with isotonic saline, but the overcorrection rate was significantly higher. On the other hand, there is an increased risk of an insufficient Na increase with conventional therapy and much greater range of Na fluctuation. Hence, redefinition of the bolus strategy by reducing the volume of boluses and/or re-evaluating the time for repetition may decrease the risk of overcorrection [24]. Nonetheless, further validation in prospective studies is warranted for safe and effective individualization of bolus doses.

Severe hyponatraemia should be urgently treated with no consideration of the type or aetiology, but simultaneous measures for Na correction in the initial 24 h should be omitted, as rapid hyponatraemia correction may also lead to complications [25]. Loop diuretics may be administered in congestive heart failure (CHF) patient, hydrocortisone in cases of adrenal insufficiency and potassium chloride in cases of hypokalaemia. Alternatively, a continuous 3% HSS infusion may be administered at doses of 0.5–1 ml/kg/h. The comparison between the two approaches is still under debate.

One of the few recent studies on severe hyponatraemia due to SIADH prospectively investigated 50 patients treated with either hypertonic saline administered as a slow continuous infusion (SCI) at 20 ml/h or as a rapid intermittent bolus (RIB) of up to two 100-ml boluses of 3% HSS [26]. The primary outcome was

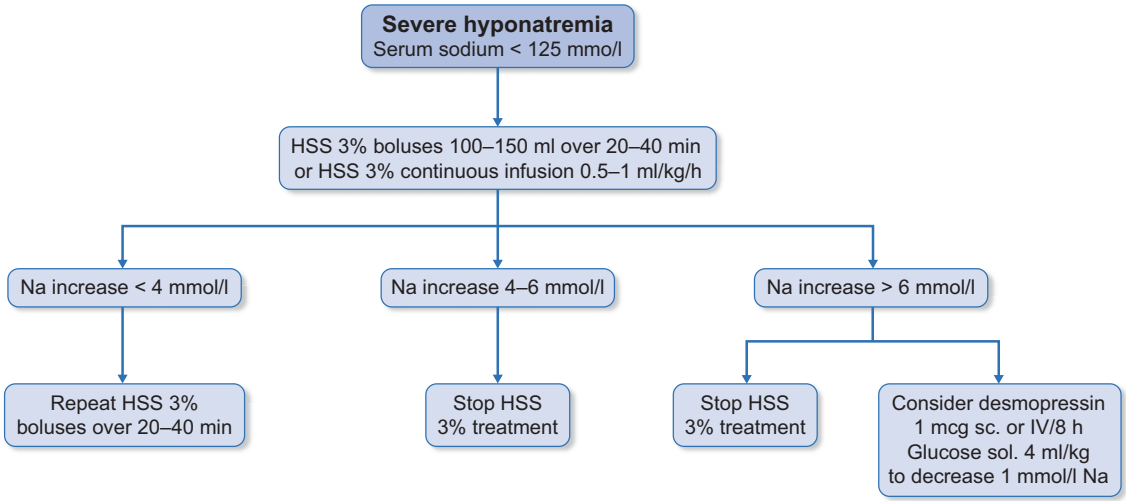

Figure 1: Treatment algorithm for severe hyponatraemia.

an 'overcorrection' at any given period, defined as an increase in the sNa level >12 or 18 mmol/l within 24 or 48 h, respectively. The results showed that both the RIB and SCI therapies with hypertonic saline for treatment of hyponatraemia 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 better efficacy in achieving the desired sNa level within the first hour compared with SCI. Overall, the results showed that rapid intermittent administration of hypertonic saline is the preferred treatment of symptomatic hyponatraemia, which is consistent with the current consensus guidelines. Hence it is recommended to use a 3% HSS bolus at doses of 100–150 ml (2–4 ml/kg) in 20–40 min with repetitions until the desired Na level is reached or as a continuous infusion strategy at doses of 0.5–1 ml/kg/h. Importantly, continuous infusion should be preferred in patients with hypokalaemia, giving the opportunity for administration of potassium chloride 20 mmol/500 ml 3% HSS. In this combined treatment of hyponatraemia and hypokalaemia, Na monitoring every 2 h is required because potassium supplementation leads to an additional sodium efflux from cells and possible rapid overcorrection, i.e. 'overshooting', with subsequent hypernatraemia and the risk of ODS [27]. Importantly, an increased urine output (water diuresis) may be also associated with a greater increase in Na, and thus a potential overcorrection.

