

*Special feature***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. It can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening, 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 have fostered diverse institution- and speciality-based approaches to diagnosis and treatment. To obtain a common and holistic view, 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 the 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 that the document focused on patient-important outcomes and included utility for clinicians involved in everyday practice.

Key words: hyponatremia, mild, moderate, severe,

acute, chronic

Chapter 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. It can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening 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.

This condensed and translated version of the Clinical Practice Guideline on Diagnosis and Treatment of Hyponatraemia focuses on recommendations on diagnosis and treatment of hyponatraemia. For aspects of conflict of interest, purpose and scope, methods of guideline development and pathophysiology of hyponatraemia, we refer to the full version of the guideline, which is free available on <http://ndt.oxfordjournals.org/content/29/suppl2/i1.full.pdf+html>.

Disclaimer: this guideline was translated with approval of ERBP, the official guideline body of ERA-EDTA. However, ERBP only takes full responsibility for the original full guideline in English as published in *Nephrol. Dial. Transplant.* (2014) 29 (suppl 2): i1-i39. doi: 10.1093/ndt/gfu040-First published online: February 25, 2014: <http://ndt.oxfordjournals.org/content/29/suppl2/i1.full.pdf+html>; <http://european-renal-best-practice.org> [1].

Chapter 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 hours. We define "chronic" hyponatraemia as hyponatraemia that is documented to exist for at least 48 hours.

Table 1. (Table 5 of the online full 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 (Glazgow Coma Scale ≤ 8)

If the hyponatraemia cannot be classified, we consider it being chronic, unless there is clinical or anamnestic evidence of the contrary (Table 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 2. (Table 8 of the online full document): Drugs and conditions associated with acute hyponatraemia (< 48 hours)

hyponatraemia (< 48 hours)
Postoperative phase
Post-resection of the prostate, post-resection of endoscopic uterine surgery
Polydipsia
Exercise
Recent thiazides prescription
3,4-methyleendioxyamfetamine (MDMA, XTC)
Colonoscopy preparation
Cyclophosphamide (intravenous)
Oxytocin
Recently started desmopressin therapy
Recently started terlipressin, vasopressin

Hyponatraemia can be classified based on different parameters, such as serum sodium concentration, rate of development, symptom severity, serum osmolality, and volume status. We intended 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.

Published research suggests using a threshold of 48 hours to distinguish "acute" from "chronic" hyponatraemia, as brain oedema seems to occur more frequently when hyponatraemia develops in less than 48 hours. Experimental studies also suggest that the brain needs approximately 48 hours to adapt to a hypotonic environment. 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. It is thus important to distinguish between acute and chronic hyponatraemia to assess whether someone is at greater risk of immediate brain oedema than of osmotic demyelination. In clinical practice, the distinction between acute and chronic hyponatraemia is often unclear, particularly for patients presenting to the emergency room. If classification as acute or chronic

is not possible or when there is doubt, it should be considered chronic, unless there are reasons to assume it is acute (see Table 10 of original document).

The 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, as patients may progress from moderately severe to severe symptoms within hours. In addition, symptoms of hyponatraemia are nonspecific and clinicians need to assess the possibility that symptoms can be caused by conditions other than hyponatraemia on itself. 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.

Patients with hyponatraemia may be hypovolaemic, euvolaemic, or hypervolaemic, and many traditional diagnostic algorithms start with a clinical assessment of volume status [2]. The sensitivity and specificity of

clinical assessments of volume status are low, potentially leading to misclassification early in the diagnostic tree. In addition, there might be confusion regarding the compartment the fluid is in (circulating or extracellular). Therefore, we have used the terms "effective circulating volume" and "extracellular fluid volume" throughout the text to reduce ambiguity.

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 hypo-

Table 3. (Table 10 of the online full document): Causes of nonhypotonic hyponatraemia

Setting	Serum osmolality	Examples
Presence of "effective" osmoles that raise serum osmolality and can cause hyponatraemia	Isotonic or hypertonic	Glucose Mannitol Glycine Histidine-tryptophane-ketoglutarate Hyperosmolar radiocontrast media Maltose
Presence of "ineffective" osmoles that raise serum osmolality but do not cause hyponatraemia	Isotonic or hyperosmolar	Urea Alcohols Ethylene-glycol
Presence of endogenous solutes that cause pseudohyponatraemia (laboratory artifact)	Isotonic	Triglycerides, cholesterol, protein Intravenous immunoglobulins Monoclonal gammopathies

natraemia as listed in table 3 (Not Graded). Estimates of the serum sodium concentration corrected for the

presence of hyperglycaemia can be obtained from the following equations:

$$\text{Corrected serum (Na}^+) = \text{measured (Na}^+) + 2.4 \times \frac{(\text{glucose (mmol/l)} - 100 \text{ (mmol/l)})}{100 \text{ mmol/l}}$$

$$\text{Corrected (Na}^+) = \text{measured (Na}^+) + 2.4 \times \frac{(\text{glucose (mmol/l)} - 5.5 \text{ (mmol/l)})}{5.5 \text{ mmol/l}}$$

† [Na⁺], serum sodium concentration; [Glucose], 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).

