European Society of Endocrinology and European Renal Association Joint Clinical Guideline: Diagnosis and Treatment of Hyponatraemia

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Abbreviations used in the guideline

AVP, arginine vasopressin

CSW, cerebral salt wasting

EABV, effective arterial blood volume

ECF, extracellular fluid

ICF, intracellular fluid

ODS, osmotic demyelination syndrome

RCT, randomised controlled trial

SGLT2, sodium-glucose cotransporter-2

SIAD, syndrome of inappropriate antidiuresis

1. Summary of recommendations and clinical practice points

1. Classification of hyponatraemia

Clinical practice point 1.a Use the same plasma sodium measurement method throughout management, particularly during emergency treatment.

Definition of hyponatraemia based on biochemical severity

Clinical practice points 1.b Biochemical hyponatraemia is defined:

- as 'mild' if plasma sodium concentration ≥130 and <135 mmol/L.
- as 'moderate' if plasma sodium concentration ≥120 and <130 mmol/L.
- as 'severe' if plasma sodium concentration <120 mmol/L.

Definition of hyponatraemia based on time of development

Clinical practice points 1.c With regard to duration of hyponatraemia:

- 'Acute' hyponatraemia is defined as hyponatraemia that is documented to exist ≤ 48 hours or when the clinical history is highly suggestive of this time course.
- 'Chronic' hyponatraemia is defined as hyponatraemia that is documented to exist for >48 hours.
- If the duration of hyponatraemia cannot be determined, it should be assumed to be chronic, unless clinical or historical evidence suggests otherwise.

Definition of hyponatraemia based on symptoms

Clinical practice points 1.d

- 'Mildly symptomatic' hyponatraemia is defined as any degree of biochemical hyponatraemia in the presence of mild symptoms of hyponatraemia.

- 'Moderately symptomatic' hyponatraemia is defined as any degree of biochemical hyponatraemia in the presence of moderate symptoms of hyponatraemia.
- 'Severely symptomatic' hyponatraemia is defined as any degree of biochemical hyponatraemia in the presence of severe neurological symptoms related to hyponatraemia.

2. Parameters to differentiate the aetiology of hyponatraemia

- **Clinical practice point 2.a** Incorporate the clinical context in the evaluation of the aetiology, chronicity, and clinical severity of hyponatraemia.
- **Clinical practice point 2.b** Exclude non-hypotonic causes of hyponatraemia.
- **Clinical practice point 2.c** If plasma glucose is elevated, assess whether the degree of hyperglycaemia explains the hyponatraemia.
- **Clinical practice point 2.d** Measure plasma osmolality to confirm hypotonic hyponatraemia (<275 mOsm/kg H_2O).
- **Clinical practice point 2.e** If the measured plasma osmolality is normal or high, calculate plasma tonicity to identify hypotonic hyponatraemia in the presence of ineffective osmoles.
- **Clinical practice point 2.f** Obtain a spot urine sample for osmolality and sodium before treatment, without delaying urgent treatment in patients with severe symptoms while awaiting results.
- **Clinical practice point 2.g** Assess signs of extracellular fluid volume expansion and accept the aetiology as hypervolaemic hyponatraemia in patients with clear signs of extracellular fluid volume excess.
- **Clinical practice point 2.h** Assess signs of extracellular fluid volume deficit and accept the aetiology as hypovolaemic hyponatraemia in patients with clear signs of extracellular fluid volume deficit.
- **Clinical practice point 2.i** In patients without clear signs of extracellular fluid volume expansion or deficit, perform an integrated assessment of volume status, spot urine osmolality, and spot urine sodium to determine the cause of hyponatraemia.
- **Clinical practice point 2.j** With regard to spot urine osmolality assessment:

- If the urine osmolality is ≤100 mOsm/kg H_2O, accept excess water intake or previous arginine vasopressin secretion (that has resolved) as the cause of hyponatraemia.
- If the urine osmolality, is >100 mOsm/kg H_2O, accept arginine vasopressin-mediated water retention.

- **Clinical practice point 2.k** With regard to spot urinary sodium assessment:
  - A urine sodium concentration ≤30 mmol/L suggests hypovolaemic hyponatraemia or hypervolaemic hyponatraemia with low effective arterial blood volume.
  - If urine sodium concentration is >30 mmol/L, the extracellular fluid volume assessment and clinical context should be used to identify the underlying cause of hyponatraemia.
- **Clinical practice point 2.l** There is no role for measuring plasma AVP or copeptin in the differential diagnosis of hyponatraemia or for confirming the diagnosis of SIAD.
- **Clinical practice point 2.m** Consider the exclusion of adrenal insufficiency prior to establishing a diagnosis of SIAD.
- **Clinical practice point 2.n** Routine assessment of thyroid function is not necessary in the work-up of hyponatraemia.

3. Immediate treatment of severely symptomatic hyponatraemia

- **Recommendation 3.1** In patients with severely symptomatic hyponatraemia, we recommend urgent treatment with a single 150 mL bolus of 3% hypertonic saline administered over 10–20 minutes to improve neurological symptoms with a target increase in plasma sodium concentration of 4–6 mmol/l within 4–6 hours ($\oplus\oplus OO$).
- **Recommendation 3.2** We recommend assessing the clinical and biochemical effects of the first bolus within 1 hour and repeat the bolus if necessary ($\oplus OOO$).
- **Clinical practice point 3.a** 3% hypertonic saline may be administered via a peripheral intravenous line.

4. 24-hourly correction limits and monitoring frequency

- **Recommendation 4.1** In patients with a baseline plasma sodium concentration <120 mmol/L, we suggest limiting the increase in plasma sodium concentration to 6–8 mmol/L in any 24-hour period and recommend monitoring plasma sodium concentration at least every 4–6 hours (⊕OOO).
- **Recommendation 4.2** In patients with a baseline plasma sodium concentration ≥120–130 mmol/L, we suggest limiting the increase in plasma sodium concentration to 8–12 mmol/L in any 24-hour period and recommend monitoring plasma sodium concentration every 12–24 hours (⊕OOO).
- **Clinical practice point 4.a** In patients with a baseline plasma sodium concentration >130 mmol/L, plasma sodium concentration may be normalized within 24 hours, and monitoring frequency should be guided by the clinical context.

5. Treatment of acute (≤48h) hyponatraemia without severe symptoms

- **Recommendation 5.1** In patients with acute hyponatraemia without severe symptoms who have moderate or severe biochemical hyponatraemia and a decrease in plasma sodium concentration ≥10 mmol/L, we recommend prompt diagnostic assessment and cause-specific treatment (⊕OOO).
- **Recommendation 5.2** In patients with acute hyponatraemia in whom cause-specific treatment is not possible or is expected to take too long, we recommend a single 150 mL bolus of 3% hypertonic saline administered over 10–20 minutes to prevent further decline in plasma sodium concentration and the development of severe symptoms, with a target increase in plasma sodium concentration of 4–6 mmol/L within 4–6 hours (⊕OOO).
- **Recommendation 5.3** We recommend assessing the clinical and biochemical effects of the first bolus within 1 hour and repeat the bolus if necessary (⊕OOO).
- **Clinical practice point 5.a** Limit the increase in plasma sodium concentration to 10–12 mmol/L over 24 hours in patients with acute hyponatraemia.

6. Preventing and treating overcorrection

- **Recommendation 6.1** In patients who have exceeded, or are on a trajectory to exceed, the 24-hour limit, we recommend discontinuing active treatment (⨁⨁◯◯).
- **Recommendation 6.2** We recommend a reactive strategy in patients with a baseline plasma sodium concentration <120 mmol/L or 120–130 mmol/L (in the presence of risk factors for osmotic demyelination syndrome), who are on a trajectory to exceed the 24-hour limit but have not yet overcorrected (⨁◯◯◯).
- **Recommendation 6.3** As a reactive strategy, we suggest a single dose of 1–2 µg desmopressin subcutaneously or intravenously and/or intravenous 5% dextrose at an initial rate of 3 mL/kg/h to prevent overcorrection (⨁◯◯◯).
- **Recommendation 6.4** We recommend a rescue strategy for patients who have overcorrected beyond the 24-hour correction limit and have a baseline plasma sodium concentration <120 mmol/L or 120-130 mmol/L in the presence of risk factors for osmotic demyelination syndrome (⨁◯◯◯).
- **Recommendation 6.5** As a rescue strategy, we suggest a single dose of desmopressin 1-2 µg subcutaneously or intravenously, combined with an initial intravenous infusion rate at 3 mL/kg/h of 5% dextrose, aiming to relower the plasma sodium concentration below the predetermined 24-hour correction limit, ideally within 6 hours (⨁◯◯◯).
- **Recommendation 6.6** We suggest adjusting the 5% dextrose infusion rate to exceed urinary output, thereby preventing a further increase in plasma sodium concentration (⨁◯◯◯).
- **Recommendation 6.7** We recommend checking plasma sodium every 1–2 hours and discontinuing intravenous dextrose and further desmopressin once the plasma sodium concentration has fallen below the predetermined 24-hour correction limit (⨁⨁◯◯).

7. Treatment of hyponatraemia according to cause

- **Recommendation 7.1** We recommend treating the underlying cause of hyponatraemia, if possible ($\oplus$OOO).
- **Recommendation 7.2** In patients with hypovolaemic hyponatraemia, we recommend restoring extracellular volume with an intravenous infusion of 0.9% saline or a balanced crystalloid solution ($\oplus$OOO).
- **Clinical practice point 7.a** Manage patients with haemodynamic instability in an environment where close biochemical and clinical monitoring can be provided.
- **Clinical practice point 7.b** In haemodynamic instability, urgent fluid resuscitation takes precedence over plasma sodium correction limits, but subsequent measures to prevent plasma sodium overcorrection within 24 hours should be considered.
- **Clinical practice point 7.c** Treat hypervolaemic hyponatraemia in patients with established heart failure or liver cirrhosis according to the respective guidelines for these diseases.

Syndrome of inappropriate antidiuresis

- **Recommendation 7.3** In the syndrome of inappropriate antidiuresis (SIAD), we recommend fluid restriction of ≤1 L/day as first-line treatment ($\oplus\oplus$OO).
- **Clinical practice point 7.d** In patients with SIAD, assess predictors of non-response to fluid restriction, including urine osmolality >500 mOsm/kg H_2O and urine sodium >130 mmol/L, to guide early consideration of second-line treatment when appropriate.
- **Recommendation 7.4** In patients with SIAD who have insufficient response to fluid restriction and who require further correction, we suggest oral urea, vasopressin-2 receptor antagonists, or an SGLT2 inhibitor as second-line treatment ($\oplus\oplus$OO).
- **Clinical practice point 7.e** Prescribe an initial total daily dose of 15–30 grams oral urea using a palatable formulation (pre-formulated powder, dissolved in flavoured beverage or commercially available preparation).

Vasopressin-2 receptor antagonists

- **Clinical practice point 7.f** If vasopressin-2 receptor antagonists are used, initiate at low dose, avoid concurrent fluid restriction, and commence in hospital to mitigate the risk of overly rapid sodium correction.
- **Clinical practice point 7.g** If overcorrection with a vasopressin-2 receptor antagonist occurs, discontinue it and start 5% dextrose at an initial infusion rate of 3 mL/kg/h, adjusting the infusion rate to exceed urinary output to prevent further increases in plasma sodium concentration.
- **Clinical practice point 7.h** Desmopressin should not be used to treat overcorrection in patients receiving vasopressin-2 receptor antagonists.
- **Clinical practice point 7.i*** Exercise caution and frequently monitor plasma sodium concentration when starting vasopressin-2 receptor antagonists in patients with a plasma sodium concentration <120 mmol/L because of the increased risk of overcorrection.

**There was no unanimous consensus on this clinical practice point among the guideline working group. Two guideline working group members preferred a recommendation against the use of vasopressin-2 receptor antagonists in patients with a plasma sodium concentration <120 mmol/L.*

- **Clinical practice point 7.j** Combine empagliflozin at 25 mg once daily (or an equivalent dose of another SGLT2 inhibitor) with fluid restriction (<1.0–1.5 litre/day).
- **Recommendation 7.5** If the second-line treatments for SIAD are unavailable, we suggest loop diuretics plus oral sodium chloride as a possible alternative ($\oplus$OOO).
- **Recommendation 7.6** We recommend against the use of lithium or demeclocycline for the treatment of the syndrome of inappropriate antidiuresis ($\oplus$OOO).

1. Introduction

Hyponatraemia is defined as a plasma sodium concentration < 135 mmol/L. Hyponatraemia is the most common electrolyte disorder, occurring in 15-30% of hospitalised patients.[1, 2] Hyponatraemia is common in all areas of clinical practice, is managed by multiple specialities, is associated with adverse outcomes and can be challenging to manage. This guideline is a revised version of the hyponatraemia guideline published in 2014.[3-5] The European Society of Endocrinology (ESE) and the European Renal Association (ERA) have supported the development of this guideline. This guideline aims to give an up-to-date evidence base to the clinical management of patients with hyponatraemia and to provide guidance for clinicians involved in everyday clinical practice.

