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Clinical practice guideline on diagnosis and treatment of hyponatraemia

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Abstract Hyponatraemia, defined as a serum sodium concentration <135 mmol/L, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. Hyponatraemia is present in 15–20 % of emergency admissions to hospital and occurs in up to 20 % of critically ill patients. Symptomatology may vary from subtle to severe or even life threatening. Despite this, the management of patients remains problematic. Against this background, the European Society of Intensive Care Medicine, the European Society of Endocrinology and the European Renal Association–European Dialysis and Transplant Association, represented by European Renal Best Practice have developed a Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia as a joint venture of three societies representing specialists with a natural interest in hyponatraemia.

Keywords Hyponatraemia · Hypotonic · Guideline · Diagnosis · Management

1 Introduction and methodology

Hyponatraemia, defined as a serum sodium concentration <135 mmol/L, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. Hyponatraemia is present in 15–20 % of emergency admissions to hospital and occurs in up to 20 % of critically ill patients [1]. It can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening [2, 3] and is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions. Despite this, the management of patients remains problematic. The prevalence of hyponatraemia in widely different conditions and the fact that hyponatraemia is managed by clinicians with a broad variety of backgrounds, has fostered diverse institution- and speciality-based approaches to diagnosis and treatment.

Against this background, the European Society of Intensive Care Medicine (ESICM), the European Society of Endocrinology (ESE) and the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA), represented by European Renal Best Practice (ERBP) have developed this Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia as a joint venture of three societies representing specialists with a natural interest in hyponatraemia. In addition to a rigorous approach to methodology and evaluation, we were keen to ensure the document focused on patient-important outcomes and had utility for clinicians involved in every-day practice.

The ERBP methods support team searched The Cochrane Database of Systematic Reviews (May 2011), DARE (May 2011), CENTRAL (May 2011) and MEDLINE (1946 to May, week 4, 2011) for both questions on diagnosis and treatment. To identify limits for the increase in serum sodium concentration above which the risk of osmotic demyelination starts to rise, they searched MEDLINE from 1997 onwards under the assumption that earlier reports would describe more dramatic increases and would not contribute to helping us set an upper limit.

A member of the ERBP methods support team screened all titles and abstracts to discard the clearly irrelevant ones. All members of the guideline development group completed a second screening. All abstracts that did not meet the inclusion criteria were discarded. Any discrepancies at this stage were resolved by group consensus. The methods support team retrieved full texts of potentially relevant studies and two reviewers examined them for eligibility independently of each other. The reviewer duos always included one content specialist and a methodologist of the ERBP methods support team. Any discrepancies were resolved by consensus. If no consensus could be reached, the disagreement was settled by group arbitrage. The evidence for outcomes on therapeutic interventions from included systematic reviews and randomised controlled trials was presented using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/).

The guideline underwent external peer review before publication.

This condensed version of the Clinical Practice Guideline on Diagnosis and Treatment of Hyponatraemia focuses on recommendations on diagnosis and treatment of hyponatraemia, the full version of the guidelines, additionally covering conflict of interest, purpose and scope, methods of guideline development and pathophysiology of hyponatraemia, is available as electronic supplemental material (ESM).

2 Diagnosis of hyponatraemia

2.1 Classification of hyponatraemia

2.1.1 Definition of hyponatraemia based on biochemical severity

We define 'mild' hyponatraemia as a biochemical finding of a serum sodium concentration between 130 and 135 mmol/L as measured by ion specific electrode.

We define 'moderate' hyponatraemia as a biochemical finding of a serum sodium concentration between 125 and 129 mmol/L as measured by ion specific electrode.

We define 'profound' hyponatraemia as a biochemical finding of a serum sodium concentration <125 mmol/L as measured by ion specific electrode.

2.1.2 Definition of hyponatraemia based on time of development

We define 'acute' hyponatraemia as hyponatraemia that is documented to exist <48 h. We define 'chronic' hyponatraemia as hyponatraemia that is documented to exist for at least 48 h. If the hyponatraemia cannot be classified, we consider it being chronic, unless there is clinical or anamnestic evidence of the contrary (Tables 1, 2).

2.1.3 Definition of hyponatraemia based on symptoms

We define 'moderately symptomatic' hyponatraemia as any biochemical degree of hyponatraemia in the presence of moderately severe symptoms of hyponatraemia (Table 1).

We define 'severely symptomatic' hyponatraemia as any biochemical degree of hyponatraemia in the presence of severe symptoms of hyponatraemia (Table 1).

Table 1 (Table 5 of the online document): classification of symptoms of hyponatraemia

Severity	Symptom
Moderately severe	Nausea without vomiting
	Confusion
	Headache
Severe	Vomiting
	Cardio-respiratory distress
	Abnormal and deep somnolence
	Seizures
	Coma (Glasgow Coma Scale ≤8)

The guideline development group wants to underscore that these symptoms can also be induced by other conditions. Clinical and anamnestic data should be taken into account when assessing the causal relation between the hyponatraemia and a certain symptom (i.e. to assess whether the symptom has been caused by the hyponatraemia or the hyponatraemia by the underlying condition/symptom). The less pronounced (e.g. mild) the biochemical degree of hyponatraemia, the more caution should be taken when considering that the hyponatraemia is the cause of the symptoms. This list is not exhaustive, and all symptoms that can be signs of cerebral oedema should be considered as severe or moderate symptoms that can be caused by hyponatraemia

Table 2 (Table 8 of the online document): drugs and conditions associated with acute hyponatraemia (<48 h)

Postoperative phase
Post-resection of the prostate, post-resection of endoscopic uterine surgery
Polydipsia
Exercise
Recent thiazides prescription
3,4-Methyleendioxymethamfetamine (MDMA, XTC)
Colonoscopy preparation
Cyclophosphamide (intravenous)
Oxytocin
Recently started desmopressin therapy
Recently started terlipressin, vasopressin

- Why did we choose to set definitions?

