



Clinical aspects of symptomatic hyponatremia

Dirk Weismann¹, Andreas Schneider¹ and Charlotte Höybye^{2,3}

¹Department of Internal Medicine I, Intensivecare Unit, University Hospital of Würzburg, Würzburg, Germany

²Department of Endocrinology, Metabolism and Diabetology, Karolinska University Hospital, Stockholm, Sweden

³Department of Molecular Surgery and Medicine, Karolinska Institute, Stockholm, Sweden

Correspondence should be addressed to D Weismann
Email
weismann_d@ukw.de

Abstract

Hyponatremia (HN) is a common condition, with a large number of etiologies and a complicated treatment. Although chronic HN has been shown to be a predictor of poor outcome, sodium-increasing treatments in chronic stable and asymptomatic HN have not proven to increase life expectancy. For symptomatic HN, in contrast, the necessity for urgent treatment has broadly been accepted to avoid the development of fatal cerebral edema. On the other hand, a too rapid increase of serum sodium in chronic HN may result in cerebral damage due to osmotic demyelination. Recently, administration of hypertonic saline bolus has been recommended as first-line treatment in patients with moderate-to-severe symptomatic HN. This approach is easy to memorize and holds the potential to greatly facilitate the initial treatment of symptomatic HN. First-line treatment of chronic HN is fluid restriction and if ineffective treatment with tolvaptan or in some patients other agents should be considered. A number of recommendations and guidelines have been published on HN. In the present review, the management of patients with HN in relation to everyday clinical practice is summarized with focus on the acute management.

Key Words

- ▶ hyponatremia
- ▶ clinical

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Introduction

Hyponatremia (HN) is the most common electrolyte disturbance in hospitalized patients constituting at least about 30% of patients in medical, surgical and psychiatric wards (1, 2). The syndrome of inappropriate antidiuresis (SIAD) accounts for about 50% of all cases, whereas HN in cirrhosis and congestive heart failure ranges from 20% to 25%, each (3). In euvoletic patients, SIAD accounts for about 95% of cases.

Two major complications are framing the clinical spectrum of hyponatremia (HN) (4): first, cerebral edema due to untreated HN, and second, cerebral damage due to overcorrection of HN. Balancing the risks and benefits of treatment against non-treatment was – and still is – a challenge (5, 6). The perception, that acute and chronic HN need different treatment, has greatly improved the

care of HN patients since the eighties (7). Today, it is accepted, that chronic HN is associated with increased morbidity and mortality (8, 9), whereas the long-term benefits of increasing serum sodium (sNa) in chronic HN is still unclear (10). In the presence of overt HN-associated symptoms, instead, the need of (urgent) treatment has since long been accepted (6, 11). During the years, there has been discussions regarding the maximum rate of correction, which can safely be applied, and a gradual decrease in recommended upper limits over time can be observed (10, 12).

HN is a complicated condition with a large number of etiologies and treatment options. From a practical point of view, the treating physician needs to know, which symptoms qualify for which treatment, and which



measures comply with the steadily decreasing range of accepted maximum increases in sNA. A number of recommendations and guidelines have been published for the guidance on HN. The aim of the present review was to summarize the management of patients with HN in relation to everyday clinical practice with focus on the acute management.

Pathophysiology

HN, defined as a sNA <135 mmol/L, is primarily a disorder of water balance, with a relative excess of body water compared with total body sodium (13). In most cases, an altered vasopressin (ADH) regulation is responsible (14). Vasopressin regulates the reabsorption of water by increasing the permeability of cell membranes via aquaporins in the collecting duct of the kidney (15). The release of vasopressin from the posterior pituitary gland is regulated by the osmolality of the serum (15). In this context, it is important to differentiate between total osmolality and effective osmolality (tonicity). Total osmolality is defined as the concentration of all solutes in a given weight of water (mOsm/kg), and effective osmolality refers to the number of osmoles that contribute to water movement between the intracellular and extracellular compartment (13). Only effective solutes create osmotic pressure gradients across cell membranes leading to osmotic movement of water between the intracellular and extracellular fluid compartments (13). In the majority of cases, HN reflects low effective osmolality (hypotonicity), which causes cellular edema. HN may also appear as non-hypotonic hyponatremia, and the type of irrigant used, e.g. mannitol, glycine, sorbitol, dextrose, makes a difference in the type of therapy that should be given (13).