Key challenging areas addressed by this guideline

1. Various classifications of hyponatraemia based on biochemical severity, symptom severity, volume status and acuity of onset **(Table 1)**.
2. The need to recognize that patients with hyponatraemia can present with a spectrum of symptoms and how this should be considered when assessing the acuity of onset and the need for immediate treatment **(Figure 1)**.
3. The need to identify which patients are at risk of cerebral oedema due to acute hyponatraemia (or acute on chronic hyponatraemia), which are at risk of osmotic demyelination syndrome (ODS) due to overly rapid correction of chronic hyponatraemia, and which are at low risk of either neurological complication **(Table 2, Table 3)**.
4. Emphasis on the importance of integrating clinical parameters (history and physical examination) into the diagnostic algorithm for patients with hyponatraemia **(Figure 2)**.
5. In patients with severely symptomatic hyponatraemia there is an increased morbidity and mortality if there is a delay in treatment or inappropriate treatment; the optimal management will be discussed **(Figure 3)**.

6. Specific guidance is provided for a specific subgroup of patients, namely those with acute hyponatraemia (≤48 hours) without severe symptoms. The goal in these patients is to prevent a further decline in the plasma sodium concentration and the development of severe symptoms **(Figure 4).**
7. We introduce a target range and a limit for both the change in plasma sodium concentration and the time to achieving it, as we believe this better reflects clinical practice. The target range is defined as the range of increase in plasma sodium concentration aimed for with a specified therapy; the limits are the boundaries beyond which sodium correction is considered unsafe. It should be emphasized that no studies have compared different target ranges, and the rates of plasma sodium correction achieved in studies are not a good surrogate for such comparisons.[6]
8. Overcorrection of chronic hyponatraemia can cause severe neurological deficits and death due to ODS; we will provide guidance on how best to limit this risk **(Table 4, Figure 5)**.
9. In patients with SIAD who fail to respond to fluid restriction we will provide an evidence-based approach to second-line treatment options **(Figure 3)**.

Summary of changes from the previous guideline

1. Classification of severe hyponatraemia as <120 mmol/L and abandonment of the term 'profound hyponatraemia'.
2. Reintroduction of volume assessment in the diagnostic algorithm.
3. No longer recommending routine exclusion of hypothyroidism in patients suspected of having the syndrome of inappropriate antidiuresis.
4. No longer routinely repeating the 150 mL bolus of 3% hypertonic saline.
5. Stratification of 24-hour correction limits based on the baseline plasma sodium concentration and the risk of ODS.
6. Recommendations for preventing and treating overcorrection using a reactive or rescue approach with desmopressin and/or intravenous 5% dextrose (or as equivalent intravenous 5% glucose).

7. Expanded options for second-line treatment of the syndrome of inappropriate antidiuresis, including oral urea, vasopressin-2 receptor antagonists, and SGLT2 inhibitors, with practical guidance on their use.

3. Physiology and pathophysiology

We provide a brief summary of water balance and sodium (patho)physiology, emphasizing key concepts. More detailed reviews of the (patho)physiology of water balance can be found elsewhere.[7-11]

3.1 Plasma sodium, osmolality, and effective osmolality

Osmolality is the molar quantity of solutes in a given weight of water (expressed as mOsm/kg H_2O), regardless of whether the osmoles can move across biological membranes. It can be measured or can be estimated using a standard equation **(Table 5)**. ***Osmolarity*** is the molar quantity of solutes in 1 litre of water; as physiological solutions are dilute, osmolarity and osmolality values are similar. Plasma sodium concentration reflects the amount of sodium in plasma relative to water and is typically maintained within a narrow range by a balance between fluid and solute intake and urine excretion.[12] Sodium is the principal cation contributing to plasma osmolality because the concentration of other cations (such as potassium) is low in extracellular fluid (ECF); potassium, however, plays an important role in osmotic balance, as potassium is the major cationic osmole in intracellular fluid (ICF), which is in osmotic equilibrium with ECF. ***Effective osmolality***, also called *tonicity,* refers to osmoles that drive water movement between body compartments and typically is estimated as sodium (with accompanying anions) and glucose. It is a function of the relative solute permeability across membranes and transmembrane concentration differences.[13] Only effective solutes create osmotic pressure gradients across cell membranes and can drive osmotic water movement. In steady state situations, however, urea is considered 'ineffective' in body water and is therefore omitted from the calculation of plasma tonicity **(Table 5)**.

3.2 Regulation of water intake, arginine vasopressin secretion, and urine concentration

Thirst is a critical physiological process[14] mediated by distinct neurons.[15] One set of neurons responds to hypertonicity and drives water consumption. The other set responds to ECF volume depletion and

drives salty fluid consumption. Anticipatory and gut-driven effects can suppress thirst even before plasma osmolality changes.[16, 17] Although thirst is physiologically regulated, daily fluid consumption in most developed countries is not linked to salt intake and reflects behavioural factors.[18] Kidneys filter fluid isosmotically; fluid becomes concentrated and then diluted as it courses through of the loop of Henle, thereby entering the distal convoluted tubule hypotonic to plasma. These processes occur whether the urine is concentrated or dilute. The osmolality of excreted urine is modulated primarily by arginine vasopressin (AVP), also called antidiuretic hormone. Urine osmolality typically ranges from 50 to 1200 mOsm/kg H_2O, depending primarily on circulating concentrations of AVP.[19] AVP secretion is driven primarily by rises in plasma osmolality, which is sensed by osmoreceptors in the brain, thereby sending signals to neurons in the supraoptic and paraventricular nucleus of the hypothalamus driving AVP synthesis and secretion. As with thirst, AVP synthesis and secretion is modulated by 'presystemic' signals that include fluid drinking and feeding cues.[20] While it is often suggested that the osmotic threshold for AVP release is lower than the osmotic threshold for triggering thirst[21], this has been contested[22] and the thirst threshold may change in some cases of the syndrome of inappropriate antidiuresis (SIAD).[23] AVP is generated as a pre-pro hormone that is cleaved, producing equimolar amounts of AVP, neurophysin II and copeptin. Once released into the circulation, AVP acts on V1a receptors in vascular smooth muscle, V2 receptors in the kidney, and V1b (V3) receptors in anterior pituitary corticotroph cells.[24] The activation of V2 receptors by AVP leads to the insertion of aquaporin 2 water channels into the apical membrane of principal cells of the collecting duct.[25] It also activates the furosemide-sensitive sodium-potassium-chloride type 2 cotransporter via adenylyl cyclase 6 along the thick ascending limb leading to an increase of medullary osmolality.[26] Both effects foster urinary concentration. AVP secretion is also stimulated by baroreceptors, leading to 'non-osmotic' or baroregulated AVP release. Stretch-sensitive receptors in the left atrium, carotid sinus and aortic arch sense effective arterial blood volume (EABV). When EABV decreases, the discharge rate of firing slows, increasing AVP secretion.[27] Reductions in blood pressure by as little as 5% increase the plasma AVP concentration[28] and EABV affects AVP secretion across a range of values. Osmoregulated and

baroregulated AVP secretion are interdependent, therefore, renal water excretion can be maintained around a lower setpoint of osmolality (lower plasma sodium concentration) when the EABV is decreased only modestly.[29] If circulatory hypovolaemia is substantial, the plasma AVP concentration increases dramatically and baroregulation overrides the osmoregulatory system.[29]

3.3 Pathophysiology of hyponatraemia

The sequelae of hyponatraemia result from plasma hypotonicity, which shifts water from the blood into cells. It is important, however, to recognize that hyponatraemia can occur without low osmolality. Pseudohyponatraemia is a measurement error that results from an excess of protein or lipid fraction of plasma without affecting the measured osmolality.[30] This phenomenon is observed with traditional analysis methods like photometry but also with indirect potentiometry (ion-selective electrode) as is used in most modern laboratories. In contrast, direct potentiometry (blood gas analyser) will provide the correct sodium concentration. Additionally, true but non-hypotonic hyponatraemia occurs when water translocates from cells into the ECF, driven by endogenous (e.g., glucose) or exogenous osmotically active solutes (e.g., mannitol) in the plasma. The much more common hypotonic hyponatraemia results from an imbalance between fluid intake and electrolyte free water excretion. Healthy individuals can dilute urine to 50 mOsm/kg H_2O. Therefore, with a typical daily osmotic load near to 600 mOsm/kg, excess fluid intake alone rarely causes hyponatraemia (i.e., only if water intake is > 12 litres per day). When solute intake is low or diluting capacity is impaired (due to presence of AVP), hyponatraemia can develop from much less excessive fluid consumption. Most cases of hypotonic hyponatraemia therefore are driven by AVP secretion, whether 'appropriate' (physiological) or 'inappropriate'. When the plasma is hypotonic, osmotic AVP secretion should be suppressed, unless non-osmotic physiological factors, such as ECF volume depletion, are present. Therefore, AVP secretion in the absence of non-osmotic stimuli and below the physiological osmotic threshold for AVP secretion defines SIAD.[31] Many diagnostic algorithms for hyponatraemia classify patients according to their ECF volume status. This serves to emphasize that hyponatraemia can be present when the ECF volume is

high, low, or 'normal'; the latter is often referred to as *euvolaemic* hyponatraemia. Recent reviews often emphasize that clinical estimation of ECF volume is of limited value; for this reason, the algorithm presented in the previous guidelines emphasized these limitations.[3-5] Yet, the studies of clinical assessment nearly always exclude patients with oedema[32, 33], and other studies suggesting the limited value of clinical exam primarily focus on distinguishing euvolaemia and hypovolaemia.[32-36] Patient interactions nearly always begin with a history and physical exam, which includes ECF volume assessment. Such assessments provide a 'pretest probability' before further diagnostic tests are interpreted, therefore impacting the positive and negative predictive values of clinical assessment of hyponatraemia.[37] In fact, hypervolaemic hyponatraemia most often occurs in later stages of heart failure or liver cirrhosis and carries an ominous prognosis; in these cases, history and physical examination are relatively accurate, meaning that ancillary tests may not be essential.[31, 37] In contrast, a clinician's ability to distinguish between hypovolaemic hyponatraemia and euvolaemic hyponatraemia by history and physical exam is limited, making further diagnostic tests useful and more reliable, as the pretest probability is uncertain.

3.4 Pathophysiology of the syndrome of inappropriate antidiuresis (SIAD)

SIAD was first characterised in two patients with hyponatraemia who had bronchogenic carcinoma but appeared euvolaemic; it was postulated to result from excessive AVP secretion[38], either ectopic, as from a tumour, or eutopic (from the neurohypophysis itself). Such AVP secretion seemed dissociated from either osmotic or volume-driven signals and was therefore deemed 'inappropriate'. It is now known to follow several different patterns and result from a host of factors **(Figure 6)**.[39-42] In rare cases, AVP cannot be detected, and these patients have activating genetic variants in the vasopressin-2 receptor[43], favouring the use of the more general term SIAD rather than SIADH.[31] Characteristic diagnostic criteria for SIAD typically include decreased effective osmolality, inappropriate urine concentration, clinical euvolaemia, and urine sodium >30 mmol/L **(Table 6**).[31, 38, 44]

3.5 Pathophysiology of hypovolaemic hyponatraemia

Approximately 25% of patients presenting to the emergency department with hyponatraemia have low ECF volume as a contributing cause.[45] Hypovolaemic hyponatraemia results when ECF volume depletion stimulates non-osmotic (baroregulated) AVP release and thirst. In this case, ingested fluid is not excreted, owing to the effects of AVP.[46] As low ECF volume is the pathophysiological cause, affected patients require saline administration (or salt intake), which by correcting the ECF volume depletion allows AVP to decline and water excretion to ensue. As noted above, while clear historical or physical findings may point to hypovolaemia as a cause, additional diagnostic tests are often useful in distinguishing low from normal ECF volume.

3.6 Pathophysiology of thiazide-induced hyponatraemia

Hyponatraemia is associated with the use of thiazides and thiazide-like diuretics (e.g. indapamide, chlorthalidone) in susceptible individuals leading to substantial morbidity. Risk factors include age, female sex, and perhaps low muscle mass.[47, 48] Although initially described as developing early after thiazide initiation, the time frame is likely wider.[49] Many cases are asymptomatic or have mild symptoms but serious complications may result. The pathophysiology is likely multifactorial and includes excessive fluid intake, sodium and potassium depletion, and reduced ability to excrete free water, related in part to prostaglandin E2 production.[50] Patients with thiazide-induced hyponatraemia may either be hypovolaemic or euvolaemic.[51, 52]

3.7 Pathophysiology of hypervolaemic hyponatraemia

Hypervolaemia is the cause of hyponatraemia in 10-20% of patients presenting to emergency departments.[45] In most of these cases, AVP is stimulated because of EABV depletion despite ECF volume expansion.[53] In patients with heart failure, this results from poor cardiac function. Cirrhosis of the liver causes splanchnic vasodilation and low plasma oncotic pressure, favoring fluid transudation out of capillaries. In both cases, baroreceptors (discussed above) sense that arterial pressure is below

the haemodynamic set point, thereby secretion AVP despite hyponatraemia. Hyponatraemia is less commonly encountered in the setting of nephrotic syndrome, but in 'underfilled' paediatric patients, especially those with minimal change disease, hyponatraemia may also result from low EABV.