Hyponatraemia can be classified based on different parameters. These include serum sodium concentration, rate of development, symptom severity, serum osmolality, and volume status. For this guideline, we wanted the classification to be consistent and clear so all users would have a correct understanding of the terminology used. We also wanted to make the classification directly relevant for patient management. However, treatment strategies cannot be adequately classified with reference to a single criterion. Hence, treatment strategies have been classified according to combinations of these criteria.

- What are these definitions based on?

Classification based on serum sodium concentration

Authors mostly use the terms 'mild', 'moderate', and 'severe' [4–6]. We have chosen to replace 'severe' by 'profound' to avoid confusion with the classification based on symptoms, for which we have reserved the term 'severe'. The definitions of mild, moderate and profound hyponatraemia in published research are variable; especially the threshold used to define profound hyponatraemia for which values have ranged from 110 to 125 mmol/L [7, 8]. Several studies report that when serum sodium concentrations drop below 125 mmol/L, symptoms become more common [1, 4, 9–13], and the correction to normonatraemia necessitates careful monitoring to avoid overly rapid correction [14].

Classification based on duration and speed of development

Published research suggests using a threshold of 48 h to distinguish "acute" from "chronic" hyponatraemia. Brain oedema seems to occur more frequently when hyponatraemia develops in <48 h [15–18]. Experimental studies also suggest that the brain needs approximately 48 h to adapt to a hypotonic environment, achieved mainly by extruding sodium, potassium, chloride and organic osmoles from its cells [19–21]. Before adaptation, there is a risk of brain oedema, because the lower extracellular osmolality promotes a shift of water into the cells. However, once adaptation is completed, brain cells can again sustain damage if the serum sodium concentration increases too rapidly. Breakdown of the myelin sheath insulating individual neurons can result in what is called the osmotic demyelination syndrome [22–25]. Consequently, it is important to distinguish between acute and chronic hyponatraemia to assess whether someone is at greater risk of immediate brain oedema than of osmotic demyelination [26]. Unfortunately, in clinical practice, the distinction between acute and chronic hyponatraemia is often unclear, particularly for patients presenting to the emergency room. It is often unknown when the serum sodium concentration has started decreasing. If classifying hyponatraemia as acute or chronic is not possible, we have decided to consider the hyponatraemia as being chronic, unless there are reasons to assume it is acute (Table 10). There is a good reason for this approach. Chronic hyponatraemia is much more common than acute hyponatraemia and should be managed accordingly to avoid osmotic demyelination [27, 28].

Classification based on symptoms

We have divided symptoms of hyponatraemia into 'moderately severe' and 'severe'. The distinction is based on selected observations in acute hyponatraemia; those who subsequently die more often experience what we define as severe symptoms than those who live [15, 16]. Moderately severe symptoms caused by brain oedema are less frequently associated with death. Nevertheless, they may rapidly progress to more severe symptoms associated with an adverse outcome.

We have purposefully omitted the category 'asymptomatic' as we felt this might create confusion. Patients are probably never truly 'asymptomatic' in the strictest sense of the word. Very limited and subclinical signs such

as mild concentration deficits are seen even with mild hyponatraemia [29].

A classification based on symptoms aims to reflect the degree of brain oedema and the extent of immediate danger. It allows matching treatment to the immediate risk, with more aggressive treatment for symptoms that are more severe. Nevertheless, a classification based only on symptom severity has several shortcomings. First, symptoms of acute and chronic hyponatraemia may overlap [29]. Second, patients with acute hyponatraemia can present without clear symptoms, but go on to develop moderately severe to severe symptoms within hours [15]. Third, symptoms of hyponatraemia are nonspecific. Consequently, assessment of symptoms needs to happen with caution. Clinicians need to be wary that symptoms can be caused by conditions other than hyponatraemia; by other conditions in combination with hyponatraemia; or by conditions that cause the hyponatraemia. In general, one should be particularly careful when attributing moderately severe to severe symptoms to hyponatraemia when the biochemical degree of hyponatraemia is only mild (Table 1).

Classification based on serum osmolality

As this guideline aimed to cover the aspects of diagnosis and treatment specifically of hypotonic hyponatraemia, we needed to define what distinguishes hypotonic from non-hypotonic hyponatraemia. Because this distinction is a necessary first step in the diagnostic evaluation of any hyponatraemia, we have devoted a separate chapter to this topic (chapter 8.2). For reasons of completeness, we briefly mention it here. A *measured* serum osmolality <275 mOsm/kg always indicates hypotonic hyponatraemia, as effective osmolality can never be higher than total or measured osmolality. In contrast, if *calculated* osmolality <275 mOsm/kg, the hyponatraemia can be hypotonic, isotonic or hypertonic, depending on which osmotically active agents are present and whether or not they are incorporated in the formula [30].

Classification based on volume status

Patients with hyponatraemia may be hypovolaemic, euvolaemic, or hypervolaemic [31]. Many traditional diagnostic algorithms start with a clinical assessment of volume status [32]. However, it is often not clear if volume status in this context refers to the extracellular fluid volume, to the effective circulating volume or to the total body water. In addition, the sensitivity and specificity of clinical assessments of volume status are low, potentially leading to misclassification early in the diagnostic tree [33, 34]. Therefore, we have used the terms 'effective circulating volume' and 'extracellular fluid volume' throughout the text to reduce ambiguity.