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

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

If urine osmolality ≤ 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 ≤ 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).

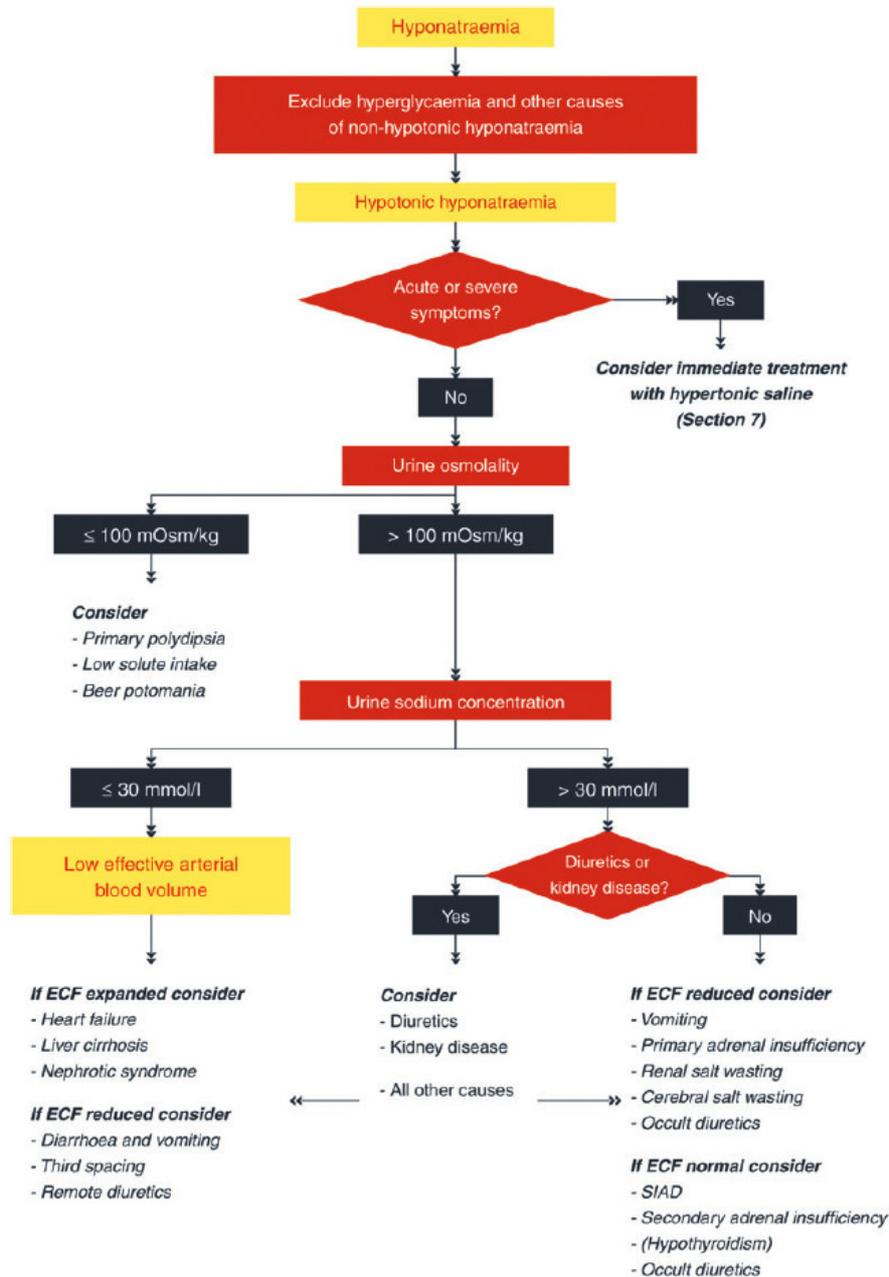


Fig. 1. (Figure 6 of the online full document): Algorithm for the diagnosis of hyponatraemia

Advice for clinical practice

Correct interpretation of laboratory measurements requires contemporaneous collection of blood and urine specimens. For practical reasons, urine osmolality and sodium concen-

tration are best determined in the same urine sample. If clinical assessment indicates the volume of extracellular fluid is not overly increased and the urine sodium concentration > 30 mmol/L, exclude other causes of hypotonic hyponatraemia before implicating SIAD.