The adaptation of the brain to an increase in plasma-osmolality consists of very different and much slower mechanisms compared with the fast adaptations in decreasing osmolality (16, 17). Overcorrection in HN refers to situations in which cerebral adaptations are overstrained, increasing the risk for the osmotic demyelination syndrome (18). Based on this knowledge, sNA is recommended not to raise more than 10–12 mmol/L during the first 24 h, sometimes even a maximum increase of as low as 6–8 mmol/L is advocated (19). Limiting the increase of sNA to 6 mmol/L per day is challenging as sNA changes are often unpredictable (20).

Definitions and classification

To diagnose acute HN, sNA levels must have shown to be normal within the last 48 h before onset of HN (21). All cases that do not meet this criterion are defined as chronic. This distinction is important as acute HN can be corrected rapidly, whereas chronic HN requires a slow, controlled rise in sNA.

The degree of HN can be defined as mild (135–130 mmol/L), intermediate (129–125 mmol/L) and profound (<125 mmol/L). However, the degree of HN poorly correlates with the level of seriousness in the individual patient (22, 23). Instead, the European Practice Guidelines suggest using symptoms as a marker for severity (13). Symptoms range from harmless nausea to life-threatening coma. According to the practice guidelines, we adopted the terms asymptomatic, moderately symptomatic and severely symptomatic to clinically estimate and characterize the severity of HN (Table 1).

It is common to consider HN without overt symptoms to be asymptomatic (24), but it has been questioned whether HN can be asymptomatic at all (25). Data suggest improved quality of life after treatment of chronic HN in cancer patients (26). However, assessment of subtle symptoms usually requires additional evaluation and testing in contrast to the more clear diagnosis of severely or moderately symptomatic HN.

According to the practice guidelines, neurologic impairment triggers intervention with hypertonic saline as described in Tables 2 and 3. In asymptomatic patients or those who have subtle signs of HN, a diagnostic work-up should be initiated before treatment is started (see the 'Asymptomatic hyponatremia' section below).

Table 1 Classification of HN according to symptoms (according to Spasovski *et al.* 2014 (10)).

| Severity | Symptoms |
|--|--|
| Asymptomatic or subtle symptoms after detailed investigation | Concentration and cognitive deficits Gait disturbances Osteoporosis |
| Moderate | Headache Confusion |
| Severe | Nausea (no vomiting) Vomiting Cardiorespiratory distress Somnolence Seizures Coma |

Table 2 Treatment of severely symptomatic hyponatremia.

| | |
|---|--|
| <p>Spasovski <i>et al.</i> 2014 (10)</p> <ol style="list-style-type: none"> 1. First bolus (150 mL 3% saline/20 min) 2. Check sNa 3. Second bolus 4. Check sNa 5. Repeat step 3, if treatment goals are not achieved <p>Treatment goals</p> <ol style="list-style-type: none"> 1. Increase in sNa by 5 mmol/L in the first hour 2. Relieve of severe symptoms <p>Follow-up treatment</p> <ul style="list-style-type: none"> • 0.9% Saline until cause-specific treatment is started • Check sNa after 6 and 12 h and daily afterward. • Limit sNa increase to 10 mmol/L in the first 24 h and to 8 mmol/L thereafter until sNa reaches 130 mmol/L | <p>Sterns <i>et al.</i> 2009 (18)</p> <p>Bolus of 100 mL 3% i.v./10 min</p> <p>Repeat up to 3 times to control symptoms</p> <p>Control of symptoms, which should be the case after increase of sNa by 4–6 mmol/L</p> |
|---|--|

Diagnostic work-up

During the initial work-up, the cause of HN is correctly diagnosed in only about 50% of cases (27). Although the correct diagnosis greatly facilitates treatment (28, 29), physicians should be familiar with the more often and the most importantly occurring clinical situations, such as acute HN, volume depletion, SIAD and adrenal insufficiency. The assessment of volume status is essentially the first step. Overt hypervolemia and hypovolemia can readily be identified, whereas the diagnosis of euvoolemia is often challenging. Infusion of isotonic saline and the subsequent changes in sNa can be used to rule out subtle hypovolemia (see the ‘Overcorrection and deterioration of hyponatremia’ section below). The diagnosis of SIAD is based on the criteria published by Schwartz and Bartter (30) in their initial report on 1957, and, the diagnosis of SIAD is still done based on exclusions. Essential criteria for the diagnosis of SIAD consist of plasma sodium <135 mmol/L, plasma-osmolality <275 mOsm/kg, urine osmolality >100 mOsm/kg, euvoolemia, urine sodium >20 mmol/L (without diuretics), normal thyroid and adrenal function and no treatment with diuretics. Supplemental criteria include low serum concentrations of uric acid and urea, a fractional urea excretion >55%, a fractional uric acid