- Note of caution

We wanted the classification of hyponatraemia to be consistent, easy to use and helpful for both differential diagnosis and treatment. Hyponatraemia can be classified according to different factors, each with advantages and pitfalls depending on the clinical setting and situation. We have prioritized the criteria such that we would obtain a classification that would be clinically relevant and as widely applicable as possible.

Nevertheless, the user should keep in mind that differential diagnosis of hyponatraemia is difficult and no classification can be 100 % accurate in every situation. We emphasize that the different classifications of hyponatraemia are not mutually exclusive, and that classification should always occur with the clinical condition and the possibility of combined causes of hyponatraemia in mind.

2.2 Confirming hypotonic and excluding non-hypotonic hyponatraemia

We recommend excluding hyperglycaemic hyponatraemia by measuring the serum glucose concentration and correcting the measured serum sodium concentration for the serum glucose concentration if the latter is increased. (1D)

Hyponatraemia with a measured osmolality <275 mOsm/kg always reflects hypotonic hyponatraemia. (not graded)

Accept as 'hypotonic hyponatraemia' a hyponatraemia without evidence for causes of non-hypotonic hyponatraemia as listed in Table 3. (not graded)

Advice for clinical practice

Estimates of the serum sodium concentration corrected for the presence of hyperglycaemia can be obtained from the following equations [35]:

$$Corrected\ serum\ [Na^+] = measured\ [Na^+] + 2.4 \times \frac{[Glucose\ (mg/dl) - 100\ (mg/dl)]}{100\ mg/dl}$$

$$Corrected\ [Na^+] = measured\ [Na^+] + 2.4 \times \frac{[Glucose\ (mmol/L) - 5.5\ (mmol/L)]}{5.5\ mmol/L}$$

where [Na^+] is the serum sodium concentration, [Glucose] is the serum glucose concentration.

This translates into adding 2.4 mmol/L to the measured serum sodium concentration for every 5.5 mmol/L (100 mg/dL) incremental rise in serum glucose concentration above a standard serum glucose concentration of 5.5 mmol/L (100 mg/dL).

Alternatively, the estimated value of the corrected serum sodium concentration across a range of serum glucose concentrations can be obtained from (ESM Table 10).

Table 3 (Table 10 of the online document): causes of non-hypotonic hyponatraemia

Setting	Serum osmolality	Examples
Presence of "effective" osmoles that raise serum osmolality and can cause hyponatraemia	Isotonic or hypertonic	Glucose [35] Mannitol [38] Glycine [39] Histidine–tryptophane–ketoglutarate [40] Hyperosmolar radiocontrast media [41] Maltose [42]
Presence of "ineffective" osmoles that raise serum osmolality but do not cause hyponatraemia	Isotonic or hyperosmolar	Urea [43] Alcohols [43] Ethylene-glycol [43]
Presence of endogenous solutes that cause pseudohyponatraemia (laboratory artifact)	Isotonic	Triglycerides [44] Cholesterol [44] Protein intravenous immunoglobulins [45] Monoclonal gammapathies [46]

2.3 Which parameters to use for differentiating causes of hypotonic hyponatraemia? (Fig. 1)

We recommend interpreting urine osmolality of a spot urine sample as a first step. (1D)

If urine osmolality $\leq$100 mOsm/kg, we recommend accepting relative excess water intake as a cause of the hypotonic hyponatraemia. (1D)

If urine osmolality >100 mOsm/kg, we recommend interpreting the urine sodium concentration on a spot urine sample taken simultaneously with a blood sample. (1D)

If urine sodium concentration $\leq$30 mmol/L, we suggest accepting low effective arterial volume as a cause of the hypotonic hyponatraemia. (2D)

If urine sodium concentration >30 mmol/L, we suggest assessing extracellular fluid status and use of diuretics to further differentiate likely causes of the hyponatraemia. (2D)

We suggest against measuring vasopressin for confirming the diagnosis of SIADH. (2D)

Advice for clinical practice

- Correct interpretation of laboratory measurements requires contemporaneous collection of blood and urine specimens.
- For practical reasons, urine osmolality and sodium concentration are best determined in the same urine sample.
- If clinical assessment indicates the volume of extracellular fluid is not overtly increased and the urine sodium concentration >30 mmol/L, exclude other causes of hypotonic hyponatraemia before implicating SIAD. Consider using the diagnostic criteria listed in Tables 4, 5 and looking for known causes of SIAD.
- Consider primary or secondary adrenal insufficiency as an underlying cause of the hypotonic hyponatraemia.
- Kidney disease complicates differential diagnosis of hyponatraemia. Besides possibly contributing to the hyponatraemia, the ability of the kidneys to regulate urine osmolality and urine sodium is often diminished, much like with the use of diuretics. As urine osmolality and sodium may no longer reflect the effects of the regular hormonal axes regulating water and sodium homeostasis, any diagnostic algorithm for hyponatraemia must be used with caution in patients with kidney disease.
- The water-loading test is generally not helpful for differential diagnosis of hypotonic hyponatraemia and may be dangerous in this setting.

3 Treatment of hypotonic hyponatraemia

How to use the treatment recommendations

The advice provided in this chapter follows a specific hierarchy as illustrated in Fig. 2. Individual recommendations and statements can only be correctly interpreted and implemented if considered within this structure.

The guideline development group felt that with severe or moderately severe symptoms, the risk of brain oedema outweighs the risk of osmotic demyelination syndrome. They felt it justifies urgent treatment in these conditions, irrespective of biochemical degree or timing (acute versus chronic) of hyponatraemia. Conversely, the guideline development group believed that in the absence of severe or moderately severe symptoms, there is time for diagnostic assessment, and cause-specific treatment is the most reasonable approach.

