Review

Optimal treatment of hyponatremia in clinical practice

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Practice Points

- Hyponatremia can be classified as hypo-, eu-, or hyper-volemic. Proper workup should include thorough physical examination and assessment of urinary osmolality as well as urinary sodium.
- In situations in which cerebral edema is suspected – for example, in acute hyponatremia (i.e., hyponatremia that has developed in <48 h) or in the presence of severe signs and symptoms such as headache, vomiting, confusion, seizures, noncardiogenic pulmonary edema or coma – aggressive therapy with 3% saline is warranted.
- Hypovolemic hyponatremia is treated with volume repletion.
- Hypervolemic hyponatremia should be managed by treating the underlying cause (e.g., congestive heart failure and liver cirrhosis) and fluid restriction. Since baroreceptor-stimulated vasopressin secretion is the reason for the hyponatremia in this circumstance, the use of vasopressin receptor antagonists (i.e., vaptans) may be warranted.
- Syndrome of inappropriate secretion of antidiuretic hormone accounts for approximately 35% of hyponatremia cases and is caused by several conditions; for example, malignancies, pulmonary diseases, cerebral processes or drugs. Therapy of the primary disease is key to hyponatremia management.
- Fluid restriction is the classical treatment for hyponatremia secondary to syndrome of inappropriate secretion of antidiuretic hormone. Other options include loop diuretics together with replacement of salt losses, salt tablets, oral urea or demeclocycline. Vaptans constitute an effective treatment option in patients without severe symptoms.

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- Overly rapid correction of hyponatremia may harm the patient by inducing osmotic demyelination syndrome. Therefore, sodium levels should not be raised by more than 12 mmol/l within 24 h. In cases of longstanding hyponatremia or in the presence of other risk factors for osmotic demyelination syndrome (alcoholism and malnutrition among others), a limit of 8–10 mmol/l/24 h should not be exceeded.

SUMMARY: Hyponatremia is the most common electrolyte disorder and can lead to a wide spectrum of symptoms, from apparently asymptomatic to life-threatening. Severe symptoms are usually a consequence of cerebral edema and should prompt immediate treatment with hypertonic fluid. In less severe cases, or after resolution of severe symptoms thorough clinical examination of volume status, additional laboratory tests are needed in order to identify the underlying cause and to classify the hyponatremia as hypo-, eu- or hyper-volemic. Although most cases of hyponatremia are attributed to an excessive action of antidiuretic hormone (vasopressin), optimal therapy regimes differ. While hypovolemic hyponatremia is treated appropriately with the administration of isotonic saline, eu- and hyper-volemic hyponatremia are classically treated with fluid restriction. In recent years a new class of drugs, vasopressin receptor-2 antagonists, called vaptans, have emerged as a potent and safe choice for the treatment of fluid restriction-resistant nonsevere hyponatremia.

With an occurrence of up to 30%, hyponatremia, defined as a serum sodium concentration of <135 mmol/l, is the most commonly encountered electrolyte disorder in hospitalized patients [1,2]. Retrospective analyses clearly show an association between hyponatremia and mortality [3,4]. However, it remains unclear whether this association is causative or whether hyponatremia is just a surrogate marker for the severity of the underlying disease causing the disorder.

Although often referred to as an electrolyte disorder, it is essential to understand that hyponatremia is characterized by accumulation of excess water in relation to sodium and, hence, dilution of sodium (and other solutes). At the same time, whole-body sodium content can be reduced (e.g., in true volume depletion), normal or elevated (e.g., in cardiac failure).

Sodium and its associated anions are the predominant determinants of serum osmolality. Thus, in the absence of other osmotically active solutes such as glucose or mannitol, hyponatremia reflects a low serum osmolality which, in turn, reflects a low tonicity in the extracellular fluid. As long as there is a difference of tonicity between the extracellular and intracellular compartment, water is shifted across the cell membrane, which leads to cell swelling. Although these changes affect all cells in principle, it is the brain that is highly susceptible to volume changes owing to its limited ability to expand within the rigid skull. In particular, rapid development of hyponatremia within hours may lead to overt cerebral edema and transtentorial herniation of the brain with deleterious effects. Other risk factors for the development of cerebral edema include ecstasy use [5], concurrent hypoxemia [6], young age (children <16 years of age, owing to increased brain:intracranial space ratio) [7], female sex (especially postmenopausal) [8], endurance exercise [9], primary polydipsia and the postsurgical setting (especially in menstruant women) [10]. Headache, vomiting, confusion, seizures, respiratory depression [11], noncardiogenic pulmonary edema [9] or coma identify patients at risk. Within hours after the onset of hyponatremia, brain cells start pumping out electrolytes and organic osmoles, thereby restoring osmotic equilibrium and reducing cerebral edema. This process is usually completed after 48 h. It is crucial to acknowledge that the time course of development of hyponatremia is much more important than the degree of sodium reduction. In fact, life-threatening cases have been reported with serum sodium levels well above 120 mmol/l, but where hyponatremia had developed very

rapidly [9,10]. On the other hand, the true duration of hyponatremia is frequently not known precisely. Furthermore, sometimes severe symptoms can also be seen in longstanding hyponatremia. The often used classification of hyponatremia according to the time of duration as acute (i.e., <48 h) or chronic (i.e., >48 h), therefore, has its shortcomings and the appropriate treatment should not be determined based on a putative duration of hyponatremia or any specific sodium concentration. Instead, it is recommended that the initial management should be guided primarily by symptomatology.

