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Hyponatremia in the emergency department

Gregor Lindner [a,b,*], Christoph Schwarz [c], Michael Haidinger [a], Svenja Ravioli [a]

[a] Department of Internal and Emergency Medicine, Buergerspital Solothurn, Switzerland
[b] Department of Emergency Medicine, Inselspital, University Hospital Bern, Switzerland
[c] Department of Internal Medicine I, Pyhrn-Eisenwurzen Klinikum, Steyr, Austria

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ABSTRACT

Hyponatremia, defined as a serum sodium <135 mmol/L, is frequently encountered in patients presenting to the emergency department. Symptoms are often unspecific and include a recent history of falls, weakness and vertigo. Common causes of hyponatremia include diuretics, heart failure as well as Syndrome of Inappropriate Antidiuresis (SIAD) and correct diagnosis can be challenging. Emergency treatment of hyponatremia should be guided by presence of symptoms and focus on distinguishing between acute and chronic hyponatremia.

1. Background

Hyponatremia is the most common electrolyte disorder in clinical medicine [1]. It affects up to 10% of patients on hospital admission [2]. The mechanisms leading to hyponatremia are complex and cause confusion and misconceptions in physicians dealing with the electrolyte disorder. Since treatment of hyponatremia is guided by the underlying mechanism, a thorough understanding of the pathophysiology is crucial to initiate successful treatment. This review will provide an overview on hyponatremia, its epidemiology, pathophysiology, symptoms and therapy with special regard to patients presenting to the emergency department. The recommendations on management of hyponatremia are in accordance with the European clinical practice guideline from 2014, which is supported by three societies [3]. It should be noted that the American guidelines published in 2013 are very similar and differ relevantly only in details not central for the emergency physician (e.g. use of vasopressin-antagonists, urea and loop diuretics for free water clearance) [4,5].

2. Definition

Hyponatremia is defined by a decrease of serum sodium below the respective laboratory cut-off, which can vary between institutions. Most commonly, a serum sodium below 135 mmol/L defines hyponatremia – a definition supported by the European clinical practice guideline [3]. Occurrence of symptoms is strongly linked to the rapidity of hyponatremia development and a categorization into mild (130–135 mmol/L), moderate (125–129 mmol/L) and profound (<125 mmol/L) was suggested [3].

Emergency physicians should be aware that significant variations in sodium levels between serum and whole blood can occur [6]. Variations of up to four mmol/L between point-of-care and central laboratory measurements may be less important for diagnosis but are unacceptable for serial measurements during course of correction [6,7].

3. Epidemiology of hyponatremia in the emergency department

In patients presenting to the emergency department (ED), prevalence of hyponatremia varies between 3% and 10%, probably depending on the setting and demographics of the local population [2,8]. In special patient populations such as the elderly, hyponatremia was even more common at presentation to the ED [9]. Studies focusing on the prevalence of hyponatremia according to patients' age clearly demonstrated a dramatic increase in prevalence from patients between 16 and 21 years (2%) to patients aged >80 years (17%) [10]. Possible reasons for the higher prevalence of hyponatremia in the elderly are the higher daily rate and number of medications used in this population, comorbidities and a decreased concentration/dilution spectrum of the kidneys and consequently their reduced capacity to excrete diluted urine [11-13]. Moreover, prevalence of hyponatremia in emergency patients can vary seasonally: a higher prevalence was found during heat periods, when heat might trigger increased ingestion of hypotonic fluids

* Corresponding author at: Department of Internal and Emergency Medicine, Buergerspital Solothurn, Schoengruenstrasse 42, 4500 Solothurn, Switzerland.
E-mail address: lindner.gregor@gmail.com (G. Lindner).

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replacing relative hypertonic fluid loss [14]. This finding appears to be even more prominent for elderly patients [15]. In addition, patients with acute or acute on pre-existing chronic kidney disease at presentation to the ED were found to have a significantly higher likelihood of suffering from hyponatremia with prevalence rates as high as 30% for those with acute on chronic kidney disease [16].

In view of these data, emergency physicians should suspect hyponatremia in vulnerable patient groups such as the elderly, patients taking diuretics, especially aldosterone-antagonists and thiazide(−like) diuretics, or patients with acute and/or chronic kidney disease. The seasonal variation with a trend towards higher hyponatremia rates during periods of heat should be kept in mind too.

4. Pathogenesis of hyponatremia

4.1. Serum sodium concentration

The mechanisms leading to hyponatremia are manifold and often confusing. A thorough understanding of the pathogenesis is crucial for understanding the electrolyte disorder and initiating correct treatment.