For a correct interpretation of the algorithm in Fig. 2, it is crucial to understand that for correctly classifying

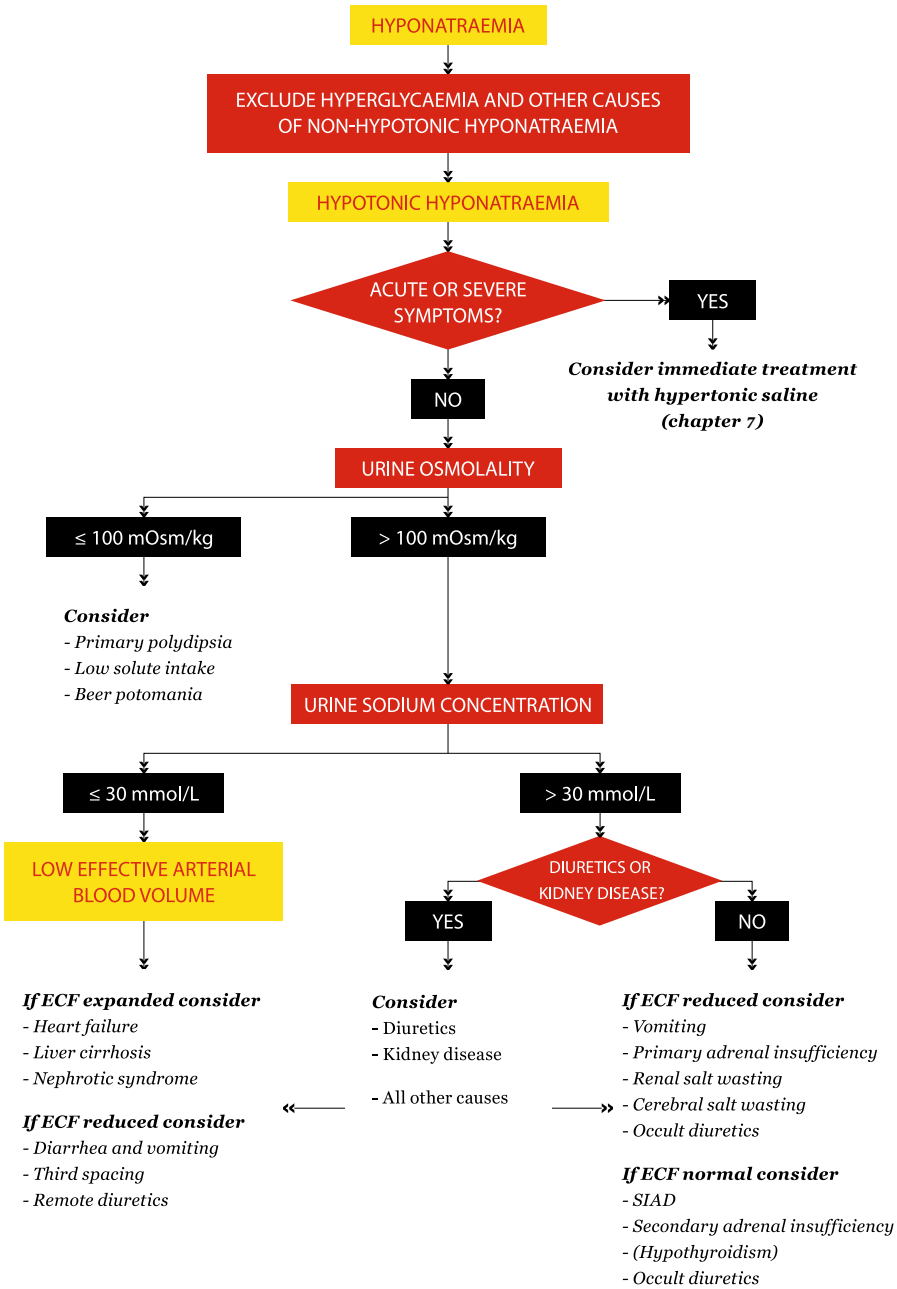

Fig. 1 (Fig. 6 of the online document): algorithm for the diagnosis of hyponatraemia

symptoms as ‘severe’ or ‘moderately severe’, there must be sufficient confidence that the symptoms are caused by hyponatraemia. If hyponatraemia is mild and symptoms are severe or moderately severe (Table 5 of the online document), the guideline development group advises to only accept causality in exceptional cases. Consequently, generally, chapters 3.1, 3.2, and 3.3 are not applicable when hyponatraemia is mild. It is also essential to understand that the guideline development group distinguishes between targets and limits. A target is a goal one is aiming for; it is the change in serum sodium concentration that one wishes and expects to achieve with a particular treatment. In contrast, a limit is a change in serum sodium concentration one does not want to exceed and if surpassed, requires prompt counter-regulating intervention as described in chapter 9.5 (ESM). In addition, the reader should bear in mind that the absolute numbers provided as ‘targets’ or ‘limits’

Table 4 (Table 6 of the online document): diagnostic criteria for the syndrome of inappropriate antidiuresis

Essential criteria
Effective serum osmolality <275 mOsm/kg
Urine osmolality >100 mOsm/kg at some level of decreased effective osmolality
Clinical euvolaemia
Urine sodium concentration >30 mmol/L with normal dietary salt and water intake
Absence of adrenal, thyroid, pituitary or renal insufficiency
No recent use of diuretic agents
Supplemental criteria
Serum uric acid <0.24 mmol/L (<4 mg/dL)
Serum urea <3.6 mmol/L (<21.6 mg/dL)
Failure to correct hyponatraemia after 0.9 % saline infusion
Fractional sodium excretion >0.5 %
Fractional urea excretion >55 %
Fractional uric acid excretion >12 %
Correction of hyponatraemia through fluid restriction