Severely symptomatic hyponatremia is a medical emergency reflecting cerebral edema and must be treated quickly and aggressively with hypertonic fluid, regardless of the underlying cause, in order to rapidly raise sodium levels and to prevent further deterioration. The benefit of such a rapid correction of serum sodium in this situation certainly outweighs the therapy-associated risks. By contrast, once the volume regulatory adaptation process is completed and the brain cell volume has been restored, that is, in chronic hyponatremia, overly rapid sodium correction can lead to osmotic demyelination syndrome (ODS) owing to osmotically driven cell shrinkage. The clinical picture of pontine myelinolysis, the most common disorder in this regard, includes lethargy, dysarthria, mutism, tetraparesis and pseudobulbar palsy. Other risk factors for ODS include malnutrition, alcoholism, the use of thiazide diuretics in elderly women, polydipsia, hypoxia and hypokalemia [12–19]. In these cases, treatment with hypertonic saline (or any other measure) must be performed cautiously and mandates intensive monitoring of serum sodium concentration (see detailed discussion below on hypertonic saline). Hypertonic saline should be discontinued once the symptoms of cerebral edema have resolved. Subsequently, proper workup of the underlying etiology should be performed and the appropriate further treatment commenced.

Hyponatremia without severe signs and symptoms is frequently encountered in clinical practice and does not need emergency treatment. Usually, the hyponatremia is of a chronic nature, and, due to cerebral adaptation, symptoms may be subtle or absent, even in severe hyponatremia with sodium levels below 120 mmol/l. Signs and symptoms include, among others, nausea, drowsiness, cognitive impairment, memory deficits, depression, muscle cramps or gait instability. Traditionally, patients with chronic mild-to-moderate hyponatremia (commonly defined as a sodium concentration of >125 mmol/l) are often perceived as being asymptomatic and, hence, do not receive any treatment at all. However, recent investigations have repeatedly demonstrated that these patients have a significantly increased risk for falls and fractures [20–22]. Anecdotic reports have shown that some of these patients that were believed to suffer from depression or dementia improved markedly after correction of the hyponatremia. From this perspective, it seems sensible to revisit the concept of asymptomatic hyponatremia and to carefully assess such patients.

Assessment of hyponatremia

The overall treatment goal in hyponatremia is elimination of the excess water. However, the strategies to accomplish this task depend on the underlying cause of hyponatremia and, thus, a proper workup of the disease. Given the high prevalence of this disorder and its associated risk, clinicians should be familiar with the diagnostic and therapeutical algorithms. Recent investigations; however, have revealed that the management of hyponatremia in western hospitals is far from being satisfactory, one of the reasons being that hyponatremia is often considered too complex by physicians [23]. Therefore, a short overview of the mechanisms leading to hyponatremia and the diagnostic workup is presented here.

■ Pathophysiologic basis & causes of hyponatremia

Serum osmolality is determined by two factors, water intake and renal clearance of water under the control of antidiuretic hormone (ADH). ADH is synthesized in the supraoptic and paraventricular nuclei in the hypothalamus as a response to high serum osmolality and secreted from the posterior pituitary gland. Binding of ADH to the vasopressin 2 (V_2) receptor located at the basolateral cell membrane of the principal cells of the collecting duct induces the insertion of aquaporin-2 water channels at the apical cell membrane, which, in turn, leads to reabsorption of water and subsequently the elimination of concentrated urine, thereby lowering serum osmolality [24,25]. Inversely, a low serum osmolality inhibits ADH secretion and prompts the elimination of dilute urine. In disease, almost all cases of hyponatremia are caused by an

inappropriately high antidiuretic response in relation to serum osmolality. Various conditions can be responsible for such an 'unphysiological' response. Marked reduction of the arterial blood volume by true volume depletion (e.g., diarrhea, bleeding, diuretics and hypoaldosteronism among others) or reduction of the effective arterial blood volume (EABV) as a consequence of late-stage congestive heart failure, liver cirrhosis or nephrotic syndrome leads to a nonosmotic, baroreceptor-mediated ADH secretion [26–28]. In any of these cases, impairment of volume homeostasis is the primary disorder and patients present with either signs of hypo- or hyper-volemia. By contrast, the syndrome of inappropriate ADH secretion (SIADH) is characterized by primary excess ADH secretion, which is not the consequence of plasma hyperosmolality or reduced blood volume. The ensuing excessive antidiuresis together with ongoing water intake leads to volume expansion, but only one-third of this extra fluid load is located in the extracellular compartment. Hence, patients with SIADH always present without signs of volume depletion or overload. Interestingly, patients with SIADH have been shown to have a downward resetting of the osmotic threshold for thirst, which might contribute to the development of hyponatremia [29].