Table 3 Treatment of moderately symptomatic hyponatremia.

| |
|--|
| <p>Spasovski <i>et al.</i> 2014 (10).</p> <ol style="list-style-type: none"> 1. One bolus of 150 mL 3% hypertonic saline 2. Check sNa at 1, 6 and 12 h and daily thereafter 3. Aim for at least 5 mmol/L increase in sNa in 24 h 4. Limit sNa increase to 10 mmol/L in the first 24 h and 8 mmol/L thereafter until sNa reaches 130 mmol/L 5. Stop offending medications, if possible 6. Initiate prompt diagnostic assessment |
|--|

excretion >12%, the failure to correct sNa after infusion of isotonic saline and a response to fluid restriction (31, 32). Measurement of urine osmolality is important. A high urine osmolality of >500 mOsm/kg puts the patient at risk for a further deterioration of HN after infusion of isotonic saline. Also, fluid restriction is unlikely to be beneficial (see the ‘Fluid restriction’ section below).

Thus, special attention should be given to identify the SIAD as well, so as to exclude adrenal insufficiency.

One study found that out of 139 patients with intermediate-to-profound HN consecutively treated in a tertiary endocrine center, 28 patients (mean age 68 years) had hypopituitarism (33). In 25 of the 28 patients, hypopituitarism was not recognized before work-up for HN. Importantly, 75% had nausea or vomiting and 36% had impaired consciousness or coma. None of these patients had hyperkalemia, and also patients with primary adrenal insufficiency and HN normal potassium levels have been found (34). Thus, normokalemia in hyponatremic patients cannot rule out adrenal insufficiency. Cortisol is secreted in a certain diurnal rhythm, and single measurements are difficult to evaluate. A random s-cortisol of 440–450 nmol/L (15.9–16.3 µg/dL) or higher will often exclude adrenal insufficiency (33, 34). To rule out adrenal insufficiency, stimulation tests are needed (35), but in the acute situation, administration of hydrocortisone therapy should be initiated as soon as adrenal insufficiency is suspected. The basic laboratory evaluation is summarized in Table 4.

The more symptomatic a patient with HN is, the less important is the diagnostic work-up, and prompt treatment should be initiated according to Tables 2 and 3 (see the ‘Hypertonic sodium chloride infusion’ section below).

Table 4 Basic diagnostic laboratory evaluation.

| Analyte | Comment |
|-----------------------------|---|
| P-glucose | Pseudohyponatremia |
| S-osmolality | Confirm hypotonic HN; compare with urine osmolality |
| U-osmolality | >100 mOsm/kg points to SIAD <200 mOsm/kg in primary polydipsia |
| U-Na and U-K (spot-check) | U-Na <15 mmol/L proves a reduced arterial blood volume, e.g. in exsiccosis, liver cirrhosis |
| S-Kalium | Hypokalemia is a risk factor for ODS |
| Liver enzymes, S-creatinine | Liver disease, renal failure |
| Random cortisol and ACTH | Adrenal insufficiency |
| TSH, fT4, fT3 | Hypothyroidism |

ODS, osmotic demyelination syndrome; SIAD, syndrome of inappropriate antidiuresis.

Advanced diagnostic approach

It may be difficult to differentiate primary polydipsia from SIAD in euvoletic patients with a urine osmolality of >100 mOsm/kg. Here, the combined evaluation of urine osmolality and serum copeptin may be a reliable marker with a sensitivity and specificity of 100%. Copeptin is derived from a pre-pro-hormone, consisting of vasopressin, neurophysin II and copeptin. Thresholds to diagnose primary polydipsia are diluted urine of less than 200 mOsm/kg and a suppressed copeptin of less than 3 pmol/L (36). The SIAD, in turn, can accurately be diagnosed using the fractional urea excretion (37).