Adapted from Schwartz et al. [36] and Janicic et al. [37]

Table 5 (Table 11 of the online document): differences between SIADH and cerebral salt wasting

	SIADH	Cerebral salt wasting
Serum urea concentration	Normal–low	Normal–high
Serum uric acid concentration	Low	Low
Urine volume	Normal–low	High
Urine sodium concentration	>30 mmol/L	>>30 mmol/L
Blood pressure	Normal	Normal–orthostatic hypotension
Central venous pressure	Normal	Low

Adapted from Sherlock et al. [47] and Brimioulle et al. [48]

should always be interpreted in the clinical context of the individual patient.

3.1 Hyponatraemia with severe symptoms

3.1.1 First hour management, regardless of whether hyponatraemia is acute or chronic

We recommend prompt intravenous infusion of 150 mL 3 % hypertonic saline or equivalent over 20 min. (1D)
We suggest checking the serum sodium concentration after 20 min while repeating an infusion of 150 mL 3 % hypertonic saline or equivalent over the next 20 min. (2D)
We suggest repeating therapeutic recommendations 3.1.1.1 and 3.1.1.2 twice or until a target of 5 mmol/L increase in serum sodium concentration is achieved. (2D)

Manage patients with severely symptomatic hyponatraemia in an environment where close biochemical and clinical monitoring can be provided. (not graded)

3.1.2 Follow up management in case of improvement of symptoms after a 5 mmol/L increase in serum sodium concentration in the first hour, regardless of whether hyponatraemia is acute or chronic

We recommend stopping the infusion of hypertonic saline. (1D)

We recommend keeping the intravenous line open by infusing the smallest feasible volume of 0.9 % saline until cause-specific treatment is started. (1D)

We recommend starting a diagnosis specific treatment if available, aiming at least to stabilize sodium concentration. (1D)

We recommend limiting the increase in serum sodium concentration to a total of 10 mmol/L during the first 24 h and an additional 8 mmol/L during every 24 h thereafter until the serum sodium concentration reaches 130 mmol/L. (1D)

We suggest checking the serum sodium concentration after 6 and 12 h, and daily afterwards until the serum sodium concentration has stabilised under stable treatment. (2D)

3.1.3 Follow up management in case of no improvement of symptoms after a 5 mmol/L increase in serum sodium concentration in the first hour, regardless of whether the hyponatraemia is acute or chronic

We recommend continuing an intravenous infusion of 3 % hypertonic saline or equivalent aiming for an additional 1 mmol/L/h increase in serum sodium concentration (1D).

We recommend stopping the infusion of 3 % hypertonic saline or equivalent when the symptoms improve, the serum sodium concentration increases 10 mmol/L in total or the serum sodium concentration reaches 130 mmol/L, whichever occurs first (1D).

We recommend additional diagnostic exploration for other causes of the symptoms than hyponatraemia (1D).

We suggest checking the serum sodium concentration every 4 h as long as an intravenous infusion of 3 % hypertonic saline or equivalent is continued (2D).

Advice for clinical practice

- Prompt infusion of hypertonic saline may save lives. However, preparing a 3 % hypertonic saline infusion takes time and errors may occur in calculating the required amount of sodium chloride. Therefore, it may be wise for the pharmacy to store pre-prepared 150 mL bags of 3 % hypertonic saline. It ensures that solutions