The question remains whether to treat severe chronic hyponatraemia <120 mEq/l. Although there is still no randomized controlled trial (RCT) on such a treatment, a slow 3% HSS (15–30 ml/h) administered intravenously, even in asymptomatic patients with a regular follow-up to prevent ODS, would be useful [28].

In cases of mild to moderate hyponatraemia with symptoms, a slow infusion of 3% NaCl should be administered after calculation of the Na deficit and frequently monitored [9]. However, mild to moderate chronic hyponatraemia is usually asymptomatic since the central nervous system is gradually adapted to the osmotic changes. Hence evaluation of the volume status and aetiological assessment of hyponatraemia may be crucial for administering appropriate therapeutic measures (Fig. 2). In addition, there are a variety of pharmacological options for each particular type of hyponatraemia (Table 1), despite the scarce evidence for firm recommendations of their practical use.

In general, less aggressive treatment is certainly required in mild to moderate asymptomatic hyponatraemia. If hypovolaemic, an isotonic NaCl fluid without diuretics should be administered, and if euvolaemic, it should be restricted to 1 L of daily fluid. In hypervolaemia, the underlying cause should be treated by restricting salt and fluids and diuretics should be regularly used.

Most frequently, mild to moderate hypovolaemic hyponatraemia may be viewed as a consequence of the compensatory response of ADH to the loss of electrolytes and free water, either through the gastrointestinal system (diarrhoea or vomiting), kidneys (high doses of diuretics, tubulopathies, primary adrenal insufficiency or hypoaldosteronism) [29] or bleeding. Hence an aetiological treatment along with volume replacement is essential.

Parenteral administration of physiological saline (NaCl 0.9%), at a dose of 23–30 ml/kg/day [30], is considered sufficient for Na correction but safe in terms of a possible overcorrection. In cases of stable patients with feasible oral intake of fluids, daily ingestion of 9 g NaCl (equivalent to 1 L NaCl 0.9%) in a couple of smaller liquid portions and meals has been suggested. Regardless of the route of administration, initial Na monitoring after 6–8 h, and at 24 h is required, in order to avoid overcorrection with an appropriate treatment adaptation.

Basically, mild to moderate hypervolaemic hyponatraemia may occur in patients with either CHF [31] or liver failure [32] and nephrotic syndrome. The expansion of extracellular fluid and low intravascular circulatory volume is a common characteristic for all three conditions. A differential diagnosis of hyponatraemia due to any other cause and continuous assessment of the blood volume is crucial for appropriate treatment.

FR should be the first choice of treatment in CHF and liver failure, with a recommendation for water intake only when thirsty and monitoring of diuresis.

Loop diuretics restrict tubular permeability for electrolytes eflux and reduce the osmolality of the medulla with subsequent ADH stimulation. They are most effective for treatment of hyper- and euvolaemic hyponatraemia. Furosemide doses vary between 20 and 40 mg every 8–12 h, being particularly effective with a daily salt intake of 3–5 g and in cases of an increased urine osmolality (uOsm) >350 mOsm/kg [33].

In the EVEREST study (NCT00674323), tolvaptan was shown as a safe and efficient drug with a Na increase of 5–6 mmol/l in

Table 1: Pharmacological options for the treatment of hyponatraemia.

Characteristics	Isotonic saline	3% HSS	Loop diuretics	Vaptans	Urea	SGLT2 inhibitor
Indication	Hypovolaemic hyponatraemia	Severe hyponatraemia	SIADH, hypervolaemic hyponatraemia (CHF patients)	SIADH, hypovolaemic hyponatraemia (CHF patients)	SIADH	SIADH
Daily dose	23–30 ml/kg	2–4 ml/kg as boluses or 0.5–1 ml/kg/h continuous infusion	Furosemide 20–40 mg/12 h, torasemide 2.5–10 mg/24 h	Tolvaptan 7.5–60 mg	15–60 g	10–25 mg
eGFR Ineffective response	No limits	No limits		>15 ml/min Water intoxication	>30 ml/min	>60 ml/min uOsm <350 mOsm
Projected Na increase			2–4 mmol/l in the first 2 days	4–6 mmol/l in 24 h	4–6 mmol/l (2–7 days)	
Precautions or contraindications	Hypervolaemia	Hypervolaemia	Hypovolaemia	Pregnancy CYP3A4	CKD, liver disease, dehydration	Hypovolaemia