Serum sodium is determined by the total amount of exchangeable sodium and potassium as well as the total body water as can be seen in the Edelman equation [17]:

$$\left[Na^{+}\right] = \frac{Na^{+}_{exchangeable} + K^{+}_{exchangeable}}{\text{Total body water}}$$

It is important to note that there are osmotically inactive, not exchangeable sodium stores in the body which are not included in the formula [18]. Potassium is included in the formula since the Edelman equation implies equal solute concentrations across cell membranes with sodium being the main extra- and potassium being the main intracellular solute. Since water can move through cell walls, the solute concentration is equal intra- and extracellularly [18].

According to the Edelman equation, hyponatremia can only develop if there is either a loss of sodium, a gain of water or a combination of both. It can be concluded that an increase in total exchangeable potassium can influence serum sodium concentration. In the ED, this is important when treating a patient with both hyponatremia and hypokalemia: Substitution of potassium can lead to a higher correction rate of serum sodium. Additionally, hyponatremia can develop by a shift of free water from the intra- to the extracellular space, possibly caused by any osmotically active substance not freely passing the cell membrane. Hyperglycemia is the most important cause of this phenomenon: Traditionally, it was suggested that serum sodium declines 1.6 mmol/L for every 5.6 mmol/L (100 mg/dL) rise in serum glucose [19]. However, more recent studies show a wide variety of results depending on various factors such as anthropometry of the individuals studied [19,20].

4.2. Water homeostasis

As expressed by the Edelman equation, the serum sodium concentration is a result of the ratio of the amount of sodium and total body water [17]. Therefore, serum sodium reflects the state of water homeostasis. Development of thirst, drinking, thirst satiation and the actions of anti-diuretic hormone (ADH) are essential for regulation of body water [3]. If plasma osmolality rises over approximately 285 mosm/kg, ADH is secreted and at slightly higher values thirst develops [21,22]. Consequently, fluid will be ingested and by mediation of ADH, aquaporines, water conducting channels, will be expressed in the collecting duct of the kidney to reabsorb free water from the urine. Thereby, plasma osmolality will reach the normal range again. It is noteworthy, that ADH secretion is also triggered by stretch-sensitive baroreceptors: Even small reductions in blood pressure can lead to increased ADH secretion [23]. In case of more severe hypovolemia, baroregulation can override osmoregulation leading to ADH secretion despite marked hypoosmolarity [24].

5. Classification of hyponatremia

Various competing approaches exist to classify the etiologies of hyponatremia. However, since most relevant and clinically seen forms of hyponatremia are hypotonic, we prefer a classification of hyponatremia on basis of volume state. Limitations and pitfalls of this approach are outlined below.

5.1. Determination of volume status

Volume depletion, defined by a loss of sodium (and fluid), occurs through hemorrhage, gastrointestinal or renal losses and should be distinguished from dehydration, which is caused by a pure loss of free water and usually accompanied by hypernatremia and consequent hyperosmolarity [25]. Distinguishing the two entities is important as dehydration should be addressed by mainly substituting free water, while volume depletion should be treated by administration of isotonic crystalloids [26].

Clinical signs of hypovolemia include severe postural dizziness, a postural increase in pulse rate exceeding 30 beats/min, a dry axilla, dry mucous membranes and a furrowed tongue [25]. Skin turgor and capillary refill time had no proven diagnostic value in the assessment of volume status in adults [25].

Laboratory parameters such as serum creatinine, urea or hemoglobin point to the presence of dehydration or hypovolemia, but should be interpreted with caution and only if baseline values are available.

Point-of-care ultrasound either alone or in combination with passive leg raising is suggested for the evaluation of volume status [27]. Usually, diameter and collapsibility of large veins is assessed by ultrasound, but some authors also propose to include large arteries in the evaluation [27]. Although some studies appear promising, systematic reviews show limited prognostic ability of ultrasound evaluation of the inferior vena cava [28].

Taken together, for the emergency physician it appears crucial to evaluate volume status by applying a combination of different tests: clinical signs of which postural blood pressure and heart rate measurements are the mainstay should be combined with laboratory parameters and potentially ultrasound evaluation of large veins ideally paired with passive leg raising. However, it should be noted, that determination of volume status is challenging, methods to do so are discussed controversial and reported sensitivities and specificities are low, which can lead to misinterpretations [3].