The causes of SIADH are manifold. Schwartz *et al.* were the first to describe the syndrome in two patients with pulmonary carcinomas [30] and subsequent enquiries have shown that neuroendocrine tumors, especially small-cell lung carcinomas, are one of the most common causes of SIADH [31]. Furthermore, pulmonary diseases (e.g., chronic obstructive lung disease and pneumonia, among others), diseases of the brain (e.g., tumors, bleeding, trauma, encephalitis and others), stress, pain and many drugs, especially those with a marked action on the CNS, such as anticonvulsives, antidepressives and neuroleptics, can induce SIADH. Finally, true idiopathic SIADH can be frequently seen in the elderly. With 35% of all hyponatremic patients, SIADH is the most common entity followed by hypovolemic hyponatremia and hypervolemic hyponatremia with 32 and 20%, respectively [32]. Thiazides interfere with the dilutional segment of the nephron, the distal tubule, and account for approximately 7% of hyponatremic episodes [33]. Since thiazide-induced hyponatremia cannot often be easily discriminated from SIADH by clinical examination and further laboratory tests (see 'Diagnostic workup' section), these drugs should always be discontinued in patients with hyponatremia. Hypothyroidism [34], pituitary insufficiency [35], adrenal insufficiency [36] and cerebral salt wasting (CSW) [37] are rare causes of hyponatremia but should be considered and excluded if considered possible [31]. Reduced levels of cortisol, a physiologic tonic inhibitor of ADH secretion, as a result of pituitary insufficiency, leads to euvolemic hyponatremia while Addison's disease induces volume depletion due to concomitant impairment of aldosterone secretion. CSW is an important differential diagnosis for SIADH in the neurosurgical setting, particularly in patients with subarachnoid hemorrhage. By contrast to SIADH, CSW is characterized by urinary salt wasting and hypovolemia [38]. The precise mechanisms responsible for the salt loss are not yet completely understood. Laboratory features in CSW are very similar to those found in SIADH and the diagnosis CSW can only be made if there is clear evidence for volume depletion in the presence of a high urinary sodium concentration. Occasionally, patients present with hyponatremia but maximum dilute urine (urinary osmolality <100 mOsm/kg), indicating that ADH is not acting in this situation. This can be found when large quantities of fluids and only minute amounts of solutes are consumed. Since the kidney's dilutional capabilities are limited, this hypotonic challenge results in hyponatremia. Psychogenic polydipsia or binge drinking are the most common conditions in which this constellation is seen but it can also be observed in elderly patients (mostly women) with already reduced dilutional capacity and a so-called 'tea-and-biscuit' diet [39,40]. Interestingly, it has been demonstrated that the hyponatremia seen with excessive water drinking is not only a consequence of volume expansion and solute dilution but also of salt depletion [41]. Patients suffering from this kind of water intoxication carry a high risk of developing cerebral edema. On the other hand, fluid restriction will immediately abolish hyponatremia, and close monitoring is mandatory to prevent overcorrection. Finally, it should be mentioned that hyponatremia can sometimes be found despite a normal or even supranormal serum osmolality, for example with very high blood glucose levels or in the presence of other osmotically active substances (e.g., mannitol). This can be ruled out easily by assessing serum

osmolality directly [28]. Depending on the laboratory method used, problems can arise in the presence of marked elevation of lipids or proteins in the serum sample volume leading to artifactual low sodium levels (pseudohyponatremia).

Diagnostic workup

After confirmation of hypo-osmolar hyponatremia and exclusion of pseudohyponatremia, the next step is to check whether hyponatremia is a result of ADH action. A urinary osmolality below 100 mOsm/kg H_2O rules out a significant ADH effect and water intoxication secondary to increased fluid ingestion is confirmed. In all other cases further diagnostic steps include thorough examination of volume status and assessment of urinary osmolality and sodium levels. Analysis of serum creatinine, urea and uric acid also help in drawing the right conclusions. Although in many hospitals these analyses are not readily available at all times (e.g., in the night) it is desirable that the samples are collected prior to any kind of treatment in order to allow for a precise diagnosis in retrospect.

In general, it is quite easy to spot the patients with hypervolemic hyponatremia since volume overload is usually evident. However, it is far more difficult to distinguish the hypovolemic from the euvolemic patients. Assessment of heart rate, blood pressure, orthostatic reaction, jugular venous pressure and skin turgor, among others, helps in this task and should be carried out accurately.