3.8 Pathophysiology of cerebral salt wasting

This is a disorder that is characterised by increased release of natriuretic peptides and reduced sympathetic stimulus to the kidneys, causing salt wasting and suppression of the renin-angiotensin-aldosterone system. It is important to distinguish cerebral salt wasting from SIAD as these two conditions can be present in patients with traumatic brain injury and other neurological conditions, but their management is very different **(Table 7)**.[54-58] Cerebral salt wasting is a rare cause of hyponatraemia in neurosurgical patients compared to SIAD.[56] Patients with cerebral salt wasting are hypovolaemic with large volumes of urine with significantly elevated urinary sodium concentrations and require aggressive fluid resuscitation to restore circulating blood volume and normalise plasma sodium. Treatment is generally required for a short term as this condition typically resolves within days to weeks.

4. Diagnostic algorithm

The 2014 guideline proposed a diagnostic algorithm that did not include the clinical assessment of the volume status due to previous studies showing low sensitivity and specificity, especially when distinguishing between euvolaemia and mild hypovolaemia, with concerns of misclassifying the cause of hyponatraemia.[59] However, the current guideline working group believes that each diagnostic parameter for hyponatraemia has limitations and therefore proposes to integrate clinical history, the assessment of volume status in conjunction with laboratory testing as a start point to guide the evaluation of patients with hyponatraemia **(Figure 2).** In addition, we recommend incorporating the clinical context including medical history and medications in the evaluation of the aetiology **(Table 8)**. Severely symptomatic hyponatraemia is associated with significant morbidity and mortality if untreated[1, 10, 60]; therefore, these patients require a rapid intervention (**Figures 2–3**) and awaiting the results of laboratory testing with the aim of differentiating aetiologies of hyponatraemia should not delay their management. When severe symptoms requiring immediate treatment are absent, an integrated assessment of volume status, urine osmolality, and urine sodium will usually allow identification of the cause of hyponatraemia. In addition to urine osmolality and urine sodium, the fractional excretion of uric acid ([uric acid urine/plasma] / [creatinine urine/plasma]) is another marker that can help determine the aetiology of hyponatraemia, particularly in patients receiving thiazide or loop diuretics.[61] Uric acid is reabsorbed in the proximal tubule and is therefore not affected by diuretics. In a study of 86 patients with hypotonic hyponatraemia, patients were divided into SIAD and non-SIAD groups, of whom 15/31 (48%) and 42/55 (76%) were on diuretics, respectively. A fractional excretion of uric acid >12% had a 100% positive predictive value for SIAD, whereas a fractional excretion < 8% had a 100% negative predictive value for SIAD.[61] Finally, it is important to emphasize that if there is not an appropriate and lasting response in plasma sodium concentration to treatment, then clinical assessment, diagnostic testing and therapeutic approach should be reassessed. The clinical practice points regarding the diagnostic approach to hyponatraemia, together with their rationales, are discussed in Section 8.2.

5. Methods

Guideline working group

This joint clinical guideline was initiated and developed on behalf of the European Society of Endocrinology (ESE) and the European Renal Association (ERA). The co-chairs of the guideline working group, Mark Sherlock (ESE) and Ewout J. Hoorn (ERA), were appointed by the ESE Clinical Committee and the ERA Council, respectively. Olaf Dekkers served as the methodology lead, supported by Leonie van Hulsteijn. Jule Pinter was the ERA Young Nephrologists' Platform representative. Christie Turin served as representative of the Endocrine Society and David Ellison as representative of the American Society of Nephrology. The other members were suggested by the co-chairs and approved by the ESE Clinical Committee and ERA Council, including Stephen Ball, Volker Burst, Mirjam Christ-Crain, Evi Nagler, Alberto Ortiz, Alessandro Peri and Julie Refardt. Prior to the process, all participants completed conflict of interest forms (see **Supplementary Table 1**). The process was approved by the ESE Executive Committee and the ERA Council.

Aims

The overall purpose of this guideline is to provide clinicians with practical guidance for diagnosing and managing hyponatraemia in adult patients. Recommendations are not meant to replace clinical acumen and may need adaptation to local circumstances.

Guideline methodology

The methods used for establishing the guideline have been described in detail previously.[62, 63] In short, Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) was used as a methodological basis. The first step was to define the clinical questions (see below) followed by systematic literature searches. We estimated an average effect for specific outcomes where possible and rated the quality of the evidence behind the recommendations as very low (⨁OOO), low (⨁⨁OO), moderate (⨁⨁⨁O), or high (⨁⨁⨁⨁). Not all recommendations were formally graded

(see below). Considered for the recommendations were the quality of the evidence, the balance of desirable and undesirable outcomes, and individual values and preferences (patient preferences, goals for health, costs, management inconvenience, feasibility of implementation).[62, 64] The recommendations are worded as 'recommend' (strong recommendation) or 'suggest' (weak recommendation). The meaning of a strong recommendation ('recommend') is that all reasonably informed persons (clinicians, policy makers and patients) would want the management in accordance with the recommendation, while for a weak recommendation ('suggest'), most persons would still act in accordance with the guideline, but a substantial number would not.[65] Formal evidence syntheses were performed and graded only for recommendations addressing our initial clinical questions (see 'Clinical questions, eligibility criteria, and definition of endpoints' section). Recommendations that were based on clinical practice and experience of the guideline working group are not formally graded[66], but acknowledged in the guideline as a 'clinical practice point'. Recommendations that were neither based on evidence synthesis or good clinical practice, are not graded at all. Consensus was reached upon discussion; potential minority positions could be considered in the rationale behind recommendations and when unanimous consensus was not achieved this is highlighted in the guideline.

6. Results of the systematic reviews

Clinical questions, eligibility criteria, and definition of endpoints

At the start of the guideline process, the working group formulated clinical questions regarding several treatment aspects of patients with hyponatraemia, i.e., optimal treatment algorithm, optimal use of hypertonic saline, incidence of and risk factors for the ODS, plasma sodium relowering treatment, and optimal strategies for treating chronic hyponatraemia due to SIAD. The clinical questions that formed the basis for the systematic reviews are summarized in **Table 9**. For the final question (i.e. optimal treatment of SIAD), we relied on data derived from the updated Cochrane Review on interventions for chronic non-hypovolaemic hypotonic hyponatraemia.[67] Eligible articles were required to present data on adult patients (≥ 18 years). Case reports or case series, which are more prone to selection and publication bias, were not included; only studies reporting a population of 25 or more (Clinical questions I, II and IIIc) or 50 or more patients (Clinical question IIIa and b) were eligible. In case of multiple studies describing the same cohort, the study comprising the highest number of subjects was included. For clinical question IIIa (ODS incidence), the number of patients with ODS (numerator) and the total number of patients being treated for hyponatraemia (denominator) were used to estimate the incidence of ODS.

Description of search and selection of literature

PubMed, MEDLINE, Embase, Web of Science, and Cochrane Library were searched with the help of a specialized librarian to identify potentially relevant studies. The literature searches for the clinical questions were performed in April 2025. Searches can be found in **Appendix 1** in the Supplementary Materials. All studies obtained from the searches were entered into a web-based collaboration software platform that streamlines the production of systematic and other literature reviews (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia), and title and abstract were screened. Potentially relevant studies were retrieved for detailed assessment and independently reviewed by three reviewers. Any discrepancies were resolved by consensus. References

of included studies were assessed for additional relevant articles. Prisma flowcharts can be found in the Supplementary Materials.

Summary and interpretation of evidence from the systematic reviews

Clinical question I: ***What is the optimal correction rate (i.e. change in plasma sodium concentration per unit time) during treatment of adult patients with hypotonic hyponatraemia?***

Sixteen retrospective studies were identified with a total of 32,169 patients that provided information on plasma sodium change during treatment and the following outcomes: mortality (*n* = 13 studies), central nervous system status/neurological outcome (mainly occurrence of ODS; *n* = 11), time to recovery from hyponatraemia (*n* = 2) and length of hospital stay (*n* = 8). None of these studies assessed symptom improvement or quality of life. Study populations were heterogenous with a variety of hyponatraemia aetiologies, treatment strategies and comorbidities (see Supplementary Materials for details of included studies), and inclusion criteria including the threshold for initial plasma sodium concentration, differed between studies.

Mortality and correction rate: Thirteen studies assessing mortality found the highest mortality in those with the lowest absolute change in plasma sodium concentration over a specified time frame (taken as correction rate)[68-77] and the highest survival in those with the fastest correction rates.[72, 78-80] One of these studies compared data between patients with biochemically severe hyponatraemia (defined as a plasma sodium concentration < 125 mmol/l) and biochemically mild hyponatraemia (plasma sodium concentration 125-135 mmol/l)[71]: although in severe hyponatraemia odds ratio's for mortality were lowest for patients with the most rapid increase of plasma sodium concentration, in mild hyponatraemia the odds ratio's for mortality were similar for subgroups with different correction rates.

Neurological outcome and correction rate: Eleven studies assessed neurological status, of which ten assessed the development of ODS.[68, 69, 73-76, 78, 81-84] In five of these studies there were no cases of ODS, but in the studies in which ODS did occur, this was generally with faster correction rates (see also **Clinical question III**).[69, 74, 76, 78, 84] Three studies reported on neurological complications with inconsistent

results; while two studies found that a rapid correction rate was associated with development of neurological complications[73, 82], this could not be confirmed by a study reporting similar percentages of patients with neurological complications in those with correction rates of > 12 mmol/L/24h and/or > 18 mmol/L/48h vs. ≤ 12 mmol/L/24h and/or ≤ 18 mmol/L/48h (22% vs. 23%, p = 0.77).[75]

Time to recovery of hyponatraemia: Two studies assessed time to recovery from hyponatraemia (defined as a normal plasma sodium), reporting a higher percentage of patients reaching normonatraemia after 72 hours with a correction rate of > 12 mmol/L/24h and/or > 18 mmol/L/48h vs. ≤ 12 mmol/L/24h and/or ≤ 18 mmol/L/48h (43% vs. 22%, p-value not reported)[75], and a higher plasma sodium concentration at discharge with a faster correction rate (mean 135 ± 5 mmol/L with correction rate > 10 mmol/L/24h vs. mean 132 ± 5 mmol/L at 6-10 mmol/L/24h and mean 130 ± 6 mmol/L at < 6 mmol/L/24h, p-value not reported).[76]

Length of stay: All eight studies reported a shorter length of stay in patients with faster correction rates[68, 70, 75-80], although this reached statistical significance in only one study.[68]

Risk of bias: The data preclude us from concluding that correction rates > 8 to 10 mmol/L are safe with respect to development of ODS. Residual confounding is a potential bias in all observational studies. Moreover, time-dependent confounding and selection bias were mostly not considered. Most importantly, these studies did not investigate different treatment strategies, but achieved rates, which, however, are not actionable.[6] This makes the results of limited value to inform treatment.[6, 85] These methodological considerations lead to a very low certainty of evidence (description of the GRADE evidence can be found in the Supplementary Materials).

Clinical question II: ***What is the (optimal) use of 3% hypertonic saline in the treatment of hypotonic hyponatraemia in adult patients?***

Results of this question were divided in “use” and “optimal use”, with the following outcomes of interest: improvement in severe symptoms of hyponatraemia, biochemical outcomes, overcorrection, and mortality. Eight studies on the use of hypertonic saline in a total of 873 patients were included: an

RCT, a historically controlled trial and six retrospective studies. All but one study used 3% hypertonic saline (hereafter referred to as hypertonic saline), whereas one study used 170 mls of 2.7% hypertonic saline.[68] In two studies slow continuous infusion (SCI) of hypertonic saline was used[86, 87]; in six studies a rapid intermittent bolus (RIB) whether or not followed by SCI.[68, 88-92] Five studies were non-comparative[68, 86, 89-91], one compared hypertonic saline to conventional treatment (not further specified)[88], and two to vasopressin-2 receptor antagonists (see Supplementary Materials for further study details).[87, 92] The quality of evidence was very low due to the mostly retrospective design, (residual) confounding, heterogeneity and small numbers. Besides the apparent, and physiologically expected, rise in plasma sodium concentration with hypertonic saline[68, 86-92], one study reported a steeper increase in plasma sodium concentration in patients with severely symptomatic hyponatraemia with hypertonic saline than with conventional treatment (mean change in plasma sodium after 24h: 9 ± 5 mmol/L vs. 6 ± 4 mmol/L).[88] Overcorrection after 24 hours of hypertonic saline treatment ranged from 0% to 44.9%[68, 86, 88-91], but no cases of ODS were reported. Three studies were identified assessing *optimal use* of hypertonic saline in a total of 358 patients. Two studies, of which one was an RCT, compared effects of RIB (2 mL/kg and 100 mL, respectively; repeated depending on symptom severity or effect on plasma sodium concentration increase) vs. SCI (0.5 mL/kg/h in moderately severe and 1.0 ml/kg/h in severe symptoms, and 20 mL/h, respectively)[93, 94], and one study the effects of an initial hypertonic saline bolus of 100 mL vs. an initial hypertonic saline bolus of 250 mL.[95] The RCT showed no clear difference in efficacy of increasing plasma sodium concentration or improving symptoms, but RIB, when compared with SCI, showed better efficacy in achieving target correction rate within 1 hour (intention-to-treat analysis: 28 of 87 (32.2%) vs. 16 of 91 (17.6%) patients, respectively).[93] Lower rates of overcorrection with RIB vs. SCI were reported (17% vs. 24%), although this was non-significant.[93] Results of the non-randomised study showed RIB was more effective than SCI in plasma sodium concentration rise and improving neurological status after 6 hours and 12 hours, but equally effective at ≥ 24 hours.[94] When RIB is given, a 250 mL initial bolus seems more effective than a 100 mL initial bolus, while the safety does not show marked differences.[95] However, real world data show that lower

total volumes are associated with lower risk of overcorrection (overcorrection after 1st bolus: 22.6%, after 2nd bolus 34.6% and after 3rd bolus 41.7%).[68] Finally, one study on hypertonic saline use found overcorrection to be independently associated with lower body weight (≤ 60 kg), and under correction with body weight ≥ 100 kg.[90] Future studies should therefore investigate whether bolus volumes should be adjusted according to body weight.