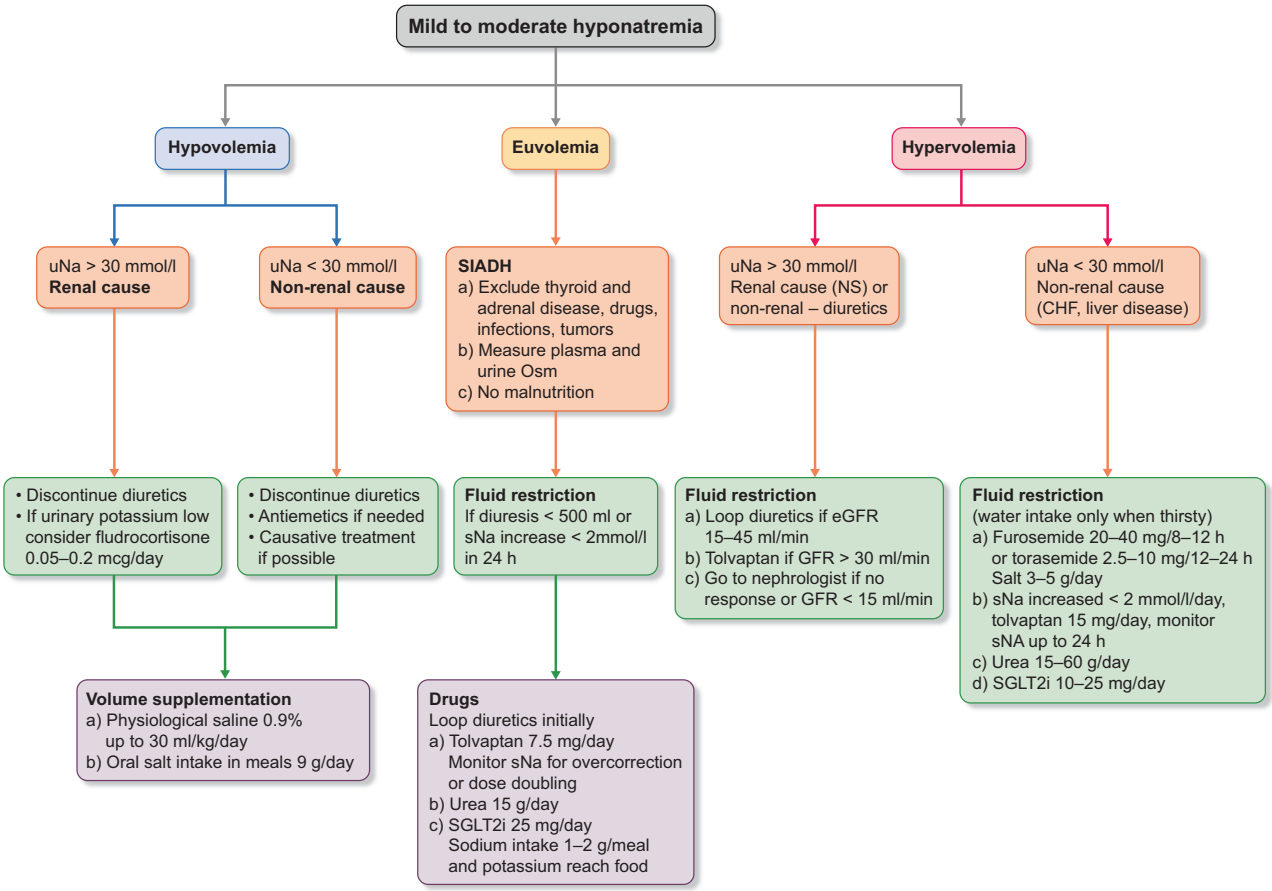

Figure 2: Treatment algorithm for mild to moderate hyponatraemia. uNa: urinary sodium; GFR: glomerular filtration rate.