Treatment of symptomatic hyponatremia

Treatment goals in symptomatic hyponatremia

Severely symptomatic HN as defined in Table 1 is a medical emergency and physicians must make themselves familiar with the treatment. In the two Tables 2 and 3, two recently published recommendations are summarized. Usually an increase of sNa by 5 mmol/L is sufficient to improve symptoms even in severely symptomatic patients (38). Therefore, the first-hour goal in severely symptomatic HN is to achieve an increase of sNa by 5 mmol/L together with a significant clinical improvement in symptoms. In all other cases, the increase should be limited to 10–12 mmol/L in the first 24 h and to 8 mmol/L/day in the following days until a sNa of 130 mmol/L is obtained. Limiting the increase of sNa is difficult, but is greatly facilitated by the introduction of desmopressin (see the

‘Desmopressin’ section below) and infusion of glucose 5% (‘free water’) in the treatment of hyponatremia.

Overcorrection and deterioration of hyponatremia

The risk of overcorrection is especially high in patients with volume and sodium depletion e.g. due to vomiting and diarrhea. Volume resuscitation with isotonic saline in HN may result in an overshooting increase of sNa, because volume resuscitation quickly suppresses ADH secretion (38). In turn, urine volume increases, whereas sodium reabsorption is still at maximum (38). Plasma sodium rises quickly and, therefore, careful monitoring of hypovolemic patients with hyponatremia who receive isotonic saline is mandatory.

The highest risk for an osmotic demyelination syndrome is found in patients with malnutrition, alcoholism, concomitant hypokalemia, advanced liver disease or very pronounced HN (<106 mmol/L) (19). In these patients, more stringent treatment targets are recommended. In the first 24 h, a maximum increase of 8 mmol/L is reasonable with 6 mmol/L/day increase in the following days.

In contrast, uncontrolled deterioration with a further decrease in serum sodium may occur after 0.9% sodium chloride infusion in patients with severe SIAD. Patients with a urine osmolality higher than 500 mOsmol/mL in the presence of HN are prone to a further drop in serum sodium.

Desmopressin

Desmopressin administration to limit sNa increase has been recommended for a long time (21). A very recent review on the use of desmopressin in HN identified three treatment strategies (19): proactive, reactive and rescue. Proactive was defined as early administration, reactive as administration as soon as a change in sNa or urine output was documented and rescue was defined as administration after treatment targets are exceeded. According to the authors, the overall quality of the reviewed studies was poor, and the proactive approach was based only on one study from a specialized center (39). However, in the proactive group, only 27.6% exceeded the upper limit of sNa correction of 8 mmol/day in the high-risk population compared with 87.9% in the reactive group. The proactive approach was combined with the infusion of 3% hypertonic saline, occasionally with initial bolus infusion. Most patients received desmopressin 2 µg every

8 h either intravenously or subcutaneously. Hypertonic saline (3%) was titrated and stopped whenever a 6 mmol/L increase was achieved (39).

An observational study on 20 patients treated for severely symptomatic HN in an ICU described the reactive and rescue approach to limit sNA increase (40). Desmopressin doses ranged between 2–4 µg, repeated dosing was necessary in 12 of 20 patients. The median dosing interval was 25 h. In 11 patients, sNA was re-lowered because the 24-hour limit was exceeded.

Overall, the combined administration of hypertonic saline and desmopressin seemed to facilitate the correction of hyponatremia, and especially, the proactive strategy is a promising approach to prevent overcorrections.

Hypertonic sodium chloride infusion

The use of 3 and 5% saline was reported as early as during the initial characterization of SIAD by Schwartz and Bartter (41). Since then, the use of 3% hypertonic saline has been widely recommended for the correction of profound HN (21). Saline concentration higher than 5% was used in other conditions, but is not evaluated for the treatment of HN. For example, small volumes (i.e. 250 mL) of a 7.5% saline have been tested during trauma and shock (42). Infusion of 23.4% and even 30% saline has been reported for the treatment of refractory intracerebral hypertension (43, 44). However, changes in sNA are inconsistently reported in these studies. In one study, the use of 7.2% saline hydroxyethyl starch (200/0.5) with a rate of 1.4 mL/kg and a mean infused volume of 100 mL resulted in a maximum increase in serum sodium from 143 (136–148) mmol/L to 148 (144–153) mmol/L (45).

The concept of bolus administration was first introduced for treatment of HN after endurance exercise (46) and has later been advocated by Sterns and coworkers (18). In the European Guidelines, a bolus infusion is defined as 150 mL of 3% hypertonic saline (13). Although these recommendations are not based on robust clinical data, clinicians may favor this approach due to its simplicity in daily practice.