True hypovolemia or reduction of the EABV in hypervolemic disorders is accompanied by activation of the renin–angiotensin–aldosterone system, which results in enhanced renal reabsorption of sodium. Fractional sodium excretion (FE_{Na^+}) is calculated as:

$$FE_{Na^+} = \frac{(Na^+_{urine} \times creatinine_{serum})}{(Na^+_{serum} \times creatinine_{urine})}$$

Typically, FE_{Na^+} falls below 0.5%, and urinary sodium concentration is below 10 mmol/l under these circumstances. However, the use of diuretics may limit the value of urinary sodium. In these cases, FE_{urea} is a reasonable substitute and a FE_{urea} below 35% indicates reduced arterial blood volume or EABV [42]. Furthermore, serum creatinine, urea and uric acid are usually above the normal range. On the other hand, since volume homeostasis is not affected in SIADH, the urinary sodium output matches the input. Sodium concentration in a urine spot sample is therefore usually above 30 mmol/l as long as the subject ingests a normal diet. Moreover, the accumulation of water leads to an expansion of intravascular blood volume and, hence, to an increase of glomerular filtration rate and a corresponding decrease of serum creatinine, urea and uric acid. A low- or sub-normal uric acid concentration is considered to be a sensitive indicator for SIADH [43]. Fenske *et al.* proposed fractional excretion of uric acid (see above formula) and demonstrated that values above 12% are highly suggestive for SIADH even in the presence of diuretics [44]. However, it has to be emphasized that all these laboratory parameters can be misleading and it is widely accepted that SIADH should be a diagnosis of exclusion **(Box 1)**. Sometimes the differentiation between hypovolemic and euvolemic hyponatremia cannot be made unequivocally. In these cases, a test dose of 1–2 l of isotonic saline can be safely administered over 24 h (or 0.5–1 l in 12 h) as long as urinary osmolality does not exceed 500 mOsm/kg H_2O substantially [45,46]. In patients with volume depletion serum, sodium will usually increase by more than 5 mmol/l within 24 h in response to infusion of 2 l isotonic saline. A similar evolution of serum sodium levels can also be seen in patients suffering from SIADH, namely in those cases where urinary osmolality is well below 500 mOsm/kg H_2O. However, by contrast to volume-depleted patients, in which the infused sodium will be continuously reabsorbed until hypovolemia is completely corrected and hyponatremia has abated, the administered sodium load in SIADH patients will be excreted by the kidney raising urinary sodium levels. Additionally, it is also recommended to assess the patient's weight before and after volume challenge. In hypovolemic hyponatremia, sodium concentration and body weight should increase, whereas in SIADH no, or only small, changes can be observed. A simplified diagnostic algorithm for practical use is shown in **Figure 1**.

Box 1. Diagnostic criteria of syndrome of inappropriate antidiuretic hormone secretion.

- Hyponatremia <135 mmol/l
- Plasma hypo-osmolality <275 mOsm/kg H_2O
- Urinary osmolality >100 mOsm/kg H_2O
- Clinical euvolemia (no clinical signs of hypo- or hyper-volemia)
- Spontaneous urinary sodium >30 mmol/l (with normal dietary salt intake)
- Normal adrenal and thyroid function, no renal dysfunction