7 days in hypervolaemic hyponatraemia caused by CHF [34]. Importantly, the initial dose of 15 mg leads to a slow and continuous increase in sNa, without a risk of overcorrection, hence the monitoring of Na levels is not required unless there is a simultaneous use of loop diuretics. Tolvaptan may exert a possible adverse effect of hypertransaminasaemia and should not be used in liver failure unless needed before immediate preoperative transplant preparation [35].

Albumin treatment is not justified except in advanced liver disease with hypoalbuminaemia and low circulatory volume [34], in order to increase the oncotic pressure and extracellular volume, which in turn decreases ADH stimulation. In this regard, the levels should be maintained as close as possible to the lower limit of normal.

Although without firm evidence, it is believed that urea, at a dose of 15–60 g/day, increases the osmotic effect on the proximal tubule and thus the amount of diuresis, mainly in patients with CHF [36]. Additionally, it seems to be a very effective and safe treatment for prevention of the possibly associated morbidity and mortality [37].

The osmotic diuresis increased by sodium–glucose cotransporter 2 (SGLT2) inhibitors may be helpful as a last treatment option in HF patients as well, yet it is not an evidence-based recommendation.

Mild to moderate euvolaemic hyponatraemia is the most common type of hyponatraemia in hospitalized patients, but also in outpatients. The most frequent cause is SIADH. Thus other plausible aetiological causes (hypothyroidism, hypercortisolism, elevated ADH, use of specific drugs, paraneoplastic processes etc.) need to be excluded (or treated) before the initial therapy for SIADH is commenced. Selection of the treatment option should be based on clinical evaluation and a risk–benefit analysis since there is no 'best' therapy that fits all SIADH patients [38].

With FR, body free water elimination should exceed the daily intake of water (IV or orally). Although recommended as a first-line option by the European [9] and American guidelines [10] for treatment of hyponatraemia, the efficacy of FR is questionable [39]. However, as evidenced from a single RCT at present, only two-thirds of SIADH patients on FR, compared with non-treated patients, reached the Na goal of >130 mmol/l after 3 days of treatment [40]. The standard recommendation to drink only when thirsty or eating might, to a certain extent, be efficient. That is, if strictly respected, it was shown in a retrospective study of 34 SIADH patients with chronic mild hyponatraemia that such restriction may be efficient in normalization of sNa in 76.5% of cases [41]. Nevertheless, the Na correction is at a very slow rate of 1–2 mEq/l every 24–48 h for only a couple of days [40]. In addition, FR may be more efficient in cases of preserved renal function (diuresis >1500 ml/day and uOsm >500 mOsm/kg) that is usually reduced in the elderly [42]. FR is not recommended in malnourished patients and those with no compliance, with a need for IV fluids >1 L/day, and especially during climate conditions with high temperatures.

Loop diuretics are efficient in the treatment of euvolaemic hyponatraemia, particularly when uOsm is >350 mOsm/kg [33],

although the evidence is scarce. However, in a recent RCT in 92 SIADH patients, the combination of furosemide, NaCl and FR was not superior in correction of sNa compared with FR alone [43]. In addition, the incidence of acute kidney injury and hypokalaemia was increased in the furosemide group.

At present, though relatively expensive, vaptans are drugs with best existing evidence for Na normalization in almost 48 h [32]. However, American and European guidelines did not reach the same conclusion regarding this medication use [44]. In addition to common use in SIADH patients [25], the US guidelines, unlike the European guidelines, recommend their use in patients with cirrhosis or HF who fail to limit their fluid intake [45]. The scarce evidence suggests that vaptans may be slightly more effective than FR alone in hyper- or euvolaemic hyponatraemia, but should not be used in people with hypovolaemia [46]. Vaptans should be used cautiously, by trained professionals in the hyponatremia field, with adequate hospital facilities and the possibility for immediate reaction in cases of overcorrection. The initial vaptan dose is 7.5 mg and should be carefully monitored if Na increases >5 mmol/l in 6 h. The dose may be doubled if the correction of sNa is ≤8 mmol/l at 24 h, with the same repetition after 48 h. However, in specific patients with hypokalaemia, alcoholism, malnutrition, liver disease [47] and at high-risk for ODS, the Na correction should be limited to up to 8 mmol/l, in the average-risk patient up to 10 mmol/l and up to 12 mmol/l for 24 h in others. sNa should be measured every 4–6 h and if the increase has reached 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. The overcorrection should be treated by the 'braking' protocol with desmopressin administration of 2 μg subcutaneously if the Na increase is up to 5 mmol/l within the first couple of hours. If between 6 and 8 mmol/l, additional IV glucose 5% should be administered at a rate of 2–3 ml/kg/h for 2–3 h. If an inadvertent overcorrection has occurred, there is a window of opportunity to again decrease the sNa levels using desmopressin to prevent brain lesions [48].