5.2. Hyponatremia with reduced volume status

Various mechanisms cause volume depletion, secretion of ADH and consequently hyponatremia.

Diuretics are leading causes of hyponatremia [11]. Diuretic-associated renal sodium loss can induce slight hypovolemia and thus release of ADH – substitution of hypotonic fluid compared to the lost fluid leads to development of hyponatremia. Most importantly, thiazide and thiazide-like diuretics directly cause hyponatremia [3]. The thiazide effects on sodium levels are type- and dose-dependent: hydrochlorothiazide showed the least and chlorthalidone the strongest association with hyponatremia [29,30]. Of note, thiazides can impair free water excretion by volume-induced release of ADH, reduced distal-delivery of filtrate, inhibition of the thiazide-sensitive sodium chloride cotransporter (NCC) impairing maximal urine dilution and increased collecting duct permeability [31]. These factors together can cause a significant impairment of urine dilution capacity. Older age and female sex are important risk factors for the development of hyponatremia in patients taking thiazides, while low body mass index is discussed controversial as a risk factor [32,33]. Thus, in the ED it is crucial to carefully

assess current medication of patients with hyponatremia since thiazide (−like) diuretics are often contained in combination antihypertensive drugs.

Gastrointestinal sodium loss can occur through severe diarrhea. Moreover, severe vomiting triggers renal sodium loss to counteract metabolic alkalosis since sodium needs to be excreted along with bicarbonate in the urine [3]. Sodium can also be lost in significant amounts via the skin through heavy sweating – however, excess drinking of hypotonic fluids plays a major role in addition to transdermal sodium losses under these circumstances [34,35]. Adrenal insufficiency, primary as well as secondary, may lead to hyponatremia by hypovolemia and sodium loss triggered by decreased aldosterone activity [36,37]. Increased levels of ADH were noticed in patients with glucocorticoid deficiency and a loss of hypotonic suppression of the osmostat for secretion of the hormone was described [38]. Kidney disease can induce renal salt wasting: Various chemotherapeutic agents can induce salt wasting nephropathy, for example cisplatin, which appears to directly decrease epithelial sodium channel (ENaC) expression [39,40]. Renal salt wasting is characterized by polyuria, hypovolemia and hyponatremia [39].

Cerebral salt wasting, similar to renal salt wasting, is characterized by hypovolemia, hyponatremia and polyuria but usually occurs as a consequence of intracranial pathologies, trauma or surgery [41]. The mechanisms underlying cerebral salt wasting are incompletely understood and therapy consists of fluid and sodium replacement to maintain volume status and sodium within physiological limits [41].

5.3. Hyponatremia with expanded volume status

In patients with heart failure, the prevalence of hyponatremia is approximately 25% [42-44]. Moreover, hyponatremia on admission was independently associated with adverse outcome and correction of serum sodium proved beneficial in terms of outcome [45]. In heart failure, a reduced effective circulating volume triggering non-osmotic ADH-release and retention of free water cause hyponatremia while activation of the renin-angiotensin-aldosterone system leads to sodium retention [3]. Additionally, angiotensin II leads to increased sense of thirst via stimulation of the osmoreceptor [46]. Hyponatremia thus is the result of an increased sense of thirst, consequent fluid retention by ADH action, which in total outweighs sodium retention.

Cirrhosis of the liver is another common cause of hyponatremia: Splanchnic vasodilation and consequent activation of the renin-angiotensin-aldosterone system together with ADH release in order to compensate for the low effective circulating volume finally lead to hyponatremia [47]. Whether hyponatremia is a prognostic factor for outcome in patients with cirrhosis or whether it is just a marker of disease severity remains not fully clear [48,49].

In patients with nephrotic syndrome, the effective circulating volume may be reduced due to reduced oncotic pressure as a consequence of renal protein loss [50]. As in heart failure and cirrhosis of the liver, activation of the renin-angiotensin-aldosterone system and non-osmotic release of ADH result in the formation of edema and hyponatremia [50].

5.4. Hyponatremia with normal volume status

The syndrome of inappropriate ADH secretion (SIADH) is characterized by a non-osmotic and non-volume-based release of ADH either by the pituitary gland or through ectopic production [3]. Gain of function mutations of the vasopressin V2 receptor were described to cause SIADH, usually associated with low circulating levels of ADH [51,52]. In SIADH, free water is retained and urine is concentrated to a relatively hyperosmolar condition – thus the first diagnostic criterion for SIADH: Urine osmolality >100mosm/kg, but mostly >300 mosmol/kg. For this review, the term SIAD is used to express a syndrome of inappropriate antidiuresis not necessarily associated with increased levels of ADH.