A recent study (47) investigated the infusion of 500 mL 3% saline over 6 h in patients with a sNA <130 mmol/L and signs of hyponatremic encephalopathy consistent with moderate or severe symptoms. They documented a controlled increase from 114 ± 0.8 mmol/L to 123.9 ± 1 mmol/L at 24 h and 128.3 ± 0.8 mmol/L at 48 h. In these 64 patients, neurologic symptoms improved within hours, and no osmotic demyelination was

observed. Five patients had significant overcorrection with an increase of sNA ≥ 25 mmol/L in 48 h. Desmopressin was not used in this study (47).

Acute hyponatremia

Resorbing irrigate fluids in e.g. transurethral prostate surgery (48), hysteroscopic surgery (49) or during preparation for colonoscopy (50) can cause acute HN. Usually, a normal sNA level from the same day or the day before will document the acute fall in sNA. In one patient, even correction of sNA from 74 mmol/L to 130 mmol/L within 7 h was reported without the occurrence of neurologic deficits (49). In this case, pulmonary edema developed during hysteroscopic surgery together with an acute drop in sNA. Correction was achieved by the administration of furosemide 40 mg together with the infusion of 500 mL of 3% hypertonic saline for 1 h (sNA was 103 mmol/L thereafter) followed by the infusion of 3% hypertonic saline for additional 6 h (50 mL/h). Hepp and coworkers also reported 8 additional cases from the literature of which 4 were treated with 3% saline (49). The other 4 patients were treated with 7%, 2%, isotonic saline or furosemide, respectively. Thus, existing but limited data indicate that the rapid correction of sNA into the normal range is advisable in acute HN.

Isotonic saline

The osmolality of normal saline (0.9%) is physiological (308 mosmol/L), whereas the concentration of sodium and chloride (154 mmol/L each) is increased. Even though sodium concentration is slightly increased, rehydration without altering electrolytes is a major task of administration of normal saline. Thus, a volume effect has to be taken in to account, when normal saline is used to treat hyponatremia. Physiologically, volume resuscitation decreases ADH, which in turn increases diuresis, whereas renal sodium uptake may still be at maximum (38). As a result, a rapid and unpredictable increase of sNA may be observed, especially, in clinically volume-depleted patients with HN. In SIAD, in contrast, the water of normal saline promotes a further volume expansion, whereas the sodium will be excreted in a highly concentrated urine. The net effect will be a further drop in sNA.

In clinically euvolemic patients, two liters of isotonic saline infused over 24 h can be used to unmask hidden hypovolemia (51). sNA should be monitored every 4–6 h during the infusion. An increase in sNA (>5 mmol/L) points to sodium depletion and discloses SIAD.

Table 5 Offending medications in hyponatremia.

| | |
|-------------------------|--|
| Anticancer agents | Vinca alkaloids; platinum compounds; alkylating agents |
| Antidepressants | Tricyclic AD; SSRI; MAO |
| Anti-epileptic drugs | Carbamazepine; Valproate; Oxcarbazepine |
| Antihypertensive agents | ACEI; Amlodipine |
| Antipsychotic drugs | Phenothiazines; Butyrophenones |
| Diuretics | Thiazides; Indapamide; Amiloride; Loop diuretics |
| Proton pump inhibitors | Omeprazol |

Fluid restriction

Fluid restriction (FR) is a first-line therapy for euvolemic HN patients with SIAD. According to the hyponatremia registry (3), however, FR was the most widely used but the least effective measure to treat HN. Importantly, FR is ineffective if urine osmolality is high (e.g. >500 mOsmol/kg). To decide about FR, it is important to know the ratio of urine to plasma electrolyte concentration, but according to the registry, these parameters were rarely evaluated. Grant and coworkers proposed the use of the Furst formula (urine Na+K/sNa) (52) before commencing FR and to choose between FR of 1L or 0.5L (53). In case of a ratio of >1, FR is not recommended at all and a specialist in HN should be consulted. FR should not be initiated in patients with symptomatic HN, as this is associated with an increase in morbidity and mortality (4). Alternative therapy should be considered if sNA increases <2 mmol/L in the first 24–48 h.