Clinical question IIIa: ***What is the incidence of ODS in patients being treated for hypotonic hyponatraemia?***

Twenty-six studies assessing ODS incidence were included. A study of the Swedish National Patient Register reported a population level incidence of 0.61 per million person-years (95% CI: 0.49-0.75).[96] The other 25 studies, including 24 cohort studies[68, 69, 73, 75, 76, 78, 80, 81, 83, 84, 94, 95, 97-108] and one post-hoc analysis of the SALSA trial[109], comprised a total of 33,832 patients with a variety of hyponatraemia aetiologies, treatments and comorbidities. A meta-analysis showed a low incidence of ODS in patients being treated for hyponatraemia: 0.05% (95% CI 0.00-0.19%) **(Figure 7)**. Certainty of evidence was moderate due to concerns on bias (heterogeneity and measurement of outcome related to exposure, i.e., availability of magnetic resonance imaging in those with overcorrection; see Supplementary Materials).

Clinical question IIIb: ***What are the risk factors or subgroups at risk for developing ODS while being treated for hypotonic hyponatraemia?***

Inherent to the low incidence of ODS, there were no studies identified which systematically assessed risk factors, or subgroups at risk for ODS. Therefore, it was decided to group clinical characteristics of reported patients who developed ODS (*n* = 45 in nine studies included for Clinical question IIIa[69, 76, 78, 80, 84, 101-103, 108]). Overlapping characteristics are a low initial plasma sodium concentration (<120 mmol/L), plasma sodium overcorrection (defined at the discretion of the respective studies), alcoholism, liver cirrhosis, malnutrition and hypokalaemia (Table, Supplementary Materials).

Clinical question IIIc: ***When overcorrection develops, is correction indicated? If yes, what is the best treatment option to relower overcorrection?***

There were no studies identified which could answer the first question, i.e. studies that compared a wait-and-see approach to active correction. Four studies did assess effects of different desmopressin strategies (*n* = 473) in conjunction with hypertonic saline treatment vs. hyponatraemia treatment not including desmopressin (*n* = 1337)[101, 110-112], and one RCT compared outcomes of a proactive vs. reactive strategy in 49 patients.[113] The following relowering strategies have been applied (see also **Table 4** and the detailed description in the rationales for the respective recommendations): early administration of desmopressin ("desmopressin clamp") before correction of hyponatraemia has started, usually in combination with hypertonic saline (*proactive strategy*); administration of desmopressin and/or 5% dextrose when a rapid increase in plasma sodium concentration is projected to exceed the 24-hour correction limit (*reactive strategy*); administration of desmopressin and 5% dextrose after the rise in plasma sodium concentration has exceeded the predefined 24-hour correction limit (*rescue strategy*).[114-117] With all treatment strategies, the rate of change in plasma sodium concentration decreased after desmopressin administration and less overcorrection was reported in all studies.[101, 110-112] The change in plasma sodium concentration fell below the predefined 24-hour correction in 83-96% of patients treated with the proactive strategy, 72-82% treated with the reactive strategy and 2% treated with the rescue strategy (this latter limited by confounding by indication).[101, 113] In the RCT, the proactive group had a greater increase in mean plasma sodium concentration than the reactive group at 48 h after initial treatment (but remaining within safety limits).[113] In-hospital mortality was similar in patients who were treated with hypertonic saline proactively vs. reactively or with the rescue approach (6.8% vs. 6.4%, p > 0.99). However, using any desmopressin strategy in hyponatraemia treatment (proactive, reactive or rescue) led to lower mortality than hyponatraemia treatment without desmopressin (3.9% vs 9.4%, p = 0.007).[101] Two studies reported a longer length of stay in hospital when a proactive strategy was used[101, 110]; however, this was not confirmed by the RCT.[113] Certainty of

evidence was low due to the mostly retrospective design, confounding and relatively small numbers, but these data support a possible role for desmopressin in reducing the rate of overcorrection (see Recommendations 6.1–6.7).

Clinical question IV: ***What is the optimal treatment of the syndrome of inappropriate antidiuresis (SIAD)?***

The updated Cochrane systematic review on treatments for chronic hypotonic non-hypovolaemic hyponatraemia included 53 RCTs, including 16 conducted exclusively in participants with SIAD, 8 in participants with heart failure, 11 in participants with liver cirrhosis, and 18 in mixed populations.[67] Thirty-four studies compared a vasopressin-2 receptor antagonist versus placebo, usual care or no treatment; five compared a vasopressin-2 receptor antagonist versus fluid restriction; three studies compared a sodium-glucose cotransporter-2 (SGLT2) inhibitor with placebo; two fluid restriction vs. unrestricted fluid intake; three studies oral urea vs. no treatment; finally, one study compared fluid restriction alone with furosemide + fluid restriction and furosemide + fluid restriction + oral sodium chloride. Overall, there is little high-certainty evidence that treatment improves patient-important outcomes such as mortality, quality of life, falls, or fractures. In placebo-controlled studies, patients eligible for RCTs experience an average 'spontaneous' rise of 2.2 mmol/L. Only one RCT compared fluid restriction (<1 L/day) with placebo (n=46; baseline sodium 126–129 mmol/L).[118] After three days, plasma sodium increased by 3 mmol/L with fluid restriction vs. 1 mmol/L without intervention; 61% reached ≥130 mmol/L. After one month, the increase with fluid restriction averaged 4 mmol/L. Trials comparing vasopressin-2 receptor antagonists with fluid restriction are in line with these findings.[119, 120] Vasopressin-2 receptor antagonists have uncertain effects on mortality and health-related quality of life because studies were considered at serious risk of suffering from selective reporting and performance bias, and confidence intervals were very wide. Vasopressin-2 receptor antagonists increase plasma sodium concentration by a mean of approximately 4 mmol/L in total and roughly double the probability of a ≥5–6 mmol/L rise. Certainty of the evidence was moderate and determined

by a risk of suffering from attrition bias. At the same time, they increase the risk of overly rapid correction by approximately 67% relative to control.[121] Exploratory analyses suggest that absolute risk of overcorrection is strongly modified by baseline sodium: at plasma sodium concentrations of approximately 130, 125, and 120 mmol/L, the estimated absolute risks are approximately in the order of ~4%, ~13%, and ~22%, respectively.[67] SGLT2 inhibitors increase plasma sodium by approximately 3–4 mmol/L in two small RCTs in patients with SIAD, but evidence for patient-important outcomes remains uncertain.[122, 123] Overcorrection occurred in two of 43 hospitalised patients in the RCT investigating the SGLT2 inhibitor empagliflozin in combination with fluid restriction (<1 litre/day),[123] whereas no overcorrection occurred in the outpatient RCT of empagliflozin in combination with fluid restriction (≤ 1.5 litre/day).[122] Although no RCTs of oral urea have been conducted, recent cohort studies and two systematic reviews suggest that oral urea is generally safe and effective for gradual correction of SIAD-induced hyponatraemia, although overcorrection and hypernatraemia may occur.[104, 124-127]

7. Recommendations and clinical practice points including rationales

7.1 Classification of hyponatraemia

Clinical practice point 1.a Use the same plasma sodium measurement method throughout management, particularly during emergency treatment.

Rationale: In most laboratories, sodium is measured by indirect potentiometry using an ion-selective electrode. Both, serum or plasma can be used and the difference between the two measurements is negligible.[128] For the sake of simplicity, we will use the term plasma sodium concentration throughout the guideline. In some circumstances (e.g., in the emergency department), sodium is often measured by direct potentiometry using a blood gas analyser. Readings from direct and indirect potentiometry have been reported to differ by approximately 2 mmol/L.[129, 130] In order to counteract the impact of these differences, we recommend using the same method of plasma sodium measurement throughout the course of management of a patient, particularly in those receiving emergency management.

Definition of hyponatraemia based on biochemical severity

Clinical practice points 1.b

Biochemical hyponatraemia is defined:

- as 'mild' if plasma sodium concentration ≥130 and <135 mmol/L.
- as 'moderate' if plasma sodium concentration ≥120 and <130 mmol/L.
- as 'severe' if plasma sodium concentration <120 mmol/L.

Rationale: The normal range for plasma sodium concentration is defined according to population-level data, with normal ranges typically validated by individual laboratories. The classification of values below this range is arbitrary and has been applied inconsistently across publications. We define 'mild biochemical hyponatraemia', 'moderate biochemical hyponatraemia' and 'severe biochemical hyponatraemia' to emphasize that these terms apply only to the plasma sodium concentration and not to symptoms. We use the term 'severe' rather than 'profound' (which was used in the 2014 guideline)

as it continues to be used by most authors.[9, 131-134] We define 'severe biochemical hyponatraemia' as < 120 mmol/L, as this value is cited frequently as clinically relevant[132] and is used as a cut point in recommendations 4.1, 6.2, and 6.4, and clinical practice point 7.i.

Definition of hyponatraemia based on time of development

Clinical practice points 1.c

With regard to duration of hyponatraemia:

- 'Acute' hyponatraemia is defined as hyponatraemia that is documented to exist ≤48 hours or when the clinical history is highly suggestive of this time course.
- 'Chronic' hyponatraemia is defined as hyponatraemia that is documented to exist for >48 hours.
- If the duration of hyponatraemia cannot be determined, it should be assumed to be chronic, unless clinical or historical evidence suggests otherwise.

Rationale: Hyponatraemia is often classified according to duration because the risks of hyponatraemia and risks and benefits of treatment thereof depend on duration. This classification is to some extent arbitrary[135], but data from animal models[136, 137] and case series[138] suggest that compensatory changes in brain organic osmolytes and potassium take place when hyponatraemia is present for longer than 24 hours; a 48 hour cut-off, although arbitrary, is widely employed.[31, 132, 135, 139, 140] The distinction between acute and chronic hyponatraemia can be established with certainty only when previous plasma sodium measurements document its duration relative to the 48-hour threshold. As such measurements are often unavailable, the distinction must rely on the presumed time course or, where this is uncertain, the clinical presentation. The risks of osmotic demyelination are higher when chronic hyponatraemia is overcorrected.[141]

Definition of hyponatraemia based on symptoms

Clinical practice points 1.d

With regard to symptoms of hyponatraemia:

- 'Mildly symptomatic' hyponatraemia is defined as any degree of biochemical hyponatraemia in the presence of mild symptoms of hyponatraemia.
- 'Moderately symptomatic' hyponatraemia is defined as any degree of biochemical hyponatraemia in the presence of moderate symptoms of hyponatraemia.
- 'Severely symptomatic' hyponatraemia is defined as any degree of biochemical hyponatraemia in the presence of severe neurological symptoms related to hyponatraemia.

Rationale: The development and severity of symptoms of hyponatraemia is a spectrum **(Figure 1)** and must be carefully assessed during investigations and management. Most of the symptoms of hyponatraemia are not specific for the electrolyte disorder. Thus, clinical judgement should be used when inferring a causal relationship between hyponatraemia and a certain symptom. The less pronounced the degree of biochemical hyponatraemia, the more caution should be taken when assigning hyponatraemia as the cause of the symptoms, especially in patients with more severe neurological symptoms and signs.

7.2 Differentiating causes of hypotonic hyponatraemia

Clinical practice point 2.a Incorporate the clinical context in the evaluation of the aetiology, chronicity, and clinical severity of hyponatraemia.

Rationale: A thorough clinical evaluation is essential in the initial assessment of a patient presenting with hyponatraemia. This process should begin with a detailed medical history, focusing on identifying underlying medical conditions and medications that may predispose to hyponatraemia. Key aspects to explore include chronic illnesses (such as heart failure, liver or kidney disease, adrenal insufficiency) or recent surgical procedures. A detailed medication review is also important, as several drugs are known to increase the risk of hyponatraemia such as anticonvulsants, antidepressants, antipsychotics, and anticancer drugs (including immune checkpoint inhibitors[142]), as well as recreational substances such as 3,4-Methylenedioxymethamphetamine (MDMA) **(Table 8)**. Clinicians should evaluate for symptoms

that may indicate acute hyponatraemia with resultant cerebral oedema and increased intracranial pressure, such as headache, vomiting, confusion, seizures, or altered mental status **(Figure 1)**. It is also important to identify factors that may indicate acute onset, such as recent surgery, trauma, prolonged exercise, excess water ingestion or the use of substances known to cause rapid development of hyponatraemia **(Table 3)**.