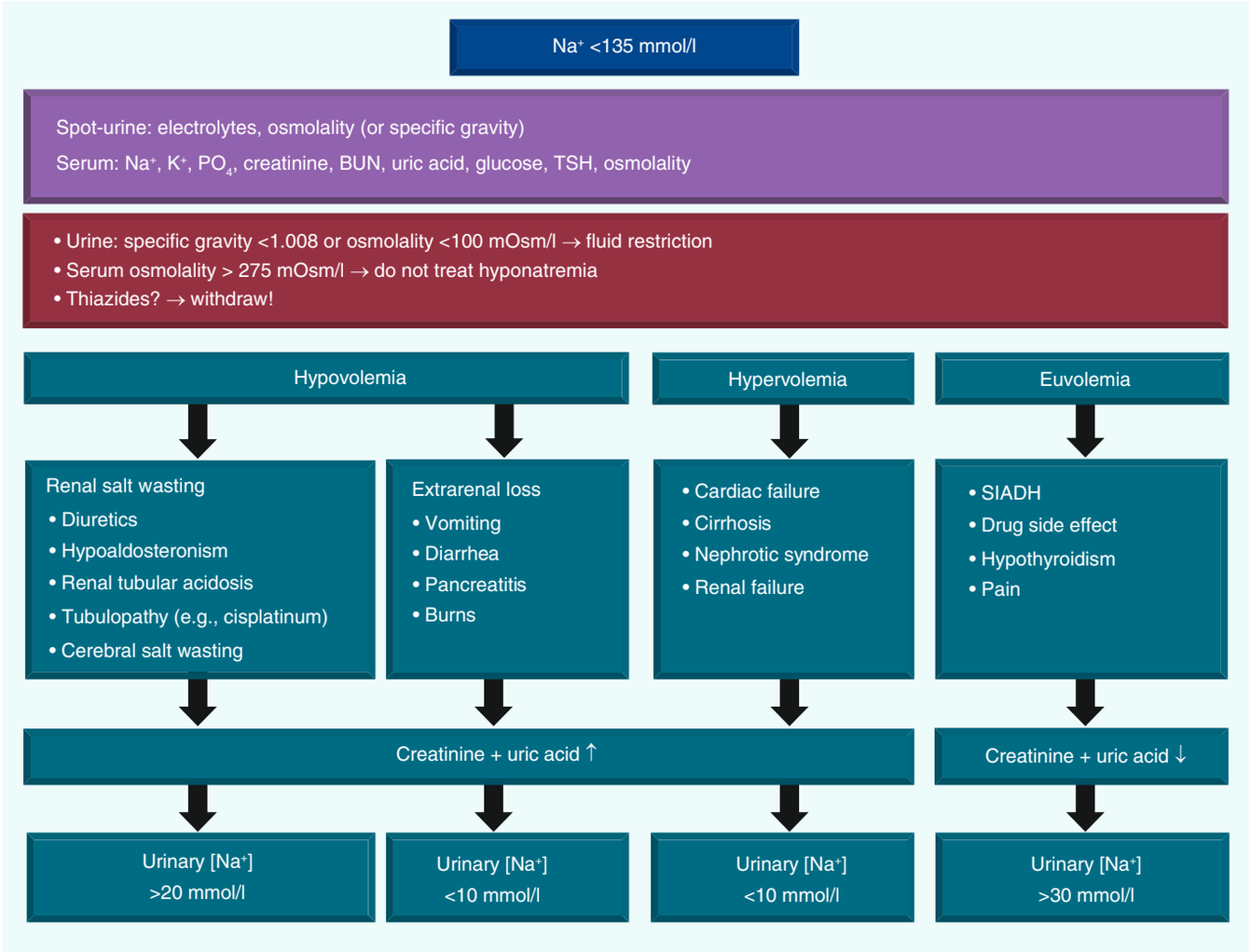

Figure 1. Simplified algorithm for diagnostic workup of hyponatremia.
↑: Increase; ↓: Decrease; BUN: Blood urea nitrogen; SIADH: The syndrome of inappropriate ADH secretion; TSH: Thyroid-stimulating hormone.

Treatment

The optimal treatment strategy is determined by the severity of symptoms as well as the underlying reason for the hyponatremia. While severe hyponatremia, particularly with an acute onset, has to be considered a medical emergency and dealt with immediately, less dramatic cases should be approached by first elaborating the primary cause of the disorder and then choosing the correct therapy option. It is recommended to always look for and withdraw drugs that might be responsible for hyponatremia, such as thiazides, antiepileptics, antidepressants and others.

In most cases of SIADH, hyponatremia has to be considered as a complicating epiphenomenon. This means that discovery and treatment of the primary disease should have highest priority; however, further efforts in this respect are sometimes hindered by symptoms related to hyponatremia. Thus, treatment options should aim at timely control of hyponatremia whenever possible. On the other hand, successful therapy of the primary disorder (e.g., chemotherapy in small-cell lung cancer) usually abolishes SIADH, and symptomatic control of hyponatremia is therefore only needed for a limited time span. Rarely, chronic idiopathic SIADH requires long-term treatment.

Hyponatremia in the context of hypervolemia should also be approached by treating the primary disorder, that is, heart failure, liver cirrhosis or less common nephrotic syndrome besides symptomatic sodium control.

An outline of a possible strategy for treatment of nonseverely symptomatic hyponatremia is depicted in **Table 1**.

Emergency treatment with hypertonic saline

Severely symptomatic hyponatremia, especially if developed acutely, is a medical emergency that makes prompt and effective treatment mandatory, irrespective of the underlying cause. The aim is to prevent brainstem herniation and this can only be achieved rapidly with the administration of hyperosmolar fluids, hypertonic saline being most commonly used. It has to be considered though, that given the fact hyponatremia is a consequence of water excess and not lack of sodium, hypertonic saline can only be considered a mere rescue measure and that, once the infusion is discontinued, the administered salt load will soon be excreted and hyponatremia may relapse, as long as no further therapies (e.g., fluid restriction) are initiated.