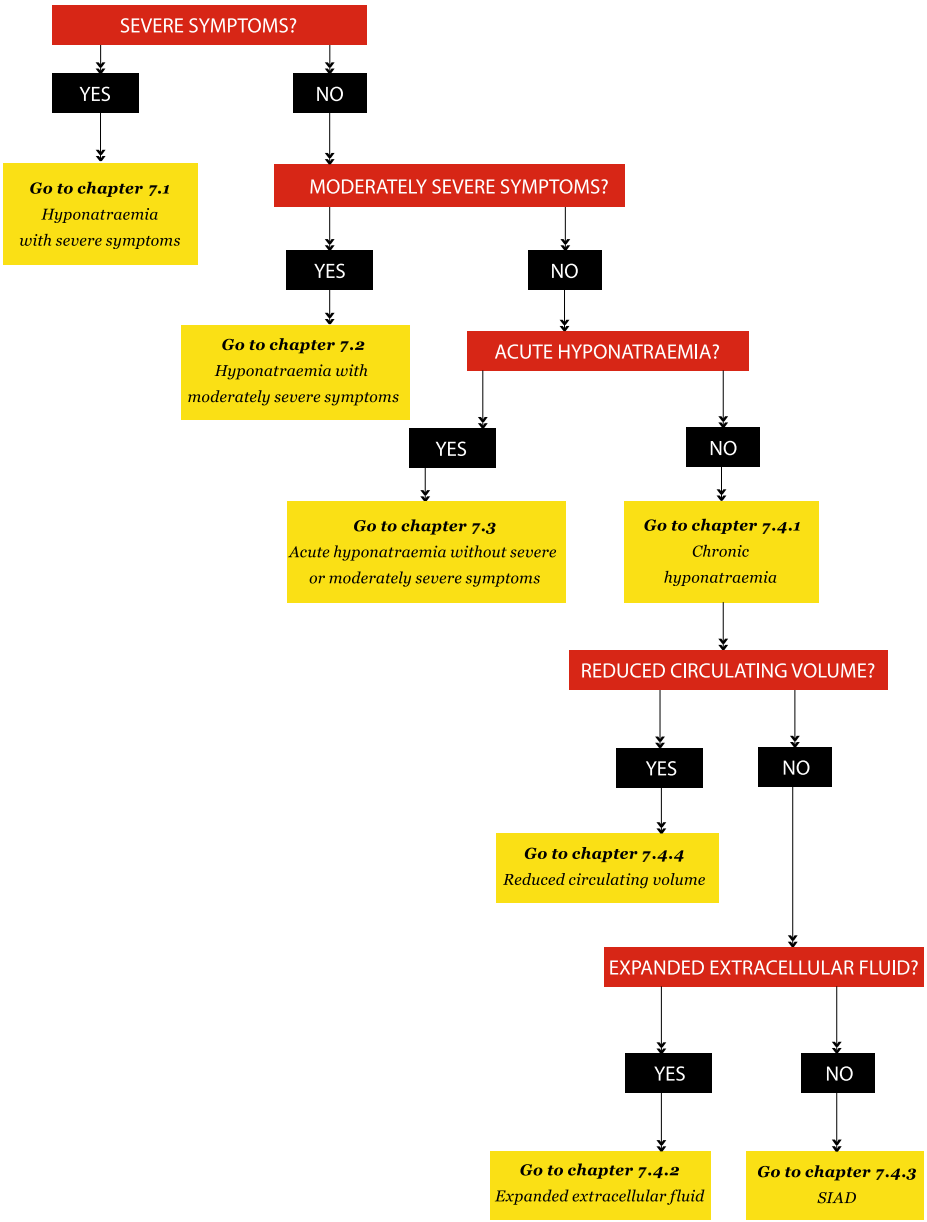

Fig. 2 (Fig. 7 of the online document): algorithm for the management of hypotonic hyponatraemia (the *numbers in the yellow boxes* refer to the online full guideline document)

are prepared under sterile conditions, by either the pharmacist or the manufacturer, and are available for immediate infusion without having to prepare them on the spot.

- Consider using weight based (2 mL/kg) rather than the fixed 150 mL infusion volumes of 3 % hypertonic saline in case of obviously deviant body composition.
- Do not expect patients with severe symptoms to completely recover immediately, as it may take some time for the brain to fully recover. Be aware that sometimes it may not be possible to assess an improvement in symptoms, e.g. because the patient is intubated and sedated. In these cases, we advise to follow guidance as described under 9.1.2.
- Keep in mind that if hypokalaemia is present, correction of the hypokalaemia will contribute to an increase in serum sodium concentration.
- To achieve the 1 mmol/L/h increase advised in 9.1.2.1, the formula of Adrogué–Madias [32] may be used, but keep in mind that the actual increase may exceed the calculated increase:

$$Change\,in\,serum\,[Na^+] = \frac{infusate\,[Na^+] - serum\,[Na^+]}{total\,body\,water + 1}$$

$$\textit{Change in serum } [Na^+] = \frac{(\textit{infusate } [Na^+] + \textit{infusate } [K^+]) - \textit{serum } [Na^+]}{\textit{total body water} + 1}$$

where $[Na^+]$ is the sodium concentration in mmol/L, $[K^+]$ is the potassium concentration in mmol/L. The numerator in formula 1 is a simplification of the expression in formula 2, with the value yielded by the equation in mmol/L. The estimated total body water (in litres) is calculated as a fraction of body weight. The fraction is 0.6 in nonelderly men and 0.5 in nonelderly women; and 0.5 and 0.45 in elderly men and women respectively. Normally, extracellular and intracellular fluids account for 40 and 60 % of total body water respectively.

3.2 Hyponatraemia with moderately severe symptoms

We recommend starting prompt diagnostic assessment. (1D)

Stop, if possible, medications and other factors that can contribute to or provoke the hyponatraemia. (not graded)

We recommend cause-specific treatment. (1D)

We suggest immediate treatment with a single intravenous infusion of 150 mL 3 % hypertonic saline or equivalent over 20 min. (2D)

We suggest aiming for a 5 mmol/L/24 h increase in serum sodium concentration. (2D)

We suggest limiting the increase in serum sodium concentration to 10 mmol/L in the first 24 h and 8 mmol/L during every 24 h thereafter, until a serum sodium concentration of 130 mmol/L is reached. (2D)

We suggest checking the serum sodium concentration after one, 6 and 12 h. (2D)

We suggest additional diagnostic exploration for other causes of the symptoms if the symptoms do not improve with an increase in serum sodium concentration. (2D)

We suggest considering to manage the patient as in severely symptomatic hyponatraemia if the serum sodium concentration further decreases despite treating the underlying diagnosis. (2D)

3.3 Acute hyponatraemia without severe or moderately severe symptoms

Make sure that the serum sodium concentration has been measured using the same technique as used for the previous measurement and that no administrative errors in sample handling have occurred. (not graded)

If possible, stop fluids, medications and other factors that can contribute to or provoke the hyponatraemia. (not graded)

We recommend starting prompt diagnostic assessment. (1D)

We recommend cause-specific treatment. (1D)

If the acute decrease in serum sodium concentration exceeds 10 mmol/L, we suggest a single intravenous infusion of 150 mL 3 % hypertonic saline or equivalent over 20 min. (2D)

We suggest checking the serum sodium concentration after 4 h, using the same technique as used for the previous measurement. (2D)

3.4 Chronic hyponatraemia without severe or moderately severe symptoms

3.4.1 General management

Stop non-essential fluids, medications and other factors that can contribute to or provoke the hyponatraemia. (not graded)

We recommend cause-specific treatment. (1D)