Clinical practice point 2.b Exclude non-hypotonic causes of hyponatraemia.

Rationale: Non-hypotonic causes of hyponatraemia include pseudohyponatraemia (a laboratory artifact) and translocational hyponatraemia (caused by a shift of water from the ICF to the ECF). Non-hypotonic hyponatraemia should be identified early in the evaluation because it is not associated with the neurological complications of hypotonic hyponatraemia and, once identified, does not require further diagnostic evaluation of the hyponatraemia itself. Pseudohyponatraemia is a laboratory artifact that results from sodium measurement by indirect ion-selective electrode potentiometry, producing a falsely low plasma sodium concentration despite a normal sodium activity in plasma water. This occurs because the indirect ion-selective electrode method assumes a fixed plasma-water fraction of approximately 93%, which is not a valid assumption when elevated protein or lipid concentrations increase the proportion of non-aqueous plasma components. Pseudohyponatraemia can be caused by hyperlipidaemia, including hypercholesterolaemia[143] and hypertriglyceridaemia in patients with pancreatitis[144] as well as hyperproteinaemia, which can be seen in patients with multiple myeloma.[145, 146] Direct ion-selective electrode methods (blood gas analysers and point-of-care devices) measure sodium in undiluted plasma water and are unaffected by variations in protein or lipid content. When pseudohyponatraemia is suspected, confirmation with a direct ion-selective electrode measurement or measured plasma osmolality can verify the artifact.[147] There are certain laboratory methods that do not require plasma dilution and could therefore eliminate risk of pseudohyponatraemia[147]; however, these may not be universally available. The most common cause of translocational hyponatraemia is hyperglycaemia. In hyperglycaemia hyponatraemia is caused by dilution due to hyperosmolality. Based

on the Hillier formula, plasma sodium concentration can be estimated from the degree of hyperglycaemia **(Table 5)**.[148] Other potential causes of non-hypotonic hyponatraemia include the infusion of mannitol or intravenous immunoglobulin which lead to a relative decrease in plasma water volume due to increase in the protein-containing nonaqueous phase of plasma.[149, 150] Recent prostate surgery with infusion of irrigation fluids is also a rare cause of non-hypotonic hyponatraemia.[151]

Clinical practice point 2.c If plasma glucose is elevated, assess whether the degree of hyperglycaemia explains the hyponatraemia.

Rationale: Hypertonic or isotonic hyponatraemia is caused by an excess of effective solutes other than sodium which induces a shift of water from the ICF to the ECF, resulting in a dilutional decrease in plasma sodium concentration. Glucose is the most common osmotically active solute responsible for this phenomenon, and the extent of dilutional hyponatraemia correlates with the severity of hyperglycaemia. To accurately assess for hyponatraemia in the setting of hyperglycaemia, the measured plasma sodium concentration should be corrected **(Table 5).**[148, 152] Of note, recent data suggest that hyperglycaemia lowers measured sodium through two mechanisms: a true translocational effect from osmotic water shifts and an analytical artifact on indirect ion-selective electrode measurement caused by a reduced plasma-water fraction.[153] Together, these mechanisms make the degree of plasma sodium concentration reduction sometimes appear greater than expected. A direct ion-selective electrode measurement avoids this interference and, when available, should be used in patients with hyperglycaemia.[153]

Clinical practice points 2.d Measure plasma osmolality to confirm hypotonic hyponatraemia (< 275 mOsm/kg H_2O).

Clinical practice points 2.e If the measured plasma osmolality is normal or high, calculate plasma tonicity to identify hypotonic hyponatraemia in the presence of ineffective osmoles.

Rationale for clinical practice points 2.d and 2.e: The normal plasma osmolality is approximately between 275 and 295 mOsm/kg H_2O. Measurement of the plasma osmolality is helpful to exclude pseudohyponatraemia and non-hypotonic causes of hyponatraemia such as translocational hyponatraemia. Although plasma osmolality measurement may not be available in all centres, particularly outside regular hours, it remains a useful tool when accessible and can help clarify whether hyponatraemia is truly hypotonic. The comparison between measured and calculated plasma osmolality is particularly useful for screening conditions where ineffective osmoles such as urea or alcohols increase plasma osmolality. There are several formulas that are used to calculate the plasma osmolality[154], one of them by Smithline-Gardner **(Table 5)**.[154, 155]

Clinical practice point 2.f Obtain a spot urine sample for osmolality and sodium before treatment, without delaying urgent treatment in patients with severe symptoms while awaiting results.

Rationale: Urine osmolality and sodium are essential for identifying the underlying mechanism and cause of hyponatraemia and guiding subsequent diagnostic evaluation and treatment. Obtaining a spot urine sample before treatment is important, as therapeutic interventions may rapidly alter urine composition and complicate interpretation. However, in patients with severe symptoms, treatment should not be delayed while awaiting urine results or further diagnostic investigations, given the risk of ongoing cerebral oedema and neurological deterioration. Urine sampling should therefore be performed promptly, provided this does not delay urgent treatment.

Clinical practice point 2.g Assess signs of extracellular fluid volume expansion and accept the aetiology as hypervolaemic hyponatraemia in patients with clear signs of extracellular fluid volume excess.

Clinical practice point 2.h Assess signs of extracellular fluid volume deficit and accept the aetiology as hypovolaemic hyponatraemia in patients with clear signs of extracellular fluid volume deficit.

Rationale for clinical practice points 2.g and 2.h: The clinical evaluation of the volume status is the next critical step in the identification of the cause of hyponatraemia, particularly when evaluating a

patient with clear signs of hypovolaemia (dry mucous membranes, increased skin turgor and postural hypotension) or hypervolaemia (peripheral oedema and jugular venous distension), which narrows the differential diagnosis.

Clinical practice point 2.i In patients without clear signs of extracellular fluid volume expansion or deficit, perform an integrated assessment of volume status, spot urine osmolality, and spot urine sodium to determine the cause of hyponatraemia.

Rationale: The diagnostic accuracy of clinical volume assessment is lower in cases of mild volume depletion, mild hypervolaemia, or euvolaemia.[32, 156] The most difficult clinical distinction is between mild hypovolaemia and euvolaemia. Given these limitations, it is recommended to supplement the clinical examination of the volume status with spot urinary sodium and urinary sodium to achieve a more accurate and comprehensive diagnostic approach **(Figure 2)**. There are only a limited number of studies that have evaluated the diagnostic accuracy of the physical exam in patients with hypovolaemia. Certain features such as postural pulse increment, postural hypotension or dizziness have a low sensitivity of 22% in patients with moderate blood loss and a higher sensitivity of 97% in patients with large blood loss.[34] In patients with decreased oral intake, vomiting or diarrhoea, dry mucous membranes, decreased skin turgor, postural tachycardia has a sensitivity that ranges from 29% to 85% and a specificity that ranges from 58% to 95%.[34] These results may be affected by the patients' age and variable physical exam methods. In a study of 58 patients with hyponatraemia who had clinical assessment of ECF volume status (jugular venous pressure, orthostatic changes, skin turgor, hydration of mucous membranes) and evaluation of response to fluids (no response in normovolaemic patients vs. correction of hyponatraemia in hypovolaemic patients), clinical assessment correctly identified 47% of hypovolaemic patients vs. 48% of normovolaemic patients.[156] The evaluation of the volume status can be especially challenging in older patients.[157] There are potential methods such as bioimpedance and point of care ultrasound which may be helpful as an adjunct to physical examination assessment of fluid status,[158] but require further validation. Due to the known limitations of the physical exam when

evaluating patients with mild hypovolaemia or euvolaemia, our recommendation is to complement the clinical exam findings with the results of laboratory testing for an optimal diagnostic approach **(Figure 2)**.

Clinical practice point 2.j

With regard to spot urine osmolality assessment:

- If the urine osmolality is ≤ 100 mOsm/kg H_2O, accept excess water intake or previous arginine vasopressin secretion (that has resolved) as the cause of hyponatraemia.
- If the urine osmolality, is > 100 mOsm/kg H_2O, accept arginine vasopressin-mediated water retention.

Rationale: Urine osmolality is the measurement of the total concentration of dissolved osmotically active particles per unit of water in urine. It is a direct indicator of the kidney's ability to concentrate or dilute the urine. In the context of hypotonic hyponatraemia, a urine osmolality $\leq$ 100 mOsm/kg is indicative of suppressed AVP activity resulting in aquaresis and a maximally diluted urine. This phenomenon can be seen in patients with primary polydipsia who consume excessive amounts of water leading to excretion of large volumes of diluted urine. Other causes of hypotonic hyponatraemia with a low urine osmolality ($\leq$ 100 mOsm/kg H_2O) are beer potomania or low solute intake (also known as 'tea and toast syndrome'). An important consideration is that patients with hypotonic hyponatraemia with low urinary osmolality are at increased risk for overcorrection (due to aquaresis).[159, 160] Therefore, careful monitoring of urine output and plasma sodium concentration and correction of hyponatraemia within target limits are essential to the management of these patients to prevent ODS, unless hyponatraemia developed in ≤48 hours. Finally, patients who develop SIAD may have a drop in their urine osmolality $\leq$100 mOsm/kg in the resolving phase, while the plasma sodium concentration is still recovering. If the urine osmolality is >100 mOsm/kg in a patient with hypotonic hyponatraemia, it indicates increased AVP activity in relationship to the plasma osmolality.[161, 162] This can be seen both in patients with true hypovolaemia and patients with hypervolaemia and a low EABV,

leading to increased baroregulated AVP secretion. Patients with euvolaemic hyponatraemia (as seen in SIAD) will also have urine osmolality measurements above 100 mOsm/kg due to inappropriate secretion of AVP. Urine osmolality higher than 500 mOsm/kg may predict lack of response to fluid restriction in patients with SIAD.[162, 163]

Clinical practice point 2.k

With regard to spot urinary sodium assessment:

- A urine sodium concentration ≤ 30 mmol/L suggests hypovolaemic hyponatraemia or hypervolaemic hyponatraemia with low effective arterial blood volume.
- If urine sodium concentration is > 30 mmol/L, the ECF assessment and clinical context should be used to identify the underlying cause of hyponatraemia.

Rationale: It is recommended to measure a spot urine sodium concentration around the same time as plasma sodium is measured as it is a helpful indicator of the extracellular volume status and will further help clarifying the underlying case of hyponatraemia and guide management. In patients with hypotonic hyponatraemia, a urine osmolality > 100 mOsm/kg H_2O and a urine sodium $\leq$ 30 mmol/L indicate that the renin-angiotensin-aldosterone system is activated and there is increased reabsorption of sodium by the kidneys (although some studies use a cut-off point of 20 mmol/L, 30 mmol/L is most widely used).[156, 164] In one study, a random urine sodium $\leq$ 30 mmol/L had a sensitivity of 80% and specificity of 100% for predicting a response in plasma sodium concentration to a saline challenge.[156] A spot urine $\leq$ 30 mmol/L is typically seen in conditions where the effective arterial blood volume is reduced, such as hypovolaemia (caused by dehydration, blood loss), heart failure, cirrhosis, or nephrotic syndrome. In a subgroup of patients with hypovolaemia, the urine sodium is >30 mmol/L, this includes patients taking diuretics and with primary adrenal insufficiency, or cerebral salt wasting. In addition, urine sodium is not a reliable marker for hypovolaemia in patients with metabolic alkalosis due to excretion of sodium with bicarbonate (e.g., in severe vomiting). Therefore, the clinical context and medication history should be considered when evaluating patients with hypotonic hyponatraemia

who have these laboratory findings. Patients with SIAD usually have urine sodium concentrations >30 mmol/L, although lower concentrations can be seen in patients with low solute intake.[156, 165-167] A urinary sodium >130 mmol/L has been associated with non-response to fluid restriction in patients with SIAD.[163, 168]

Clinical practice point 2.l There is no role for measuring plasma AVP or copeptin in the differential diagnosis of hyponatraemia or for confirming the diagnosis of SIAD.

Rationale: Although AVP plays a key role in the regulation of water balance, measuring AVP or copeptin in blood is not recommended in clinical practice. AVP has a short half-life, is unstable in blood samples, and it often takes a long time to get results which does not provide timely information to guide management. Copeptin, which is secreted with AVP, is considered a surrogate marker for AVP secretion.[169] Because copeptin is more stable in blood and easier to measure, it has been investigated as a potential diagnostic tool and it has been found to be useful in the evaluation of patients with polydipsia and polyuria syndromes,[170, 171] but its role is limited in the diagnostic evaluation of patients with hyponatraemia.[172-174] Therefore, routine measurement of copeptin for the evaluation of patients with hyponatraemia is not recommended.

Clinical practice point 2.m Consider the exclusion of adrenal insufficiency prior to establishing a diagnosis of SIAD.