Table 4. (Table 6 of the full 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 euvoalaemia
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 WB *et al.* Am J Med 1957; 23: 529-543. and Janicic N *et al.* Endocrinol Metab Clin North Am 2003; 32: 459-481 [3].

Consider using the diagnostic criteria listed in Table 4 and looking for known causes of SIAD (Table 5 and 6). 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.

Table 5. (Table 7 of the online full document): Differences between SIADH and cerebral salt wasting

Malignant diseases	Pulmonary disorders	Disorders of the nervous system
Carcinoma	Infections	Infection
Lung	Bacterial pneumonia	Encephalitis
Oropharynx	Viral pneumonia	Meningitis
Gastrointestinal tract	Pulmonary abscess	Brain abscess
Stomach	Tuberculosis	Rocky Mountain spotted fever
Duodenum	Aspergillosis	AIDS
Pancreas	Asthma	Malaria
Genitourinary tract	Cystic fibrosis	Vascular and masses
Ureter	Respiratory failure associated with positive-pressure breathing	Subdural hematoma
Bladder		Subarachnoid haemorrhage
Prostate		Stroke
Endometrium		Brain tumors
Endocrine thymoma		Head trauma
Lymphomas		Other
Sarcomas		Hydrocephalus
Ewing's sarcoma		Cavernous sinus thrombosis
Olfactory neuroblastoma		Multiple sclerosis
		Guillain-Barre' syndrome
		Shy-Drager syndrome
		Delirium tremens
		Acute intermittent porphyria

AIDS, acquired immunodeficiency syndrome; MOAI, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxymethamphetamine; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors

Drugs	Other causes
Vasopressin release or action stimulants	Hereditary
Antidepressants	Gain-of-function mutation of the vasopressin V2 receptor
SSRIs	Idiopathic
Tricyclic	Transient
MAOI	Exercise-associated hyponatraemia
Venlafaxine	General anaesthesia
Anticonvulsants	Nausea
Carbamazepine	Pain
Oxcarbazepine	Stress

Sodium valproate
 Lamotrigine
 Antipsychotics
 Phenothiazides
 Butyrophenones
 Anticancer drugs
 Vinca alkaloids
 Platinum compounds
 Ifosfamide
 Melphalan
 Cyclophosphamide
 Methotrexate
 Pentostatin
 Antidiabetic drugs
 Chlorpropamide
 Tolbutamine
 Miscellaneous
 Opiates
 MDMA (XTC)
 Levamisole
 Interferon
 NSAIDs
 Clofibrate
 Nicotine
 Amiodarone
 Proton pump inhibitors
 MABs
 Vasopressin analogues
 Desmopressin
 Oxytocin
 Terlipressin
 Vasopressin

Table 6. (table 11 of the online full 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 M *et al.* *Clin Endocrinol* 2006; 64: 250-254 and Brimiouille S *et al.* *Intensive Care Med* 2008; 34: 125-31 [5].

Chapter 3. Treatment of Hypotonic Hyponatraemia

How to use the treatment recommendations?

Individual recommendations and statements on management of hyponatraemia can only be correctly interpreted and implemented if considered within the structure illustrated in figure 2.

The guideline development group felt that with severe or moderately severe symptoms, the acute risk of brain oedema outweighs the risk of osmotic de-myelination

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.

It is crucial to understand that for correctly classifying symptoms as "severe" or "moderately severe", there must be sufficient confidence that the symptoms are caused by hyponatraemia itself. If hyponatraemia is mild and symptoms are severe or moderately severe, 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 (see chapters 7.1, 7.2 and 7.3 full guideline publication). 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. In addition, the reader should bear in mind that the absolute numbers provided as "targets" or "limits" 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 minutes (1D).

We suggest checking the serum sodium concentration after 20 minutes while repeating an infusion of 150 mL

3% hypertonic saline or equivalent over the next 20 minutes (2D).

We suggest repeating the two therapeutic recommendations above 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).