On the one hand, hyponatremia in SIAD is caused by retention of free water through excess ADH secretion (or increased activity, or gain of function mutation of the vasopressin V2 receptor) [3]. On the other hand, the resulting gain in effective circulating volume induces natriuresis – the second diagnostic criterion for SIAD: Urine sodium >40 mmol/L. Additional criteria include a reduced effective serum osmolality, clinical euvolemia, no use of diuretics and the absence of thyroid, adrenal, pituitary or relevant renal insufficiency [53]. Diagnosis of SIAD is challenging for several reasons: Determination of volume state is challenging and controversial as outlined above. Moreover, SIAD can be masked by other causes of hyponatremia: thiazide diuretics can induce SIAD by a significant impairment of urine dilution capacity for example as outlined above [31]. For the emergency physician it is essential to identify patients with potential SIAD to reduce the risk of further decline in serum sodium due to fluid administration. A broad spectrum of diseases, mainly malignancy and pulmonary diseases, medications and symptoms such as pain or nausea can trigger SIAD [53]. In transient SIAD, the trigger might have already disappeared on admission, for example after having experienced violent pain. However, in some cases of SIAD, no specific cause can be identified.

Conditions such as beer drinkers' potomania, primary polydipsia or tea-and-toast-diet-induced hyponatremia are summarized according to the mechanism leading to hyponatremia: a high intake of free water paired with relatively low solute-intake [54,55]. Since free renal water excretion is linked to solute output – at a urine osmolality of 100mosm/kg the kidneys needs to excrete 100 mmol of solutes per liter of free water – hyponatremia can develop through input of large amounts of hypotonic fluids. Considering the pathophysiology of hyponatremia development and the often chronic course in these patients, they are at risk of developing complications of hyponatremia correction [54].

Hypothyroidism is another, but rare cause of hyponatremia and usually only observed in marked cases of thyroid dysfunction with significantly increased TSH levels [3,56].

Table 1 gives an overview of the causes of hyponatremia along with important history features, clinical as well as laboratory findings.

6. Symptoms of hyponatremia

Symptoms attributable to hyponatremia range from mild, unspecific syndromes to severe, life-threatening brain edema [3]. In general, severity of symptoms is linked to the rapidity of hyponatremia development [57]: The faster hyponatremia develops, the shorter the time for the brain to adapt to the newly hypoosmolar environment by reducing its intracellular osmotically active particles [58]. These “regulatory volume decrease” mechanisms act via rapidly compensating pathways including water flow from brain parenchyma into the cerebrospinal fluid and expulsion of electrolytes from the intra- to the extracellular space [59]. These mechanisms can compensate for acute hyponatremia to a limited degree –brain cells can lose a maximum of 20% of their intracellular electrolytes in compensation of a hypoosmolar environment [59]. Therefore, more profound acute hyponatremia leads to significant brain swelling and ultimately death. Then again, slowly developing hyponatremia can be compensated even when serum sodium reaches levels around 100 mmol/L by late adaptation to hypoosmolality by reduction of organic osmolytes in brain cells, which account for approximately 30% of intracellular osmoles [60]. However, since these organic osmolytes play a role in neurotransmission and cellular metabolism, their reduction/loss might contribute to neurological deficits in chronic hyponatremia [59,61].

The difference in compensatory mechanisms occurring acutely (i.e. expulsion of intracellular electrolytes) and slowly (reduction of intracellular osmoles) requires physicians to distinguish between acute and non-acute hyponatremia to direct initial treatment.

In a retrospective analysis from a large ED, nausea, a history of falls, weakness and vertigo were the most common symptoms attributable to

Table 1
Causes of hyponatremia stratified for volume status along with important facts for diagnosis. While FePhosphate stands for fractional excretion of phosphate.