Rationale: Hyponatraemia may be the first presentation of either primary, secondary, or tertiary adrenal insufficiency. Hyponatraemia is observed in up to 70-80% of cases of primary adrenal insufficiency at diagnosis but less so in secondary or tertiary adrenal insufficiency (20-40% of patients).[175] Patients with primary adrenal insufficiency lack both glucocorticoid and mineralocorticoid activity, which causes renal salt wasting, hypovolaemia and hyponatraemia.[176, 177] However, in patients with secondary or tertiary adrenal insufficiency, characterised by glucocorticoid deficiency only, mineralocorticoid secretion remains intact, and hyponatraemia is less prevalent.[176, 177]

Hypocortisolaemia causes euvolaemic hyponatraemia through several pathophysiological mechanisms due to the central role cortisol plays in facilitating free water excretion and cortisol's inhibition of AVP secretion.[178-180] These effects reverse on initiation of glucocorticoid replacement which may lead to rapid correction of hyponatraemia.[181-184] The diagnosis of adrenal insufficiency and the underlying aetiology (i.e., whether it is primary, secondary or tertiary adrenal insufficiency) is beyond the scope of this guideline but has been covered in other publications.[175-177, 185, 186] It is recommended that cortisol deficiency should be excluded prior to the diagnosis of SIAD.

Clinical practice point 2.n Routine assessment of thyroid function is not necessary in the work-up of hyponatraemia.

Rationale: There is limited evidence supporting an association between hypothyroidism and hyponatraemia. A study including 999 patients with recently diagnosed hypothyroidism reported a decrease in plasma sodium concentration of 0.14 mmol/L for every 10 mU/L rise in thyroid-stimulating hormone.[187] Therefore, in clinical practice, thyroid status is of limited impact on salt and water balance and as such we do not recommend its routine assessment in hyponatraemia. Thyroid function may be tested in specific clinical contexts such as in patients with hyponatraemia who also have a clinical suspicion of myxoedema.[188]

7.3 Immediate treatment of severely symptomatic hyponatraemia

Recommendation 3.1 In patients with severely symptomatic hyponatraemia, we recommend urgent treatment with a single 150 mL bolus of 3% hypertonic saline administered over 10–20 minutes to improve neurological symptoms with a target increase in plasma sodium of 4–6 mmol/l within 4–6 hours ($\oplus\oplus$OO).

Rationale: 3% hypertonic saline reliably increases plasma sodium concentration and improves neurological symptoms in patients with severely symptomatic hyponatraemia.[68, 86-92 93 94 95] Delayed treatment risks progression to seizures, altered level of consciousness, or respiratory arrest and death.

A 150 mL bolus of 3% hypertonic saline over 10–20 minutes provides a practical and generally predictable early increase in plasma sodium concentration while allowing reassessment before further dosing **(Figure 3)**. In real-world data, overcorrection was observed in 22.6% patients after the first bolus, 34.6% after the second, and 41.7% after the third.[68] These findings support giving a single initial bolus, followed by clinical and biochemical reassessment before deciding whether further treatment is required. In situations where continuous infusion is preferred, administration in a critical care environment is prudent because close monitoring and timely relowering interventions (i.e., dextrose and/or desmopressin) are sometimes needed, particularly when correction exceeds intended targets or limits (see below). A starting infusion rate around 0.5 mL/kg/h, titrated to 1.0 mL/kg/h based on symptoms and the response in plasma sodium concentration, reflects dosing used in comparative protocols and should be paired with frequent and rapidly available plasma sodium measurements.[134] In most cases, a 4-6 mmol/l increase in plasma sodium will improve cerebral oedema while minimising the risk of ODS, to which more rapid correction may predispose. This 4–6 mmol/L increase is an early treatment target and should not be confused with the 24-hour correction limits described below. The early treatment target defines the increase considered sufficient to improve severe symptoms, whereas the later limits define the maximum cumulative increase that should not be exceeded. In patients with severe cerebral oedema or impending transtentorial herniation the rise in plasma sodium concentration needs to be over a shorter timeframe than 4–6 hours to reduce intracranial pressure and improve cerebral perfusion pressure.

Recommendation 3.2 We recommend assessing the clinical and biochemical effects of the first bolus within 1 hour and repeat the bolus if necessary (⊕OOO).

Rationale: The response to a single bolus is variable, and the intended 4–6 mmol/L increase may be achieved after one bolus in some patients but may require a further bolus in others. Plasma sodium concentration and neurological status should therefore be reassessed within 1 hour before additional hypertonic saline is given **(Figure 3)**. Real-world data show that overcorrection was observed more

frequently after successive boluses, supporting reassessment rather than routine administration of a second bolus.[68] This supports a pause-and-reassess approach rather than an immediate second bolus administration. Rapid plasma sodium measurement, for example by blood gas analysis, allows timely reassessment; the same measurement method should subsequently be used to reduce analytical variability. In exceptional circumstances with severe neurological compromise and imminent risk, a second bolus may be required before laboratory confirmation, but this should not be routine.

Clinical practice point 3.a We suggest that 3% hypertonic saline may be administered via a peripheral intravenous line.

Rationale: Administration of 3% hypertonic saline via a peripheral intravenous line has been shown to be safe in two prospective studies involving a total of 314 patients.[169, 171] Peripheral administration avoids the need for central venous access, thereby facilitating prompt treatment and avoiding potential complications associated with central venous catheter insertion. A systematic review and meta-analysis of 1,200 patients found low rates of local complications, including infiltration (3.3%) and phlebitis (6.2%).[189]

7.4 24-hourly correction limits and monitoring frequency

Recommendation 4.1 In patients with a baseline plasma sodium <120 mmol/L, we suggest limiting the increase in plasma sodium concentration to 6-8 mmol/L in any 24-hour period and recommend monitoring plasma sodium concentration at least every 4-6 hours ($\oplus$OOO).

Rationale: A correction limit defines the maximum cumulative increase in plasma sodium concentration that should not be exceeded; it is not a treatment target. Although ODS is rare and may occur independently of baseline plasma sodium concentration and correction rate, a baseline plasma sodium concentration <120 mmol/L is a major risk factor for overcorrection and ODS **(Table 2)**. We therefore suggest a correction limit of 6–8 mmol/L in any 24-hour period in this population **(Figure 3)**. Although retrospective studies have associated more rapid correction with lower mortality,[131, 190]

methodological limitations, including confounding by indication, time-dependent confounding and classification by achieved rather than intended correction rates, preclude conclusions about optimal treatment targets.[6, 85, 132] Evidence supports an early increase of 4–6 mmol/L in severely symptomatic patients to improve neurological function,[94] but no RCT has compared intended 24-hour correction targets. Treatment should therefore be titrated to the lowest increase required to achieve symptom improvement, while remaining within the correction limit. No studies have established optimal monitoring intervals. The recommended interval of 4–6 hours is a pragmatic approach based on the increased risk of overcorrection in patients with plasma sodium <120 mmol/L and the need to detect treatment response and impending overcorrection. The rate of plasma sodium correction depends on baseline plasma sodium concentration, treatment efficacy and changes in water and solute balance, particularly spontaneous aquaresis following resolution of the underlying cause of antidiuresis.[69, 191, 192] Overcorrection may therefore occur unpredictably, including during treatment with hypertonic saline, vasopressin-2 receptor antagonists, oral urea or other therapies. The summary of product characteristics for the vasopressin-2 receptor antagonist tolvaptan recommends starting plasma sodium concentration monitoring 4–6 hours after treatment initiation. Urinary output should also be monitored to facilitate early detection of emerging aquaresis. We acknowledge that, in patients with a baseline plasma sodium concentration <120 mmol/L and severe symptoms, there is a narrow window because plasma sodium concentration should be increased by 4–6 mmol/L in 4–6 hours while maintaining a 24-hour correction limit of 6–8 mmol/L.

Recommendation 4.2 In patients with a baseline plasma sodium concentration ≥ 120–130 mmol/L, we suggest limiting the increase in plasma sodium concentration to 8-12 mmol/L in any 24-hour period and recommend monitoring plasma sodium concentration every 12-24 hours (⨁OOO).

Rationale: As for recommendation 4.1, no evidence on monitoring strategy is available for this patient group either. Rather the recommendation is based on pragmatic considerations. In patients with baseline plasma sodium >120 mmol/L, the risk of ODS is low and at the same time the rate of change

of plasma sodium concentration is usually less pronounced. Higher rates of correction of plasma sodium concentration can therefore be allowed. In those with a baseline plasma sodium concentration of >120 mmol/L, we therefore suggest a limit of 8–12 mmol/L increase in plasma sodium concentration per 24 hour period **(Figure 3)**.

Clinical practice point 4.a In patients with a baseline plasma sodium concentration > 130 mmol/L, plasma sodium concentration may be normalized within 24 hours, and monitoring frequency should be guided by the clinical context.

Rationale: In patients with plasma sodium >130 mmol/L, treatment as well as monitoring should be tailored to the clinical context. Severe or moderate symptoms will only very rarely be encountered due to hyponatraemia at this level. Therefore, in an inpatient setting, daily measurements to ensure that plasma sodium concentrations are not declining are usually sufficient.

7.5 Treatment of acute hyponatraemia (≤48h) without severe symptoms

Recommendation 5.1 In patients with acute hyponatraemia without severe symptoms who have moderate or severe biochemical hyponatraemia and a decrease in plasma sodium concentration ≥10 mmol/L, we recommend prompt diagnostic assessment and cause-specific treatment ($\oplus 000$).

Rationale: A decrease in plasma sodium of ≥10 mmol/L within ≤48 hours that results in moderate or severe biochemical hyponatraemia represents a clinically important acute change. Because cerebral adaptation is incomplete, a further decline may lead to cerebral oedema and rapid neurological deterioration. Prompt diagnostic assessment and cause-specific treatment are therefore required, even in the absence of severe symptoms **(Figure 4)**. Acute hyponatraemia is frequently triggered by a recent intervention, medication, fluid administration, or other reversible factors **(Table 3)**. Identifying and discontinuing the precipitating cause may prevent further decline and, in some cases, may be sufficient to allow recovery of plasma sodium concentration.

Recommendation 5.2 In patients with acute hyponatraemia in whom cause-specific treatment is not possible or is expected to take too long, we recommend a single 150 mL bolus of 3% hypertonic saline administered over 10–20 minutes to prevent further decline in plasma sodium concentration and the development of severe symptoms, with a target increase in plasma sodium concentration of 4–6 mmol/L within 4–6 hours ($\oplus\mathrm{OOO}$).

Rationale: In acute hyponatraemia, a further decline in plasma sodium concentration may result in rapid development of cerebral oedema and life-threatening neurological complications. When cause-specific treatment is unavailable or unlikely to act sufficiently rapidly, a single bolus of 150 mL 3% hypertonic saline provides a prompt increase in plasma sodium concentration, aiming to mitigate cerebral oedema and prevent further neurological deterioration **(Figure 4)**. An initial increase of 4–6 mmol/L within 4–6 hours is generally sufficient to reduce cerebral oedema and improve symptoms, without requiring immediate normalization of plasma sodium.

Recommendation 5.3 We recommend assessing the clinical and biochemical effects of the first bolus within 1 hour and repeat the bolus if necessary ($\oplus\mathrm{OOO}$).

Rationale: The clinical and biochemical effect of hypertonic saline should be assessed within 1 hour because the early response in the plasma sodium concentration may be variable and further treatment may be required. Thereafter, plasma sodium concentration should be monitored every 4–6 hours until it has stabilised, as acute hyponatraemia may continue to evolve or withdrawal of the precipitating factor may result in an unexpectedly rapid rise in the plasma sodium concentration independent of hypertonic saline administration.

Clinical practice point 5.a Limit the increase in plasma sodium concentration to 10–12 mmol/L over 24 hours in patients with acute hyponatraemia.

Rationale: In patients with acute hyponatraemia (≤48 hours duration) there is less risk of ODS as the chronic compensatory mechanisms within the brain that occur in chronic hyponatraemia have not yet

developed and therefore the brain is better capable to manage osmotic shifts.[136, 193-195] For this reason, we recommend a higher 24-hour correction limit of 10–12 mmol/l over 24 hours for the plasma sodium concentration in patients with acute hyponatraemia. Previous recommendations have suggested that there should be no limit to the increase in plasma sodium concentrations in acute hyponatraemia patients.[162] However, as the main goal of increasing the plasma sodium concentration in patients with acute hyponatraemia is the improvement in cerebral oedema, this will have occurred well below a plasma sodium correction between 10–12 mmol/l[196, 197] and as such increasing the plasma sodium concentration above this limit in 24 hours may not be warranted.

7.6 Preventing and treating overcorrection

Recommendation 6.1 In patients who have exceeded, or are on a trajectory to exceed, the 24-hour limit, we recommend discontinuing active treatment (⊕⊕OO).

Rationale: Discontinuation of active treatment is the first step in managing imminent or actual overcorrection. This applies particularly to 3% hypertonic saline, which directly increases the plasma sodium concentration, and to isotonic fluids in hypovolaemic hyponatraemia, which may accelerate plasma sodium correction by restoring effective circulating volume and suppressing non-osmotic AVP secretion.[198] Other interventions, including fluid restriction, oral urea, vasopressin-2 receptor antagonists, SGLT2 inhibitors, loop diuretics, and oral sodium chloride, should also be discontinued, although their effects on the plasma sodium concentration may persist or take longer to dissipate.