Tolvaptans and other treatments

Tolvaptan is a V2-receptor antagonist approved by the EMA for the treatment of HN in patients with SIAD (54). The FDA approved Tolvaptan on May 2009 for the treatment of hypervolemic and euvolemic HN (sNA>125 mmol/L or less marked symptomatic hyponatremia) including in patients with heart failure and SIAD. Liver enzymes

should be monitored and tolvaptan should not be used in patients with liver cirrhosis.

For a detailed presentation of benefits and limitations, we refer the reader to a very recent review by Tomas Berl (55).

In brief, tolvaptan is the only approved specific treatment for SIAD. It has in randomized placebo-controlled trials been shown to effectively increase sNA and to be safe. Treatment with tolvaptan should be initiated in hospital, and sNA should be monitored to avoid rapid overcorrection. Currently, tolvaptan is not recommended in patients with severely symptomatic HN. Treatment with tolvaptan might be indicated for long-term treatment depending on the underlying course of SIAD. Improved survival after correction of asymptomatic HN has not yet been shown and need to be addressed in future studies. Treatment with tolvaptan in SIAD is recommended in all guidelines except the European Society of Endocrinology's guideline.

Other non-specific available treatments are urea, demeclocycline and lithium. Demeclocycline is licensed for treatment of chronic SIAD in France and UK, whereas urea and lithium are not licensed in any country. Previous reports have suggested that urea can also be used to treat hyponatremia (56, 57). Moreover, Kengne and coworkers recently showed that rapid correction of severe hyponatremia with urea in rats might carry a lower risk of the osmotic demyelination syndrome (ODS) than hypertonic saline or vaptans, despite similar increase in serum sodium obtained by the three drugs (58). To date, the underlying mechanism for the decreased risk of brain complications is not well understood and further investigations are needed. Treatment with urea for SIAD is recommended in the European Society of Endocrinology's guideline. However, the evidence for treatment with urea as well as with demeclocycline and lithium for HN is limited, and the support for a generalized use of these drugs is weak.

Table 6 Examples for causal therapy in hyponatremia.

| Cause | Treatment | Volume status | Comment |
|--|--------------------------------|------------------------|---------------------------------------|
| Hypertonic dehydration (e.g. vomiting, diarrhea) | Volume resuscitation 0.9% NaCl | Hypovolemic | Overcorrection likely! |
| SIAD | FR (?) Vaptans | Euvolemic | Deterioration with NaCl 0.9% possible |
| Adrenal insufficiency | Glucocorticoid substitution | Euvolemic | Overcorrection likely! |
| Congestive heart failure | Loop diuretics | Hypervolemic | |
| Offending medications | Change drug | Euvolemic | |
| Primary polydipsia | FR | Hypervolemic/euvolemic | |

FR, fluid restriction.

Asymptomatic hyponatremia

A cause-specific treatment is recommended in asymptomatic HN. Because the etiology of HN includes a multitude of conditions and therapies (13, 59), a diagnostic work-up is essential. Offending medications should be discontinued, if possible (Table 5). The clinical practice guidelines recommend against treatments with the sole aim of increasing sNa (13). The UK panel of experts does not explicitly comment on this constellation because their algorithm is not symptom based (53). However, the proposed algorithm can be used to identify the underlying diagnosis (see also Table 6). Fluid restriction is recommended in case of euvoemia, and the UK expert panel algorithm guides in the appropriate degree of fluid restriction according to the electrolyte-free water clearance (52).

Conclusion

HN has received an increased attention during the last few years, and the literature has increased correspondingly. Therapies for acute and chronic HN differ considerably, and the risk for overcorrecting chronic HN requires a thorough evaluation of the individual patient. HN can be caused by a large number of underlying diseases and an individualized treatment is necessary, which is a challenge in a stressful acute situation. In such situations, identification of patients with symptomatic HN is useful and administration of hypertonic saline bolus may greatly facilitate the initial treatment. An increase in sNa is recommended to be limited to 10–12 mmol/L during the first 24 h and to 8 mmol/L/day during the following days until a sNa of 130 mmol/L is obtained. In case of overcorrection and thereby an increased risk of osmotic demyelination, desmopressin and infusion of glucose 5% can be used. First-line treatment of subtle symptomatic chronic HN is fluid restriction and in case of refractory HN, treatment with vaptans should be considered. The care for patients with HN is complicated, and a careful individual evaluation is required for obtaining the right management.

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