	Cause of hyponatremia	History of present illness	Clinical	Laboratory
Reduced volume status	Gastrointestinal fluid loss	Vomiting, diarrhea	(Postural) hypotension, tachycardia, dry skin/mucous membranes/axillae	Rise in creatinine/urea/ hemoglobin; urine sodium <20 mmol/L; urine osmolality >100 mosm/kg
	Transdermal loss	Exercise, heavy sweating	(Postural) hypotension, tachycardia, dry skin/mucous membranes/axillae	Rise in creatinine/urea/ hemoglobin; urine sodium <20 mmol/L; urine osmolality >100 mosm/kg
	Adrenal insufficiency*	Glucocorticoid use, nausea, vomiting	Weakness, fatigue, weight loss, hyperpig-mentation, (postural) hypotension, tachy-cardia, dry skin/mucous membranes/axillae	Hyperkalemia. hypoglycemia, hypercalcemia, reduced cortisol
	Renal salt wasting [86]	Chemotherapy, polyuria	(Postural) hypotension, tachycardia, dry skin/mucous membranes/axillae	Hyponatremia, high urine volume, urine sodium >30 mmol/L, FePhosphate >20%, absence of prerenal azotemia
	Cerebral salt wasting [41]	Previous cranial trauma or intracranial pathology, polyuria	(Postural) hypotension, tachycardia, dry skin/mucous membranes/axillae	Hyponatremia, high urine volume, urine sodium >30 mmol/L
	Diuretics (mainly thiazide (−like) diuretics and aldosterone antagonists)	Diuretic medication, orthostatic hypotension	(Postural) hypotension, tachycardia, dry skin/mucous membranes/axillae	Hyponatremia, urine sodium >30 mmol/L
Expanded volume status	Heart failure	Dyspnea, orthopnea, recent weight gain	Edema, rales/crackles/wheezing on auscultation, low pulse pressure, hypotension	Hyponatremia, urine sodium <20 mmol/L (CAVE: can be higher with concomitant diuretics use), increased brain natriuretic peptide levels
	Cirrhosis of the liver	Weight gain, increase in abdominal circumference	Ascites, edema, hypotension	Hyponatremia, urine sodium <20 mmol/L (CAVE: can be higher with concomitant diuretics use), increased liver enzymes, bilirubin
	Nephrotic syndrome	Weight gain, changes in urine	Edema	Hyponatremia, urine sodium 20 mmol/L (CAVE: can be higher with concomitant diuretics use), elevated renal function parameters, proteinuria
Normal volume status	SIAD(H)	Malignancy, pulmonary diseases, psychotropic drugs+	Normal volume state if no other cause for edema; symptoms of hyponatremia	Hyponatremia, serum osmolality <275 mosm/kg, urine sodium >40 mmol/L, urine osmolality >100 mosm/kg, normal TSH, normal cortisol, low serum urea, low serum uric acid
	Beer drinkers' potomania/Primary polydipsia	Large amount of ingested hypotonic fluids/beer	Normal volume status, symptoms of hyponatremia	Hyponatremia, serum osmolality <275 mosm/kg, urine osmolality <100 mosm/kg
	Tea and toast diet	Low dietary solute intake, relevant amount of hypotonic fluid	Normal volume status, symptoms of hyponatremia	Hyponatremia, serum osmolality <275 mosm/kg, urine sodium <20 mmol/L
	Hypothyroidism	Fatigue, weight gain, depression, constipation	Normal volume status, bradycardia, dry skin, muscle weakness, puffy face, thin hair, goiter	Hyponatremia, serum osmolality <275 mosm/kg, TSH ↑↑↑

* Depending on the type of adrenal insufficiency it can also be considered to euvolemic.
\+ A detailed overview of potential causes of SIAD(H) is discussed elsewhere.

hyponatremia [2]. Moreover, somnolence, disorientation, headache, seizure and syncope were reported in patients with hyponatremia [2]. Evidence is growing that hyponatremia also induces osteoporosis [62], leads to increased fracture risk even independent of osteoporosis [63] and is an independent risk factor for falls [64]. Especially elderly patients seem to be vulnerable for this vicious circle of adverse consequences of hyponatremia [9,65]. Moreover, hyponatremia was associated with worse results for neurocognitive function and motor performance tests such as the Mini-Mental-State, DemTect or TrailMaking test [66]. Interestingly, neurocognitive function deficits were reversible after correction of hyponatremia implying causality rather than a pure association [67].

For the emergency physician, it is essential to be wary of potential hyponatremia when dealing with elderly patients presenting to the ED with unspecific complaints or falls. Moreover, hyponatremia should be considered a differential in all patients with unspecific complaints such as vertigo, headache or nausea, all the more in patients taking diuretics, especially thiazide (−like) diuretics, aldosterone-antagonists or suffering from malignancy.