Recommendation 6.2 We recommend a reactive strategy in patients with a baseline plasma sodium concentration <120 mmol/L or 120–130 mmol/L (in the presence of risk factors for osmotic demyelination syndrome), who are on a trajectory to exceed the 24-hour limit but have not yet overcorrected (⊕OOO).

Recommendation 6.3 As a reactive strategy, we suggest a single dose of 1–2 µg desmopressin subcutaneously or intravenously and/or intravenous 5% dextrose at an initial rate of 3 mL/kg/h to prevent overcorrection ($\oplus$OOO).

Rationale for recommendations 6.2 and 6.3: Different strategies for the management of overcorrection have been described **(Table 4 and Figure 5)**.[117] The reactive strategy administers desmopressin or 5% dextrose when the trajectory of the plasma sodium concentration is likely to exceed the 24-hour limit or an increase in urine output is seen. In the original description of the reactive strategy, desmopressin was the only recommended intervention.[117] However, the European survey on current clinical practice of hyponatraemia treatment showed that only a minority of physicians throughout Europe use desmopressin to relower plasma sodium concentration, and most centers indicated to have insufficient experience using desmopressin. Instead, most centers apply dextrose only to manage overcorrection.[115] Whilst we do not recommend a dextrose only strategy in patients who have already overcorrected, replacement of urinary water losses with 5% dextrose only can be used as a first step and as alternative to desmopressin in the reactive strategy. There is time to monitor the effect of treatment and add desmopressin if the trajectory is not or insufficiently changed. Dextrose can be stopped as soon as it becomes clear that target plasma sodium concentrations are not exceeded within every 24-hour period. Hourly dextrose infusion volumes may need to be adjusted and the need for this will be determined by plasma sodium response and urinary volumes. Thus, we propose two options for the reactive strategy: desmopressin alone or 5% dextrose alone **(Table 4)**. If desmopressin is used, we recommend giving a single dose of 1 or 2 µg intravenously or subcutaneously, which is often sufficient for the duration of the reactive strategy (until the 24-hour time point). If the rise in plasma sodium concentration is insufficiently curtailed, a second dose of desmopressin may be given.

Recommendation 6.4 We recommend a rescue strategy for patients who have overcorrected beyond the 24-hour limit and have a baseline plasma sodium concentration <120 mmol/L or 120–130 mmol/L in the presence of risk factors for osmotic demyelination syndrome ($\oplus$OOO).

Recommendation 6.5 As a rescue strategy, we suggest a single dose of desmopressin 1–2 µg subcutaneously or intravenously, combined with intravenous 5% dextrose at an initial infusion rate of 3 mL/kg/h, aiming to relower the plasma sodium concentration below the predetermined 24-hour correction limit, ideally within 6 hours ($\oplus$000).

Rationale for recommendations 6.4 and 6.5: The possible association of rapid correction with ODS, especially in patients with a plasma sodium concentration <120 mmol/L, warrants an attempt to relower plasma sodium concentration in case of overcorrection. Of note, this concept has recently been challenged by reporting that ODS is exceedingly rare and by challenging the dogma of an association of rapid correction with ODS.[102] However, methodological issues remain when interpreting most observational studies on achieved correction rates.[6, 132] Besides the need to discontinuing active treatment in all patients who have exceeded or are on a trajectory to exceed the 24-hour limit, active relowering may therefore be needed. This relowering approach has been shown to reduce mortality in an animal model of chronic hyponatraemia.[199] The best way to relower plasma sodium concentrations after overcorrection has occurred (rescue strategy) is the combination of desmopressin and 5% dextrose. Desmopressin is given to stop aquaresis and concentrate the urine. The usual desmopressin regimen is 1–2 µg intravenously or subcutaneously, although higher doses have been reported.[117] In a retrospective study, both 1 and 2 µg resulted in significant relowering of plasma sodium concentrations, although a dose of 2 µg resulted in a clinically meaningful greater reduction in plasma sodium concentration.[200] A single dose of desmopressin is usually sufficient for the duration of the rescue strategy, during which the plasma sodium concentration should ideally be relowered to below the 24-hour correction limit within 6 hours. However, if the effect is insufficient, desmopressin may be repeated 6–8 hours after the initial dose. To achieve a "block and replace" regimen, 5% dextrose should be added at an initial infusion rate of 3 mL/kg/h with the aim to relower plasma sodium concentrations to below the predefined 24-hour correction limit.[117] In the retrospective study mentioned above, the decrease of plasma sodium concentrations was similar, irrespective of the amount of dextrose infused (500 versus 1000 mL).[200] A recent European survey on current clinical practice of hyponatraemia

treatment showed that if desmopressin is used, most survey respondents applied it as a rescue or reactive rather than proactive approach.[115] Similarly, a retrospective study from Canada showed that desmopressin was almost always used as a rescue therapy rather than as a preventive measure.[200] These findings highlight that, due to its complexity, the proactive approach should only be used in a closely monitored setting and in centers who have experience applying the proactive strategy. ODS can also occur rarely in patients without a baseline very low plasma sodium concentration, mainly when risk factors for ODS are present **(Table 2)**. Therefore, in patients with a baseline plasma sodium concentration ≥120 to 130 mmol/L who have overcorrected, relowering using the rescue strategy may be considered based on the presence of ODS risk factors.

Recommendation 6.6 We suggest adjusting the 5% dextrose infusion rate to exceed urinary output, thereby preventing a further increase in plasma sodium concentration ($\oplus OOO$).

Recommendation 6.7 We recommend checking plasma sodium every 1–2 hours and discontinuing intravenous dextrose and further desmopressin once the plasma sodium concentration has fallen below the predetermined 24-hour correction limit ($\oplus\oplus OO$).

Rationale for recommendations 6.6. and 6.7: If plasma sodium concentrations do not decrease, dextrose should be continued with an adjusted infusion rate to make sure the infusion volume exceeds urinary output to prevent further plasma sodium rise and to help with the goal of curtailing the rise in plasma sodium concentration. If the plasma sodium concentration is again rising too quickly, particularly in association with an increase in urine output, subsequent doses of desmopressin may be given after six to eight hours. Plasma sodium concentrations should be checked every 1-2 hours after active relowering has been started and intravenous dextrose and desmopressin should be discontinued once the plasma sodium concentration is below the predefined 24-hour correction limit.

7.7 Treatment of hypovolaemic, hypervolaemic hyponatraemia and SIAD

Recommendation 7.1 We recommend treating the underlying cause of hyponatraemia, if possible. (⊕000).

Rationale: Addressing reversible and contributing causes of hypotonic hyponatraemia represents a rational first step in management and may, in some patients, be sufficient to achieve improvement in plasma sodium concentration or prevent further deterioration, while reducing the need for additional or more aggressive therapeutic interventions. Many patients with hyponatraemia use medications that may have provoked or contributed to the development or persistence of hyponatraemia **(Table 8)**. It therefore makes sense to review current drug therapy, identify potentially causative medications, reassess their indication, and to substitute or stop them, depending on the clinical context and the balance between anticipated benefits and potential harms. Similarly, unnecessary or inappropriate intravenous fluids should be stopped, excessive oral water intake discouraged, and underlying conditions that can be corrected addressed. Appropriate management of factors known to stimulate non-osmotic AVP release, such as infection, pain, nausea, or other acute stressors, may facilitate restoration of normal water balance.

Recommendation 7.2 In patients with hypovolaemic hyponatraemia, we recommend restoring extracellular volume with an intravenous infusion of 0.9% saline or a balanced crystalloid solution (⊕000).

Clinical practice point 7.a Manage patients with haemodynamic instability in an environment where close biochemical and clinical monitoring can be provided.

Clinical practice point 7.b In haemodynamic instability, urgent fluid resuscitation takes precedence over correction limits, but subsequent measures to prevent overcorrection should be considered.

Rationale for recommendation 7.2 and clinical practice points 7.a and 7.b: Although hyponatraemia with reduced extracellular volume is common in clinical practice, direct evidence specifically addressing its management from a hyponatraemia perspective is limited. Recommendations therefore largely

derive from established pathophysiological principles. Because both sodium and water are deficient, restoration of extracellular volume with isotonic fluids is physiologically appropriate. Volume repletion corrects the underlying baroregulated stimulus for AVP release, allowing suppression of AVP secretion and restoration of renal free water excretion. Both 0.9% saline and balanced crystalloids can reasonably be used for volume restoration **(Figure 3)**. Although balanced crystalloids may reduce hyperchloraemia and metabolic acidosis, systematic reviews have not demonstrated benefit over saline in terms of patient-important outcomes.[201] Once extracellular volume is restored, AVP levels may fall rapidly, resulting in a marked increase in urine output (aquaresis) and a potentially rapid rise in plasma sodium concentration.[198] Patients with hypovolaemic hyponatraemia are therefore at increased risk of overly rapid correction.[10] A sudden increase in urine output may signal impending overcorrection and warrants close monitoring. In haemodynamically unstable patients, the immediate threat of impaired organ perfusion outweighs concerns regarding plasma sodium overcorrection. Volume resuscitation takes priority in this setting and is best undertaken in an environment that allows frequent monitoring of plasma sodium concentration. If overly rapid correction is anticipated or observed, any overcorrection may be managed with administration of electrolyte-free water (e.g., dextrose) and/or desmopressin (see recommendations on preventing and treating overcorrection).

Clinical practice point 7.c We recommend treating hypervolaemic hyponatraemia in patients with established heart failure or liver cirrhosis according to the respective guidelines for these diseases.

Rationale: In this guideline, we distinguish management of hyponatraemia due to hypervolaemia that is clinically obvious from patients who have hyponatraemia caused by SIAD, as these conditions differ fundamentally in their underlying mechanisms and therapeutic priorities. Given that the management of fluid overload—whether related to cardiac, hepatic, or renal dysfunction—requires disease-specific strategies that extend beyond the scope of this guideline, we refer to the relevant international guidelines for detailed recommendations **(Figure 3)**.[202-204]

Syndrome of inappropriate antidiuresis

Recommendation 7.3 In the syndrome of inappropriate antidiuresis, we recommend fluid restriction of ≤ 1 L/day as first-line treatment (⨁⨁◯◯).

Rationale: Fluid restriction rarely causes overly rapid correction in randomised or observational data, unlike some pharmacologic therapies. Aside from the difficulty of maintaining it, it has no clear major adverse effects. Fluid restriction also directly addresses the underlying pathophysiology in dilutional states by reducing water intake below impaired excretory capacity without the risk of drug-related adverse effects and interactions which is particularly relevant in older patients with multimorbidity. Fluid restriction is therapeutically proportional in a condition with uncertain benefit from aggressive correction and is universally available and inexpensive. Fluid restriction refers to the totality of all fluids, and should be applied dynamically, with adjustment of the degree of restriction according to response and physiological parameters.[42] The Cochrane review shows that in placebo-controlled studies, patients eligible for RCTs experience an average 'spontaneous' rise of 2.2 mmol/L. Only one RCT compared fluid restriction (< 1 L/day) with placebo (n = 46; baseline sodium 126–129 mmol/L).[118] After three days, plasma sodium increased by 3 mmol/L with fluid restriction versus 1 mmol/L without intervention; 61% of those treated with fluid restriction reached ≥ 130 mmol/L. After one month, the increase with fluid restriction averaged 4 mmol/L. Trials comparing vasopressin-2 receptor antagonists with fluid restriction are in line with these findings.[119, 120] For many patients, this may be sufficient to move plasma sodium into a range where further increases are unlikely to yield additional outcome benefit. Given uncertain outcome benefit, modest spontaneous improvement, limited additional gains beyond moderate correction, and a superior safety profile, the guideline development group unanimously preferred fluid restriction as first-line therapy in stable chronic hyponatraemia secondary to SIAD.

Clinical practice point 7.d: In patients with SIAD, we suggest considering predictors of non-response to fluid restriction, including urine osmolality >500 mOsm/kg H_2O and urine sodium >130 mmol/L, to guide early consideration of second-line treatment when appropriate.

Rationale: Fluid restriction is the first-line treatment for SIAD, but non-response is common.[163] In a predefined secondary analysis of a prospective, multicentre trial, 62% of 229 patients with SIAD treated with fluid restriction did not achieve an increase in plasma sodium concentration of >3 mmol/L within 24 hours.[163] Urine osmolality >500 mOsm/kg H_2O and urine sodium >130 mmol/L were validated as predictors of non-response. The combination of both thresholds had a positive predictive value of 94% and a positive likelihood ratio of 9.62. These findings support early consideration of second-line treatment in patients with both predictors. The Fürst ratio ([urine sodium + urine potassium]/plasma sodium) >1 has previously been reported as a predictor, but this was not confirmed in the analysis.[163]

Recommendation 7.4 In patients with SIAD who have insufficient response to fluid restriction and who require further correction, we suggest oral urea, vasopressin-2 receptor antagonists, or an SGLT2 inhibitor as second-line treatment ($\oplus\oplus$OO).