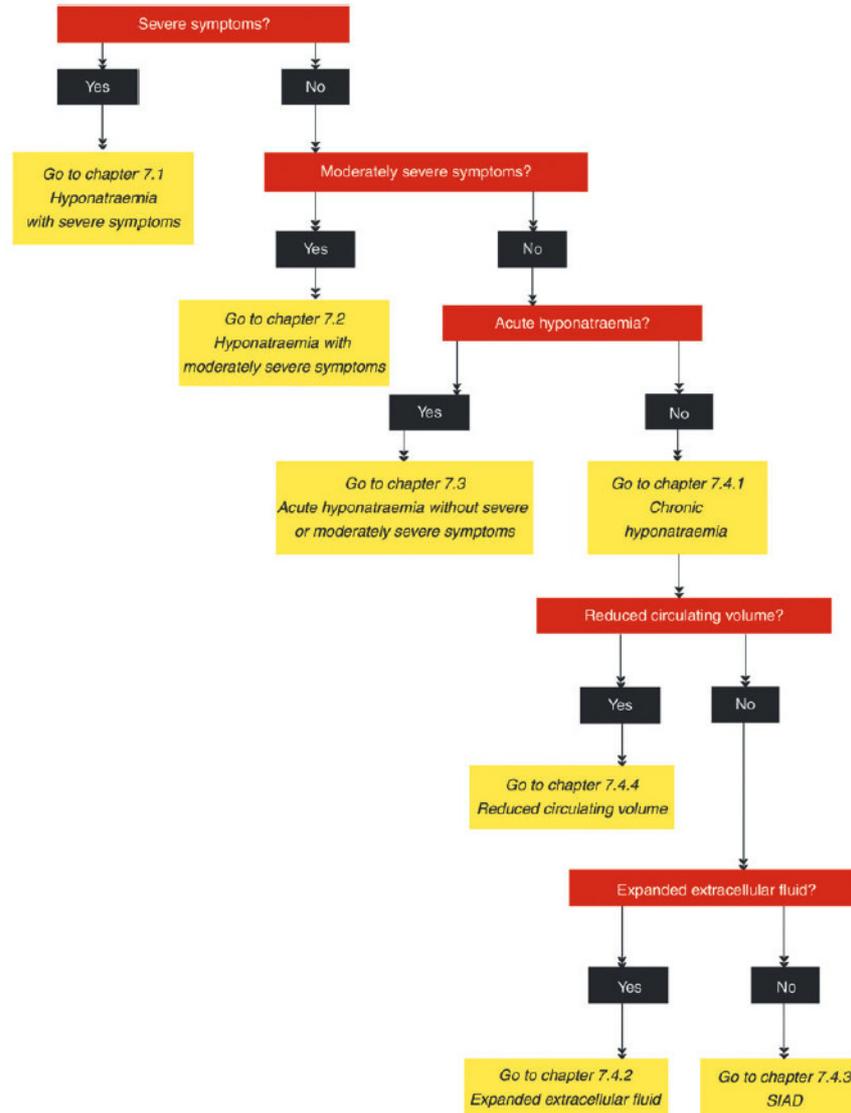


Fig. 2. (Figure 7 of the online full document): Algorithm for the management of hyponatraemia*

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 hours and an additional 8 mmol/L during every 24

hours thereafter until the serum sodium concentration reaches 130 mmol/L (1D).

We suggest checking the serum sodium concentration after 6 and 12 hours, 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 hours 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 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 (2mL/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 3.1.2. (see chapter (7.1.2. full guideline publication)). 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 3.1.3. (see chapter 7.1.3. full guideline publication), the formula of Adrogué-Madias may be used, but keep in mind that the actual increase may exceed the calculated increase [7]:

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

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

+ [Na⁺], sodium concentration in mmol/L; [K⁺], 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 minutes (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 hours and 8 mmol/L during every 24 hours 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 hours (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 minutes (2D).

We suggest checking the serum sodium concentration after four hours, 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 hours and >8 mmol/L during every 24 hours thereafter (1D).

In moderate or profound hyponatraemia, we suggest checking the serum sodium concentration every six hours 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 to 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 to 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 two hours 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 to 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+NaHCO₃ 2 g+citric acid 1.5 g+sucrose 200 mg, to be dissolved in 50 to 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 relowering the serum sodium concentration if it increases >10 mmol/L during the first 24 hours or >8 mmol/L in any 24 hours thereafter (1D).

We recommend discontinuing the ongoing 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 one hour 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 hours (1D).

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 exhaus-

tive, and all symptoms that can be signs of cerebral oedema should be considered as severe or moderate symptoms that can be caused by hyponatraemia.

Conflict of interest statement. None declared.

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