7. Diagnosis and diagnostic work-up of hyponatremia in the emergency department

Several diagnostic steps are essential after identification of hyponatremia in the emergency patient: Thorough history taking with a focus on time of symptom onset (if present) and current medication with particular attention to combination antihypertensive agents containing thiazide diuretics, corticosteroids and psychotropic drugs, is crucial. Hyponatremia-associated symptoms should be systematically assessed and absence of symptoms clearly documented. Careful determination of volume status including multiple tests as outlined above is required. A review of recently performed laboratory tests can help in distinguishing acute from chronic hyponatremia. Glucose should be measured to rule out hyperglycemia-induced hyponatremia, considering that the decrease in serum sodium can vary significantly depending on body composition [20]. Moreover, the higher the blood glucose the smaller the decline in serum sodium will be due to cellular dehydration. Since feared consequences of hyponatremia such as brain edema are linked to tonicity and not the absolute serum sodium level,

hyperglycemia induced hyponatremia does not require sodium correction, at least if it does not persist after normalization of blood glucose [58]. Pseudohyponatremia, a laboratory phenomenon caused by abnormally high lipid or protein values, can be avoided by sodium determination by an ion-selective electrode. Potassium levels should be checked since hypokalemia is a common concomitant finding in hyponatremic patients taking diuretics [29]. In addition, osmolality, creatinine, urea and TSH should be determined from serum. Serum cortisol levels should be ordered in patients with suspected adrenal insufficiency. Acquiring a urine sample to analyze urine chemistry including osmolality and sodium concentration is crucial to evaluate the response to hyponatremia. Ideally, the urine sample is acquired before treatment initiation, except for patients with severe symptomatic hyponatremia, who need treatment immediately.

8. Management of hyponatremia in the emergency department

The first step in the management of hyponatremia after ruling out hyperglycemia-induced hyponatremia is to clarify whether the sodium disorder is symptomatic. The treating physician should be confident that the symptoms are attributable to hyponatremia and not to a different cause before treatment is initiated [68]. The following treatment approach is mainly based on the current clinical practice guideline on hyponatremia [3]. Fig. 1 shows a management algorithm for hyponatremia in the ED.

8.1. Symptomatic hyponatremia

According to the European clinical practice guideline, acute hyponatremia (i.e. onset <48 h) with severe or moderately severe symptoms should be immediately treated by infusion of 150 ml of 3% NaCl solution over 20 min followed by a repeat measurement of serum sodium 20 min later [3]. Moderately severe symptoms were defined as nausea with vomiting, confusion, and headache whereas severe symptoms were defined as vomiting, cardiorespiratory distress, abnormal and deep somnolence or coma as well as seizures [3]. The American guideline also recommends treatment of acute hyponatremia with mild to moderate symptoms [5]. A weight-based infusion approach (2 ml/kg body weight) can be applied when administering 3% NaCl. Slow continuous administration of hypertonic saline did not differ in terms of rate of overcorrection compared to rapid intermittent bolus of 3% saline [69]. A rapid increase in serum sodium of 5 mmol/L is the treatment goal in patients with symptomatic hyponatremia for which administration of 3% saline can be repeated. Serum sodium should be checked at least 6 and 12 h after symptom improvement and daily afterwards until normalization [3]. In case of repeated 3% saline infusion, serum sodium should be checked more frequently (every 4 h). In total, a correction of serum sodium at a maximum of 8–10 mmol/L/24 h should not be exceeded [3]. We recommend that treatment of patients with symptomatic hyponatremia after discharge from the ED be located in a setting where frequent measurements of serum sodium and a narrow clinical observation can be performed, e.g. intermediate care unit. Diagnostic work-up (i.e. urine chemistry) should parallel treatment. After symptom relief, the underlying reason of hyponatremia should be treated.

8.2. Asymptomatic hyponatremia

In presumably asymptomatic hyponatremia, it should be determined if the fall in serum sodium occurred acutely (<48 h) or not.

Acute hyponatremia should only be assumed in case of a documented fall of serum sodium during the last 48 h. The current practice guideline for hyponatremia recommends administration of 150 ml 3% saline (or 2 ml/kg body weight) over 20 min followed by a re-check of