There is no clear evidence for the use of urea as a single or combined treatment with vaptans. The analysis of a couple of case series showed a lower frequency of overcorrection and no cases of ODS associated with urea treatment [49, 50]. The initial dose is 15 g, and if the Na is corrected above the limit, the next day's dose may be omitted. Conversely, if the Na correction is insufficient on the third day, the dose should be doubled.

The SGLT2 inhibitor empagliflozin is an effective treatment at a dose of 25 mg/day compared with placebo [51], with a median Na increase of 10 mmol/l, although randomized studies are still awaited. SGLT2 inhibitor treatment is more efficient in cases where an intake of 1–2 g of salt per meal or hypertonic (20%) NaCl in 500 ml of physiological solution is administered. In addition, potassium-rich food or IV potassium chloride infusion may be useful for a parallel Na increase.

NEW DEVELOPMENTS

Although a very frequent and complex condition, there are not many drugs under development for hyponatraemia treatment, apart from the already developed group of vaptans and a couple of trials on SGLT2 inhibitors. Instead, there is the need for various definitions and validations of previous observational and case series data and questions that have been posed from previous experiences.

At present, urea and tolvaptan are considered as the most effective second-line therapies in SIADH. Hence future research should be directed towards conducting RCTs of FR with or without urea, FR versus tolvaptan and comparisons of the possible second-option therapies after FR (urea, tolvaptan or SGLT2 inhibitors). Since all three drugs may potentially carry the risk of Na overcorrection (tolvaptan certainly the highest), direct comparison trials are warranted. In order to ensure an optimal patient outcome, close monitoring and readiness for administration of either hypotonic fluids or desmopressin may be crucial in the decision-making process for specific treatment and eventual overcorrection consequences [52].

According to both guidelines (European and USA), in cases of failed first-line treatment with FR, urea is recommended as an efficient second-line option, although without RCT evidence [9, 10]. Urea is a few-fold times more efficient compared with NaCl supplementation, i.e. 15-g oral urea sachet gives 250 mOsm renal solute load, while a 1-g NaCl tablet provides 34 mOsm. However, the poor tolerability of urea limits its wider use since the bitter taste may be only slightly improved by adjuvants such as orange juice or citric acid [9, 10]. Hence, there are newer safe and efficient oral formulations enhancing its palatability [53]. The dose of oral urea is 0.25–0.5 g/kg/day (15–30 g/day) and it should be increased in cases of a higher urine osmolality, usually >30 g/day [54]. Clinicians are also aware that the patient may have a transient increase in serum urea concentration, but it should not be assumed as a deterioration in renal function [53]. Finally, it is the cheapest drug used (<US$3 per 30-g dose) [54].

Data on the direct comparison between vaptans and urea are lacking. In a small study, 12 chronic SIADH patients (mean sNa 125 mmol/l) were sequentially treated with a vaptan (tolvaptan or satavaptan), followed by urea 15–30 g/day with a treatment break in between. The response was good with both agents (mean sNa increased to 135 mmol/l) and tolerability was similar [55]. The small size of the study was a huge limitation, but it provided a direction for future research. Today, urea may be a preferred second-line therapy, keeping in mind the small risk for overcorrection, frailty, the need for prolonged treatment of SIADH patients and to prevent recurrent hospitalization, especially considering tolvaptan's time limitation (30 days), or contraindications in patients with disordered liver function. Finally, the risk of overcorrection from previous clinical experience and individual data of each drug separately suggests a potentially lower risk of urea treatment.

The question on the use of tolvaptan as a second-line therapy in mainly hospitalized patients with SIADH when refractory to FR should be answered by a current in-patient RCT protocol (ACTRN12619001683123) that will hopefully provide evidence for a tolvaptan treatment recommendation [56]. In addition, it should offer an answer on the use of tolvaptan as initial therapy and its efficacy and safety compared with standard FR in hospital patients with moderate to severe hyponatraemia [56]. Nevertheless, it remains that the high cost of vaptans, compared with the similar response from very cheap urea treatment [55], will prompt future RCTs for this very important comparison.