Usually, 3% saline is administered at a rate of 1–2 ml/kg/h, which will raise sodium levels by approximately 1–2 mmol/l/h [46,47]. In severe and life-threatening situations (seizures, coma and noncardiogenic pulmonary edema) initial dosage can be higher (2–3 ml/kg/h) over the first few hours. Alternatively, a bolus infusion of 100 ml or 2 ml/kg of 3% saline can be given and repeated once or twice if necessary [48,49]. An overly rapid increase of serum sodium has to be avoided by all means since this can cause massive osmotic cell shrinkage and demyelination, most often seen in the pons but also at extrapontine sites [18,50,51]. This is a general precaution and the following limits apply for all patients with hyponatremia, regardless of the severity of symptoms or the chosen therapy. An increment of no more than 12 mmol/l within 24 h and 18 mmol/l in 48 h has been demonstrated to be safe and is considered acceptable in acute hyponatremia. However, for those patients with chronic hyponatremia or in which the duration of hyponatremia is unknown, a limit of 8–10 mmol/l/24 h or even less is probably more appropriate [45]. These limits do also apply to other patients at high risk for ODS (i.e., alcoholism, malnutrition and hypoxia). Blood sample testing should be performed every 1–2 h as long as aggressive therapy is continued. In the case of overly rapid increase of sodium levels, hypertonic saline should be stopped instantly and dextrose 5% administered. In fact, hypertonic infusion should be stopped once overly rapid correction is anticipated, well before reaching the recommended limit. Another option to decelerate or reverse the rise of sodium concentration, either given alone or in combination with dextrose 5%, is desmopressin [52]. This might be particularly helpful in patients where the limits have already been exceeded.

Of note, raising sodium concentration by only 5–10 mmol/l is often sufficient to eliminate immediate danger. Hypertonic saline should then be stopped and further appropriate treatment initiated.

Treatment of hyponatremia without severe symptoms

Hypovolemic hyponatremia

In patients with hypovolemic hyponatremia, volume repletion with isotonic saline or balanced crystalloid solution constitutes the treatment of choice. It is safe, effective and sufficient in the majority of cases of volume depletion. In patients with adrenal insufficiency, administration of steroids (usually dexamethasone or hydrocortisone) along with volume substitution

Table 1. Treatment strategies in hyponatremia without severe symptoms.

Subtype of hyponatremia	Therapy options
Hypovolemic hyponatremia	Volume repletion
Euvolemic hyponatremia	Fluid restriction Diuretics plus oral salt (tablets) Vaptan Urea Demeclocycline
Hypervolemic hyponatremia	Salt and fluid restriction Diuretics/treatment of the underlying cause Vaptan (approved only in North America)
Adrenal insufficiency	Hydrocortisone
Hypothyroidism	L-thyroxine
Urinary osmolality <100 mOsm/kg H_2O	Fluid restriction

will promptly abolish hyponatremia. Treatment of patients in which CSW is suspected can be challenging. Salt repletion either intravenously (isotonic saline) or orally is recommended in these cases and the administration of fludrocortisone has been advocated as an alternative by some experts [53]. However, SIADH, being the major differential diagnosis, is usually managed in the opposite way, that is, with fluid restriction. Initial therapy should, therefore, be monitored closely in order to avoid providing the wrong treatment strategy.

Euvolemic hyponatremia

By contrast to hypovolemic hyponatremia, in many cases of SIADH, administration of isotonic saline will not be effective and even might harm the patient by further deteriorating hyponatremia in specific situations. It is a widespread misconception that by infusing isotonic saline with a sodium concentration of 154 mmol/l, serum sodium levels must rise. As long as the urinary tonicity exceeds the tonicity of the infused solution, the net effect will be further accumulation of free water and aggravation of hyponatremia. The extent of this effect obviously depends on the degree of urinary osmolality, which, in SIADH, can be fixed at levels as high as 800–900 mOsm/kg H_2O (or more). Hence, isotonic saline is not an appropriate treatment choice for most SIADH patients. As previously mentioned, administration of a limited amount of isotonic saline is safe as long as the urinary osmolality is below 500 mOsm/kg H_2O [45], and can even raise sodium levels efficiently in those patients with low urinary osmolality [54].

Fluid restriction represents the classical therapy for patients with SIADH. The simple idea behind this strategy is that water excess must inevitably wane as long as water output exceeds intake. Therefore, a prescribed fluid restriction of 1.5 l/day, or more, often seen in every day practice is usually not very effective. Even if water intake is limited to below 1 l, which is often not tolerated by many patients, sodium levels tend to rise by only 2–4 mmol/l/day.