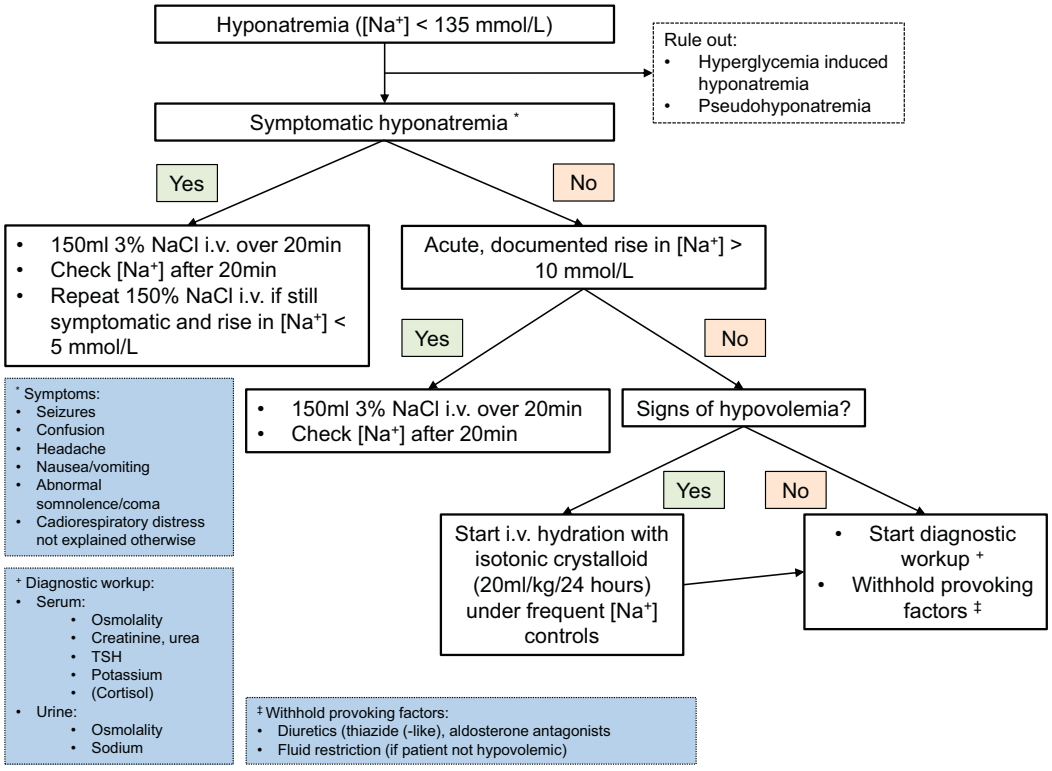

Fig. 1. Management algorithm for hyponatremia in the emergency department.

serum sodium after 4 h in case of a documented acute fall of serum sodium >10 mmol/L [3].

In case of non-acute, asymptomatic hyponatremia in hypovolemic patients, e.g. diarrhea, dehydration by excess diuretic treatment, etc. hydration should be started using isotonic crystalloids at a dose of 20 ml/kg/24 h [3,57,70]. In hypervolemic patients with non-acute, asymptomatic hyponatremia (e.g. heart failure or cirrhosis of the liver) fluid restriction should be initiated unless there is a contraindication [3].

Provoking factors such as non-essential fluids, diuretics, namely thiazide (−like) or potassium-sparing diuretics, or other drugs potentially inducing hyponatremia should be withheld by the emergency physician if possible. Diagnostic work-up as outlined above should be started as soon as possible, ideally before treatment initiation to avoid falsification of results.

Concerning further, cause-specific treatment of hyponatremia, we refer to the current clinical practice guideline [3]. Treatment of acute and symptomatic hyponatremia as well as the initiation of correct diagnostic steps should be the focus of the emergency physician. We explicitly argue against initiation of therapeutic measures in the ED for asymptomatic, non-hypovolemic patients with hyponatremia before the performance and interpretation of diagnostic measures to avoid falsification of diagnostic results and further aggravation of hyponatremia, e.g. as potentially induced by fluid administration in patients with underlying SIAD.

Table 2 gives an overview of the key messages for the emergency physician concerning the diagnosis, workup and treatment of hyponatremia.

8.3. Overcorrection of hyponatremia

Overcorrection of hyponatremia is defined as an increase in serum sodium exceeding 8–10 mmol/L/24 h [3]. Risk factors for overcorrection include a low starting value of serum sodium, associated low serum potassium level, low body mass index, chronic alcohol abuse, presence of cancer and severe symptoms attributable to hyponatremia [71-73]. Furthermore, patients with a higher urine output after treatment start had an increased risk for overcorrection [68]. Concomitant potassium substitution in case of hypokalemia can result in rapid increase of serum sodium levels through sodium-potassium exchange by the Na-K-ATPase [71]. Therefore, patients with hypokalemia are prone to overcorrection and complications associated with correction of hyponatremia [71,74-76].