In mild hyponatraemia, we suggest against treatment with the sole aim of increasing the serum sodium concentration. (2C)

In moderate or profound hyponatraemia, we recommend avoiding an increase in serum sodium concentration of >10 mmol/L during the first 24 h and >8 mmol/L during every 24 h thereafter. (1D)

In moderate or profound hyponatraemia, we suggest checking the serum sodium concentration every 6 h until the serum sodium concentration has stabilised under stable treatment. (2D)

In case of unresolved hyponatraemia, reconsider the diagnostic algorithm and ask for expert advice. (not graded)

3.4.2 Patients with expanded extracellular fluid

We recommend against a treatment with the sole aim of increasing the serum sodium concentration in mild or moderate hyponatraemia. (1C)

We suggest fluid restriction to prevent further fluid overload. (2D)

We recommend against vasopressin receptor antagonists. (1C)

We recommend against demeclocycline. (1D)

3.4.3 Patients with syndrome of inappropriate antidiuresis

In moderate or profound hyponatraemia, we suggest restricting fluid intake as first- line treatment. (2D)

In moderate or profound hyponatraemia, we suggest the following can be considered equal second line treatments: increasing solute intake with 0.25–0.50 g/kg/day of urea or a combination of low dose loop diuretics and oral sodium chloride. (2D)

In moderate or profound hyponatraemia, we recommend against lithium or demeclocycline. (1D)

In moderate hyponatraemia, we do not recommend vasopressin receptor antagonists. (1C)

In profound hyponatraemia, we recommend against vasopressin receptor antagonists. (1C)

3.4.4 Patients with contracted circulating volume

We recommend restoring extracellular volume with intravenous infusion of 0.9 % saline or a balanced crystalloid solution at 0.5–1.0 mL/kg/h. (1B)

Manage patients with haemodynamic instability in an environment where close biochemical and clinical monitoring can be provided. (not graded)

In case of haemodynamic instability, the need for rapid fluid resuscitation overrides the risk of an overly rapid increase in serum sodium concentration. (not graded)

Advice for clinical practice

- A sudden increase in urine output to >100 mL/h signals increased risk of overly rapid rise in serum sodium concentration. If vasopressin activity is suddenly suppressed, as happens when intravascular volume is restored in hypovolaemia, free water clearance can dramatically increase, resulting in serum sodium concentrations rising more rapidly than expected. If urine output suddenly increases, we would advise measuring the serum sodium concentration every 2 h until it has stabilised under stable treatment. The implicit advice to monitor urine output does not imply we advise a bladder catheter solely for this purpose. Most patients will be able to void spontaneously and collect urine for output monitoring.
- As a means of increasing solute intake, we suggest daily intake of 0.25–0.50 g/kg urea can be used. The bitter taste can be reduced by combining it with sweet tasting substances. The pharmacist may be asked to prepare the following as sachets: urea 10 g + $NaHCO_3$ 2 g + citric acid 1.5 g + sucrose 200 mg, to be dissolved in 50–100 mL water. This will result in a more palatable, slightly sparkling solution.

3.5 What to do in case hyponatraemia is corrected too rapidly?

We recommend prompt intervention for re-lowering the serum sodium concentration if it increases >10 mmol/L during the first 24 h or >8 mmol/L in any 24 h thereafter. (1D)

We recommend discontinuing the on-going active treatment. (1D)

We recommend consulting an expert to discuss if it is appropriate to start an infusion of 10 mL/kg body weight of electrolyte-free water (e.g. glucose solutions) over 1 h under strict monitoring of urine output and fluid balance. (1D)

We recommend consulting an expert to discuss if it is appropriate to add intravenous desmopressin 2 μg, with the understanding that this should not be repeated more frequently than every 8 h. (1D)

References

1. Funk GC, Lindner G, Druml W et al (2010) Incidence and prognosis of dysnatremias present on ICU admission. Intens Care Med 36:304–311
2. Beukhof CM, Hoorn EJ, Lindemans J, Zietse R (2007) Novel risk factors for hospital-acquired hyponatraemia: a matched case-control study. Clin Endocrinol 66:367–372
3. Upadhyay A, Jaber BL, Madias NE (2009) Epidemiology of hyponatremia. Semin Nephrol 29:227–238