Interest in hyponatraemia treatment with SGLT2 inhibitors that stimulate osmotic diuresis throughout increased glucosuria has been raised in the last couple of years. A recent RCT looked at 87 patients hospitalized for SIADH hyponatraemia who were treated with empaglifozin 25 mg/day in addition to the standard FR. After 4 days, patients on empagliflozin had a significantly larger increase of Na compared with those on placebo (10 versus 7 mmol/l). Favourable factors were profound hyponatraemia (<125 mmol/l) and lower osmolality at baseline levels [51]. However, this was still not sufficient evidence to recommend SGLT2 inhibitor as a specific treatment for SIADH. Thus the same group of authors performed another 4-week RCT with a crossover design

with empagliflozin 25 mg/day compared with placebo in outpatients with chronic hyponatraemia due to SIADH. While the median sNa increased during the trial from 131 to 134 mmol/l in the treatment group, no increase was observed in the placebo group [57]. Of note, there were no serious adverse events and the drug was well tolerated, although the group was small (14 patients). Hopefully the current ongoing trial with empagliflozin treatment in in- and outpatients with hypervolaemic and euvolaemic mild to moderate hyponatraemia should confirm this promising effect [58].

The answer on the outcome, i.e. whether the correction of hyponatraemia in hospitalized patients leads to a reduction in the risk of death and length of stay or rehospitalization, is an important aspect of hyponatraemia treatment [59, 60]. In a study on 18 patients with hyponatraemia (≤127 mmol/l) under specialist treatment, compared with 23 historical controls (mean sNa 124.1 mmol/l), it was shown that there was a much faster increase of Na (≥5 mmol/l) and a shorter hospital stay in the intervention group [59]. Also, another single-centre retrospective trial over a 5-year period reported that hyponatraemia (<120 mmol/l) treated by a specialist could reduce mortality risk in 91% of patients [60]. It remains to be confirmed in the current multicentre international RCT under recruitment, whether the correction of hyponatraemia in hospitalized patients reduces the risk of death or rehospitalization [61].

Concerning the prognosis, it depends on the severity and underlying cause of hyponatraemia, and is poor in acute, severe hyponatraemia, particularly in older populations [62]. The consequences of untreated or inadequately treated hyponatraemia are increased morbidity and mortality, increased hospital length of stay and the financial burden to society [63]. Rapid correction of chronic hyponatraemia may cause ODS, and it should be treated with desmopressin [64] in a dose of 2–4 μg parenterally every 6–8 h according to Na levels.

CONCLUSION

Hyponatraemia is the most common electrolyte disorder in hospital patients and is associated with short- and long-term morbidity and mortality. The speed of a correction with 3% NaCl as a 100-ml IV bolus or continuous infusion 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 hyponatraemia.

Almost half of SIADH patients do not respond to FR as the first-line therapy. At present, urea and tolvaptan are considered the most effective second-line therapies in SIADH. However, the evidence for guidance on the choice of second-line therapy of hypotonic hyponatraemia is lacking, apart from a couple of tolvaptan and empagliflozin RCTs that compare the drugs with placebo. Oral urea is considered to be a very effective and safe treatment. Mild and asymptomatic hyponatraemia is treated with adequate solute intake (salt and protein) and an initial FR with adjustments based on sNa levels. Specific treatment with vaptans may be considered in either euvolaemic or hypervolaemic patients with high ADH activity.

In order to ensure optimal patient outcomes, close monitoring and readiness for administration of either hypotonic fluids or desmopressin may be crucial for specific treatment and eventual overcorrection consequences [52]. Although there is an improved awareness of hospital-associated hyponatraemia (hypo-osmotic fluid administration) and the risk of ODS (overaggressive therapeutic correction), close monitoring to avoid iatrogenic morbidity is required. Gradual correction and clinical evaluation according to the guidelines is preferable compared with rapid normalization of sNa towards the laboratory reference range [65].

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DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article.

CONFLICT OF INTEREST STATEMENT

None declared.

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