If overcorrection is confirmed, prompt measures should be taken to re-lower serum sodium below the target correction rate of 8–10 mmol/L/24 h period [3]. *Re*-lowering serum sodium rapidly after overcorrection can prevent the occurrence of osmotic demyelination syndrome as shown in animal models and case reports [59,77,78]. Desmopressin was suggested to be effective in preventing or treating overcorrection of hyponatremia and proved successful in at least one retrospective study [79]. Infusion of free water in form of dextrose-5 solutions (2–3 ml/kg/h) can be used in adjunct to desmopressin (2–4 μg every 6-8 h) or alone to contain the rise in serum sodium or even re-induce hyponatremia in case of overcorrection [80,81].

8.4. Complications

Osmotic demyelination syndrome is a potential complication of a rise in serum sodium occurring too rapidly [58]. It is an expression of the inability of neuronal cells to adapt to rapid changes in tonicity [82]. Mostly, it occurs during overcorrection of hyponatremia, but the syndrome can also emerge in rapid increases of serum sodium without preceding hyponatremia [83]. Risk factors for the occurrence of osmotic demyelination syndrome include metabolic derangements, liver disease, chronic alcoholism, malnutrition, pregnancy, severe illness and adrenal insufficiency [83].

Table 2
Key messages for the emergency physician regarding the diagnosis, workup and treatment of hyponatremia.

When to think of hyponatremia?	• Patients taking diuretics, especially thiazide (−like) and aldosterone-antagonists • History of heart failure or cirrhosis of the liver • History of malignancy • Pulmonary diseases • Patients with psychiatric conditions
What symptoms are associated with hyponatremia?	• Falls • Weakness • Vertigo • Seizures • Neurocognitive deficits (disorientation, somnolence) • Nausea, vomiting
What diagnostic workup should be initiated in the emergency department?	• Serum: osmolality, potassium, glucose, creatinine, urea, TSH • Urine: osmolality, sodium • Perform a critical review of medications with special consideration of: o Diuretics o Psychotropic drugs
When to initiate acute therapy?	• Patients with moderate to severe symptoms *attributable* to hyponatremia o 150 ml of 3% NaCl i.v. over 20 min o Check serum sodium after 20 min o Repeat 3% NaCl if patient still symptomatic *and* increase in serum sodium <5 mmol/L • Patients with a documented acute fall in serum sodium >10 mmol/L o 150 ml of 3% NaCl i.v. over 20 min o Check serum sodium after 20 min
Other therapeutic measures?	• Withhold provoking medications whenever possible (e.g. thiazide diuretics) • Start i.v. hydration in case of hypovolemia • Perform frequent measurements of serum sodium
Important hints?	• Rule out hyperglycemia induced hyponatremia: [Na^+] declines by 1.6 mmol/L for ever 100 mg/dL increase in blood glucose • Rule out pseudohyponatremia by determination of sodium by a ion-sensitive electrode (blood gas analyzer) – common in extreme forms of hyperproteinemia or hyperlipidemia • Beware of large volumes of i.v. fluids unless patient is obviously hypovolemic in order to avoid further serum sodium decline in case of SIAD(H)
Admit or discharge?	• Severe and/or symptomatic hyponatremia: Admit the patient to a unit where frequent sodium and clinical checks are possible (e.g. intermediate care) • Asymptomatic patients with mild hyponatremia in otherwise stable condition can be treated as outpatients with ambulatory care and further workup

The most common symptom of osmotic demyelination syndrome is altered mental status followed by upper motor neuron pattern weakness [84]. However, symptoms vary widely. Diagnosis is made by clinical suspicion and confirmed by MRI of the brain, where lesions in the pons area can be found [84]. Treatment of osmotic demyelination syndrome includes plasmapheresis, immunoglobulin administration and corticosteroids although evidence is limited [85].

9. Conclusion

Hyponatremia is a common electrolyte disorder in patients presenting to the ED. Common causes include hypovolemia, diuretics, heart

failure, cirrhosis of the liver as well as SIAD. Distinguishing symptomatic from asymptomatic hyponatremia is crucial to start adequate therapy and avoid complications. In asymptomatic patients, initiating adequate diagnostic steps should have priority in the ED since treatment should be diagnosis-guided.

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Credit authorship contribution statement

Gregor Lindner: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Conceptualization. **Christoph Schwarz:** Writing – review & editing, Writing – original draft. **Michael Haidinger:** Writing – review & editing, Methodology, Investigation. **Svenja Ravioli:** Writing – review & editing, Writing – original draft, Supervision, Methodology.

Declaration of Competing Interest

None declared.

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