4. Hoorn EJ, Lindemans J, Zietse R (2006) Development of severe hyponatraemia in hospitalized patients: treatment-related risk factors and inadequate management. Nephrol Dial Transpl 21:70–76
5. Waikar SS, Mount DB, Curhan GC (2009) Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med 122:857–865
6. Doshi SM, Shah P, Lei X, Lahoti A, Salahudeen AK (2012) Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. Am J Kidney Dis 59:222–228
7. Sterns RH (1987) Severe symptomatic hyponatremia: treatment and outcome. A study of 64 cases. Ann Intern Med 107:656–664
8. Gill G, Huda B, Boyd A et al (2006) Characteristics and mortality of severe hyponatraemia—a hospital-based study. Clin Endocrinol 65:246–249
9. Arieff AI, Llach F, Massry SG (1976) Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. Medicine 55:121–129
10. Halberthal M, Halperin ML, Bohn D (2001) Lesson of the week: acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. BMJ 322:780–782
11. Darmon M, Diconne E, Souweine B et al (2013) Prognostic consequences of borderline dysnatremia: pay attention to minimal serum sodium change. Crit Care 17:R12
12. Sakr Y, Rother S, Ferreira AMP et al (2013) Fluctuations in serum sodium level are associated with an increased risk of death in surgical ICU patients. Crit Care Med 41:133–142
13. Stelfox HT, Ahmed SB, Khandwala F, Zygun D, Shahpori R, Laupland K (2008) The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. Crit Care 12:R162
14. Pirzada NA, Ali II (2001) Central pontine myelinolysis. Mayo Clin Proc 76:559–562
15. Arieff AI (1986) Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. N Engl J Med 314:1529–1535
16. Ayus JC, Wheeler JM, Arieff AI (1992) Postoperative hyponatremic encephalopathy in menstruant women. Ann Intern Med 117:891–897
17. Nzerue CM, Baffoe-Bonnie H, You W, Falana B, Dai S (2003) Predictors of outcome in hospitalized patients with severe hyponatremia. J Natl Med Assoc 95:335–343
18. Arieff AI, Ayus JC, Fraser CL (1992) Hyponatraemia and death or permanent brain damage in healthy children. BMJ 304:1218–1222
19. Verbalis JG, Drutarosky MD, Ertel RJ, Vollmer RR (1989) Adaptive responses to sustained volume expansion in hyponatraemic rats. J Endocrinol 122:421–431
20. Verbalis JG, Gullans SR (1991) Hyponatremia causes large sustained reductions in brain content of multiple organic osmolytes in rats. Brain Res 567:274–282
21. Sterns RH, Silver SM (2006) Brain volume regulation in response to hypo-osmolality and its correction. Am J Med 119:S12–S16
22. Melton JE, Patlak CS, Pettigrew KD, Cserr HF (1987) Volume regulatory loss of Na, Cl, and K from rat brain during acute hyponatremia. Am J Physiol 252:F661–F669
23. Sterns RH, Thomas DJ, Herndon RM (1989) Brain dehydration and neurologic deterioration after rapid correction of hyponatremia. Kidney Int 35:69–75
24. Verbalis JG, Martinez AJ (1991) Neurological and neuropathological sequelae of correction of chronic hyponatremia. Kidney Int 39:1274–1282
25. Videen JS, Michaelis T, Pinto P, Ross BD (1995) Human cerebral osmolytes during chronic hyponatremia. A proton magnetic resonance spectroscopy study. J Clin Invest 95:788–793
26. Hoorn EJ, Zietse R (2008) Hyponatremia revisited: translating physiology to practice. Nephron Physiol 108:46–59
27. Hsu Y-J, Chiu J-S, Lu K-C, Chau T, Lin S-H (2005) Biochemical and etiological characteristics of acute hyponatremia in the emergency department. J Emerg Med 29:369–374
28. Sterns RH (1994) Treating hyponatremia: why haste makes waste. South Med J 87:1283–1287
29. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G (2006) Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med 119(71):e71–e78
30. Fazekas AS, Funk G-C, Klobassa DS et al (2012) Evaluation of 36 formulas for calculating plasma osmolality. Intens Care Med 39:302–308
31. Adrogue HJ, Madias NE (2000) Hyponatremia. N Engl J Med 342:1581–1589
32. Hoorn EJ, Halperin ML, Zietse R (2005) Diagnostic approach to a patient with hyponatraemia: traditional versus physiology-based options. Q J Med 98:529–540
33. Chung HM, Kluge R, Schrier RW, Anderson RJ (1987) Clinical assessment of extracellular fluid volume in hyponatremia. Am J Med 83:905–908
34. McGee S, Abernethy WB 3rd, Simel DL (1999) The rational clinical examination. Is this patient hypovolemic? JAMA 281:1022–1029
35. Hillier TA, Abbott RD, Barrett EJ (1999) Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med 106:399–403
36. Schwartz WB, Bennett W, Curelop S, Bartter FC (1957) A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med 23:529–542
37. Janicic N, Verbalis JG (2003) Evaluation and management of hypo-osmolality in hospitalized patients. Endocrinol Metab Clin N Am 32:459–481 vii
38. Aviram A, Pfau A, Czaczkes JW, Ullmann TD (1967) Hyperosmolality with hyponatremia, caused by inappropriate administration of mannitol. Am J Med 42:648–650
39. Desmond J (1970) Serum osmolality and plasma electrolytes in patients who develop dilutional hyponatremia during transurethral resection. Can J Surg 13:116–121
40. Lindner G, Zapletal B, Schwarz C, Wisser W, Hiesmayr M, Lassnigg A (2012) Acute hyponatremia after cardioplegia by histidine–tryptophane–ketoglutarate—a retrospective study. J Cardiothorac Surg 7:52
41. Sirken G, Raja R, Garces J, Bloom E, Fumo P (2004) Contrast-induced translocational hyponatremia and hyperkalemia in advanced kidney disease. Am J Kidney Dis 43:e31–e35
42. Palevsky PM, Rendulic D, Diven WF (1993) Maltose-induced hyponatremia. Ann Intern Med 118:526–528
43. Oster JR, Singer I (1999) Hyponatremia, hyposmolality, and hypotonicity: tables and fables. Arch Intern Med 159:333–336
44. Lai M-Y, Lin C-C, Chung S-L, Wu C-H, Yang W-C, Tseng Y-T (2009) Milky plasma, diabetes, and severe hyponatremia. Kidney Int 75:996
45. Lawn N, Wijdicks EF, Burritt MF (1998) Intravenous immune globulin and pseudohyponatremia. N Engl J Med 339:632

46. Vaswani SK, Sprague R (1993) Pseudohyponatremia in multiple myeloma. South Med J 86:251–252

47. Sherlock M, O'Sullivan E, Agha A et al (2006) The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. Clin Endocrinol 64:250–254

48. Brimioulle S, Orellana-Jimenez C, Aminian A, Vincent JL (2008) Hyponatremia in neurological patients: cerebral salt wasting versus inappropriate antidiuretic hormone secretion. Intensive Care Med 34:125–131