Since urinary osmolality is closely related to the amount of water retained, it becomes clear that the higher the urinary osmolality, the more pronounced the fluid restriction must be in order to be effective [55]. Furst *et al.* introduced the concept of electrolyte-free water clearance (C^eH_2O) to accurately estimate renal losses of hypotonic fluid, and to use that estimation to determine the limit of fluid intake [56].

$$C^eH_2O = urine\ output \times \left(1 - \frac{Na_{urine} + K_{urine}}{Na_{serum}}\right)$$

The use of C^eH_2O is superior to solute-free water clearance since the latter takes into account all osmoles, including urea, which readily equilibrates across cell membranes and, thus, does not contribute to the water shift across cell membranes. Relating urinary and serum electrolyte concentrations rather than urinary and serum osmolalities, therefore, allows for a better estimation of the actual situation. In order to ameliorate hyponatremia, the electrolyte-free water clearance must exceed water intake. From the above formula it is evident that there is a net negative C^eH_2O once the urinary electrolyte concentration ($Na^+ + K^+$) exceeds serum sodium concentration. Using the ratio below, Furst *et al.* derived recommendations with regard to quantities of fluid restriction [56].

$$\frac{(Na^+ + K^+)_{urine}}{Na^+_{serum}}$$

When the above equation equals >1, fluid restriction should be absolute, that is, no fluid at all should be given to the patient, This will abate natriuresis and eventually raise sodium levels. Of course, absolute fluid restriction is barely possible and other therapy options should be considered in this situation. With a ratio of <0.5, a maximum daily intake of 1 l is proposed and with a ratio between 0.5 and 1, 0.5 l of fluid intake should not be exceeded.

Renal water excretion can also be augmented by increased intake of solutes, such as salt tablets, protein or urea. Oral administration of 15–30 g of urea per day (usually mixed with orange juice) leads to a marked osmotic diuresis and, thus, elimination of water. It has been established successfully as a cheap, effective and safe treatment strategy in patients with hyponatremia secondary to SIADH [57,58]. In a recent small study, patients with chronic SIADH were treated first with a vaptan (a vasopressin receptor antagonist) for 1 year and then switched to oral urea for another year [59]. In terms of efficacy, safety and tolerance, both therapy strategies were comparable. Despite these findings the use of orally administered urea has not become widely accepted due to its unpalatable taste. Particularly in patients with inadequate dietary intake

or malnutrition, a high-protein supplementation should be provided.

Loop diuretics (but not thiazides) induce a marked water diuresis and can be used effectively in SIADH either alone (e.g., furosemide 40–80 mg/day) or together with the replacement of sodium losses by the administration of salt tablets or 3% saline infusion [60,61]. Potassium replacement or potassium sparing diuretics (e.g., triamterene 50 mg/day) can be used concomitantly if hypokalemia develops.

From a physiologic point of view, inhibition of either secretion or action of ADH represents a more targeted approach compared with the above-mentioned therapies. Demeclocycline, a tetracycline antibiotic, although off-label in most countries, has been used in the past as an option for fluid restriction-resistant hyponatremia due to SIADH. It is an often observed side effect of demeclocycline, nephrogenic diabetes insipidus, which is exploited here for treatment of hyponatremia [62]. However, the drug has several shortcomings:

- The onset of action is usually delayed by several days;
- It works only in about 60% of patients;
- It is a potentially nephrotoxic drug.

Its use is, therefore, presently not very popular. Specific blockers of the V_2 receptor, called vaptans, were introduced a few years ago. Several vaptans have been developed and two are currently available on the market: conivaptan and tolvaptan. While conivaptan is a nonselective V_1/V_2-receptor antagonist approved for intravenous use in patients with eu- and hypervolemic hyponatremia by the US FDA, tolvaptan has been approved by the FDA for treatment of eu- and hyper-volemic hyponatremia and by the EMA for treatment of euvolemic hyponatremia. Since vaptans are the only approved targeted therapy with the putative potential to largely facilitate management of hyponatremia, we give here a more detailed overview on the features of these compounds, focusing on tolvaptan since it is the only vaptan available in North America and Europe at the moment.

Tolvaptan is an oral nonpeptide selective V_2-receptor antagonist that induces a marked increase of water excretion [24,25,63] by inhibiting ADH-binding to the V_2 receptor in the collecting duct without impact on renal electrolyte handling and without influencing renal hemodynamics [64]. Other vasopressin receptors include V_{1A}, which is expressed in vascular smooth muscle cells causing vasoconstriction and in the liver leading to glycogenolysis upon activation, as well as V_{1B}, which is expressed in the pituitary and pancreatic islets [25]. Chronic use of tolvaptan can lead to a reflex increase of circulating ADH levels with an especially enhanced action on the V_{1A} receptor resulting in possible vasoconstriction or hyperglycemia [65]. However, these side effects are of minor clinical importance [66,67]. Other side effects are pollakiuria, thirst, fatigue, dry mouth, polydipsia and polyuria (which are actually rather direct consequences of the desired effect rather than true side effects) [68–70]. Enhanced aquaresis starts as early as 20 min after administration and most of the action is observed within the first 6–12 h [71–73]. Treatment is started with an initial dose of 15 mg once-daily, which can be raised in 24-h intervals to a maximum of 60 mg once-daily. It is recommended to check serum sodium levels 4–6 h after initial drug administration and regularly thereafter until dose titration is completed. Patients must not be treated with fluid restriction simultaneously in order to prevent overcorrection. Two prospective, multicenter, double-blind, placebo-controlled trials (SALT-1 and -2) investigated the impact of tolvaptan on serum sodium in 448 patients with eu- or hypervolemic hyponatremia [74]. Patients with acute hyponatremia, severe symptoms, hypothyroidism or adrenal insufficiency were excluded; the average serum sodium was 129 mmol/l. After starting with 15 mg, the dose was raised to 60 mg within 4 days and maintained until day 30. Change in the average daily area under the curve for the serum sodium concentration from baseline until day 4 and until day 30, the primary end points, as well as absolute sodium concentrations were significantly higher compared with the placebo-treated control group and significantly more patients became normonatremic in the tolvaptan group. These differences were pronounced in the subgroup of patients with SIADH. With regard to safety and reported side effects, there were no differences between the two groups. In order to investigate the long-term efficacy of tolvaptan, 111 patients from the SALT trial were continuously treated with tolvaptan for a mean follow-up of 701 days (SALTWATER trial) [75]. Mean sodium levels were >135 mmol/l

throughout the observation period, which was interpreted as maintained efficacy of tolvaptan in chronic use. It has to be emphasized that vaptans have only been investigated in controlled clinical trials in patients with mild-to-moderate hyponatremia and should, therefore, not be used in acute hyponatremia or severely symptomatic cases. Recently, there has been a report concerning possible liver toxicity of tolvaptan after three patients developed significant elevations in alanine aminotransferase and total bilirubin in a trial investigating the impact of high doses of tolvaptan in patients with autosomal dominant polycystic kidney disease [76]. As a consequence, the FDA has now withdrawn approval for the usage of tolvaptan in liver cirrhosis and limited the duration of treatment to 30 days.

Although fluid restriction continues to represent the mainstay in the treatment of SIADH, tolvaptan can be used with benefit in patients in which fluid restriction is not feasible or where fluid restriction is not sufficiently effective. A possible indication for primary initiation of tolvaptan could, thus, be the situation in which the urine:plasma:electrolyte ratio (the equation below) is >1 (or maybe even >0.5).

$$\frac{(Na^+ + K^+)_{urine}}{Na^+_{serum}}$$

At least in most SIADH cases, hyponatremia has to be viewed as a transitional phenomenon that subsides once the underlying cause is treated properly. For this limited, period tolvaptan (or vaptans in general) might become the treatment of choice providing the physician with an easy-to-handle tool, particularly when concomitant therapies; for example, chemotherapy, make fluid restriction difficult.

Vaptans can also be applied in patients with hyponatremia secondary to heart failure (not approved by the EMA). Often, higher doses are needed in these hypervolemic patients compared with patients with SIADH. To date, however, there are no solid data on whether treatment of hyponatremia in these patient populations has a beneficial impact on mortality [69].

Conclusion

Optimal management of hyponatremia includes detection of acute life-threatening situations and initiation of appropriate emergency treatment with 3% saline; identification of the underlying cause of the disorder in the less severe cases or when immediate danger has subsided; and providing a therapy that is effective but does not harm the patient by overly rapid correction of sodium levels. There are various conditions that can induce hyponatremia, most of which are mediated by an excessive antidiuretic response. Thorough examination of the patient's volume status and urine chemistry assessment help in classifying the hyponatremia. In recent years a new class of drugs, vaptans, has entered the scene that block the ADH action at the V_2 receptor and promote excretion of water. Given the various disadvantages of other treatment options in terms of effectiveness, adverse effects or handling, vaptans, particularly the orally available tolvaptan is becoming increasingly popular. Notwithstanding, vaptans are very expensive, in the case of tolvaptan approximately US$250 or €110 per tablet, and one must certainly weigh this price against the advantages. From this perspective, it should also be considered that it has never been demonstrated that correction of hyponatremia, regardless of the therapy option used, has a beneficial impact on mortality. However, at least with respect to transient hyponatremia, economic cost-offset models show that the use of vaptans may be cost effective by shortening length of hospital stay and reducing resource usage. Further research on this issue is certainly warranted [68].

Future perspective

Recent investigations challenge the concept of asymptomatic hyponatremia, most commonly seen in chronic idiopathic SIADH in the elderly. It has been shown that mild-to-moderate reduction of serum sodium levels lead to marked gait instability and frequent falls and fractures and may even promote osteoporosis which, in turn, also contributes to the high incidence of fractures. We have also known for a while that subtle (and not so subtle) signs of cognitive impairment and mood instabilities are often found in such patients and were maybe falsely attributed to old age or concomitant dementia in the past. So far, it is not known whether treatment of chronic mild-to-moderate hyponatremia has an impact on these signs and symptoms or which subset of patients might benefit. However, with the new drugs at hand, this seems feasible and, consequently, appropriate trials are warranted. Furthermore, with growing experience, the application of

vaptans in more severe cases of hyponatremia is tempting, and further investigation to this end is to be expected.

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