Rationale: This recommendation applies to patients with SIAD in whom fluid restriction has been insufficient and in whom further correction is considered desirable **(Figure 3)**. Importantly, escalation should not be triggered solely by a plasma sodium concentration below 135 mmol/L, but by persistent symptoms plausibly attributable to hyponatraemia, patient preference, and overall clinical context. Given modest biochemical gains and uncertain downstream outcome effects, escalation beyond fluid restriction requires individualized risk–benefit consideration. The balance differs between agents. Choice between these options may therefore be guided by baseline plasma sodium concentration, risk of overcorrection, tolerability, comorbidity profile, availability, and cost.

Clinical practice point 7.e Prescribe an initial total daily dose of 15–30 grams oral urea using a palatable formulation (pre-formulated powder, dissolved in flavoured beverage or commercially available preparation).

Rationale: Although randomised evidence is lacking, observational studies and systematic reviews suggest that oral urea is generally effective and well tolerated for gradual correction of SIAD-induced hyponatraemia.[104, 124-127] However, overcorrection and hypernatraemia can occur, although no cases of

ODS have been reported.[104, 125, 205] This may reflect, at least in part, a potential neuroprotective effect of elevated plasma urea, although this remains hypothetical.[206] The bitter taste of urea used to be a common barrier to adherence. However, palatability may be improved by mixing urea with sweet-tasting beverages (e.g. orange juice or orange juice with grenadine) or by using a pharmacist-prepared effervescent formulation (e.g. urea 10 g, sodium bicarbonate 2 g, citric acid 1.5 g and sucrose 200 mg per sachet, dissolved in 50–100 mL water). A recent study suggests that the palatability of oral urea can be further improved by using a commercially available urea formulation.[207] Oral urea is generally inexpensive compared with vasopressin-2 receptor antagonists, although availability and cost vary across regions and healthcare systems and may influence treatment choice. Oral urea is usually prescribed at an initial total daily dose of 15–30 g, which may be increased to 60 g, also taking body weight into account (the weight-based recommended dose is 0.25–0.50 g/kg). The total daily dose may be divided in one or two daily doses. In the event of overcorrection, we suggest discontinuing oral urea and considering reactive or rescue measures with desmopressin and/or 5% dextrose, as appropriate. However, desmopressin may be less effective during urea-induced osmotic diuresis. There is no established evidence-based approach to managing urea-induced overcorrection.

Vasopressin-2 receptor antagonists

Clinical practice point 7.f If vasopressin-2 receptor antagonists are used, initiate at low dose, avoid concurrent fluid restriction, and commence in hospital to mitigate the risk of overly rapid plasma sodium correction.

Clinical practice point 7.g If overcorrection with a vasopressin-2 receptor antagonist occurs, discontinue it and start 5% dextrose at 3 mL/kg/h, adjusting the infusion rate to exceed urinary output to prevent further increases in plasma sodium concentration.

Clinical practice point 7.h Desmopressin should not be used to treat overcorrection in patients receiving vasopressin-2 receptor antagonists.

Clinical practice point 7.i* Exercise caution and frequently monitor plasma sodium concentration when starting vasopressin-2 receptor antagonists in patients with a plasma sodium concentration < 120 mmol/L because of the increased risk of overcorrection.

**There was no unanimous consensus on this clinical practice point among the guideline working group. Two guideline working group members preferred a recommendation against the use of vasopressin-2 receptor antagonists in patients with a plasma sodium concentration <120 mmol/L.*

Rationale: Vasopressin-2 receptor antagonists increase the plasma sodium concentration by a mean of approximately 4 mmol/L in total and roughly double the probability of a ≥ 5–6 mmol/L rise, but have uncertain effects on mortality and health-related quality of life. At the same time, they increase the risk of overly rapid correction by approximately 82% relative to control.[67] Exploratory analyses suggest that absolute risk of overcorrection with vasopressin-2 receptor antagonists is strongly modified by baseline plasma sodium concentration: at plasma sodium concentrations of approximately 130, 125, and 120 mmol/L, the estimated absolute risks may be in the order of ~4%, ~13%, and ~22%, respectively.[67] The risk is highest precisely in those with the lowest baseline plasma sodium concentration — the group in whom clinicians may feel most compelled to treat. It provides a strong rationale for close monitoring of plasma sodium concentration after treatment initiation to enable timely intervention should correction proceed too rapidly. Other risk factors in addition to lower starting plasma sodium concentration that are associated with overcorrection in patients who receive therapy with vasopressin-2 receptor antagonists include presence of cancer, low body mass index, low blood urea nitrogen and the use of other forms of therapy for treating hyponatraemia particularly fluid restriction. As such patients who receive vasopressin-2 receptor antagonists should be advised not to fluid restrict.[192, 208, 209] A number of studies have shown that a lower dose of the vasopressin-2 receptor antagonist tolvaptan leads to less rapid increase in plasma sodium concentrations and a consequent lower risk of overcorrection.[209-212] Therefore, when using tolvaptan as vasopressin-2 receptor antagonist, we recommend starting at 7.5 mg once daily rather than the licensed 15 mg per day. The use of desmopressin for the reactive or rescue approaches is not recommended in patients receiving a

vasopressin-2 receptor antagonist. Instead of desmopressin, we recommend that these patients should be given replacement water as a 5% intravenous dextrose infusion at a volume greater than urinary losses.

Clinical practice point 7.j Combine empagliflozin at 25 mg once daily (or an equivalent dose of another SGLT2 inhibitor) with fluid restriction (<1.0–1.5 litre/day).

Rationale: Compared with placebo, SGLT2 inhibitors increase plasma sodium concentration by approximately 3–4 mmol/L over the treatment period (4 days in one RCT[123], 4 weeks in another[122]), but evidence for patient-important outcomes remains very uncertain. Biochemical efficacy appears modest and long-term safety and outcome effects in this specific population remain insufficiently characterised. Overcorrection occurred in two of 43 hospitalised patients in the RCT investigating the SGLT2 inhibitor empagliflozin in combination with fluid restriction (<1 litre/day),[123] whereas no overcorrection occurred in the outpatient RCT of empagliflozin in combination with fluid restriction (≤ 1.5 litre/day).[122] In patients with mild hyponatraemia, SGLT2 inhibitors without fluid restriction may be considered, although there are currently no data yet to support this approach. In patients treated with SGLT2 inhibitors, we recommend ensuring adequate nutritional intake and temporarily discontinuing treatment during acute illness, prolonged fasting, or markedly reduced oral intake to reduce the risk of euglycaemic ketoacidosis.[213] SGLT2 inhibitors are not currently licensed for the treatment of hyponatraemia.

Recommendation 7.5 If the second-line treatments for SIAD are unavailable, we suggest loop diuretics plus oral sodium chloride as a possible alternative ($\oplus$OOO).

Rationale: Evidence for combining loop diuretics with oral sodium chloride is limited. A single RCT did not demonstrate clear benefits over fluid restriction alone for patient-important outcomes or plasma sodium correction and suggested an increased risk of hypokalaemia and acute kidney injury with furosemide.[214] However, in settings where other second-line therapies are unavailable, this

combination represents a pragmatic alternative, provided plasma sodium, potassium, and kidney function are monitored closely.

Recommendation 7.6 We recommend against the use of lithium or demeclocycline for the treatment of the syndrome of inappropriate antidiuresis ($\oplus$OOO).

Rationale: No RCTs have evaluated lithium or demeclocycline for the treatment of chronic hyponatraemia due to SIAD. The available evidence consists exclusively of case series and observational reports.[215-221] Given the complete absence of randomised evidence, the reliance on low-certainty observational data, the delayed and unpredictable onset of effect, the availability of safer alternative strategies, and the documented potential for nephrotoxicity[222] and neurological adverse events,[222] the balance of benefits and harms seems unfavourable. For these reasons, the guideline development group recommends against the use of lithium or demeclocycline for the management of chronic hyponatraemia in patients with SIAD.

8. Future research

Table 10 lists a number of areas of uncertainty that would benefit from future research. Many of these questions relate to the optimal treatment of patients with hyponatraemia. In addition, whether treatment can improve patient outcomes also remains uncertain, particularly in patients with chronic hyponatraemia. No RCT has demonstrated that treatment initiated on the basis of a plasma sodium concentration threshold improves mortality, fractures, or quality of life. In the absence of such evidence, justification relies on a surrogate chain: a lower plasma sodium concentration is associated with worse outcomes; raising the plasma sodium concentration would therefore be expected to improve outcomes. This reasoning is vulnerable to confounding, effect modification by illness severity, and the broader limitations of surrogate endpoints. Associations strengthen as plasma sodium concentration declines, but this may reflect increasing disease burden rather than the plasma sodium concentration itself being causally dominant. The updated Cochrane review of 46 RCTs confirms that evidence for critical outcomes remains limited. It includes a multicentre large-scale international RCT comparing a multifaceted targeted correction of hyponatraemia with routine care in hospitalised patients, which found no difference in death, readmission, length of hospital stay, neurocognitive assessment, quality of life, rates of falls or fractures at discharge or 30-day follow-up.[223] Importantly, not all aetiologies of hyponatraemia have similar degrees of mortality risk: hypervolaemic hyponatraemia patients having the highest mortality followed by hypovolaemic and then euvolaemic hyponatraemia.[224] It is reasonable to assume that as the plasma sodium concentration declines, a sustained rise is more likely to improve symptoms and well-being, and that correction becomes more desirable. Yet, this does not imply that normalization is necessary.

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Tables

1. Summary of classification of hyponatraemia according to biochemical severity, clinical severity, volume status and acuity of onset.
2. Risk stratification for neurological complications of hyponatraemia.
3. Conditions and medications associated with acute hyponatraemia (onset ≤48 hours).
4. Strategies to prevent (proactive, reactive) and treat (rescue) overcorrection of plasma sodium concentration.
5. Equations useful for the diagnosis and treatment of hyponatraemic patients.
6. Diagnosis of the syndrome of inappropriate antidiuresis.
7. Differentiating the syndrome of inappropriate antidiuresis from cerebral salt wasting.
8. Medications associated with the development of hyponatraemia according to mechanism of action.
9. Clinical questions for guideline development systematic reviews.
10. Areas of uncertainty in the management of hyponatraemia.

Figures

1. Spectrum of symptoms according to severity and duration of hyponatraemia
2. Diagnostic algorithm of aetiology of hyponatraemia.
3. Treatment algorithm for the management of hyponatraemia based on symptoms and aetiology.
4. Algorithm for the management of acute hyponatraemia without severe symptoms.
5. Reactive and rescue approaches to prevent or treat overcorrection.
6. Causes of the syndrome of inappropriate antidiuresis.
7. Meta-analysis of the incidence of osmotic demyelination syndrome in patients treated for hyponatraemia.

Table 1. Summary of classification of hyponatraemia according to biochemical severity, clinical severity, volume status and acuity of onset.

Biochemical severity • Mild (≥130–135 mmol/l) • Moderate (≥120–129 mmol/l) • Severe (<120 mmol/l)	**Symptoms severity** • Mild • Moderate • Severe
Volume assessment • Hypovolaemic • Euvolaemic • Hypervolaemic	**Acuity of onset** • Acute ≤48 hours • Chronic >48 hours

Table 2. Risk stratification for neurological complications of hyponatraemia.

Risk factor	**Relative high risk of cerebral oedema**	**Relative low risk of cerebral oedema or ODS**	**Relative high risk of ODS**
Baseline plasma sodium concentration	<120 mmol/L	≥120 mmol/L	<120 mmol/L
Onset	Acute (≤ 48 hours) or acute on chronic	Chronic (>48 hours)	Chronic (>48 hours)
Symptoms of hyponatraemia	Moderate to severe	No or mild	Not applicable
Specific risk factors	Co-existing neurological conditions (e.g., traumatic brain injury, brain tumour, subarachnoid haemorrhage)*	Not applicable	Malnutrition, alcohol, hypokalaemia, liver cirrhosis

Footnote: ***In these settings cerebral oedema can occur at plasma sodium concentrations >120 mmol/L.

Table 3. Conditions and medications associated with acute hyponatraemia (onset ≤48 hours).

Clinical setting	Typical examples	Predominant mechanism
Neurosurgical procedures	Transsphenoidal surgery; pituitary surgery; craniotomy	Non-osmotic AVP release (SIAD); administration of hypotonic fluids; cerebral salt wasting (less common)
Urological procedures	Transurethral resection of the prostate (TURP); transurethral bladder surgery	Absorption of hypotonic irrigation fluid (TURP syndrome; less common with isotonic irrigation); postoperative SIAD
Gynaecological procedures	Hysteroscopic surgery; endometrial ablation	Absorption of irrigation fluid; postoperative AVP release
Endurance exercise	Marathon; ultramarathon; triathlon; military training	Exercise-associated hyponatraemia due to excessive hypotonic fluid intake with persistent AVP secretion
Recreational drug use	MDMA (ecstasy); amphetamines	Drug-induced vasopressin release combined with excessive water intake
Postoperative state	Major surgery (particularly abdominal, thoracic and orthopaedic surgery)	Stress-induced vasopressin secretion; hypotonic fluid administration
Acute polydipsia	Psychiatric illness; water-drinking competitions; hazing rituals	Water intake exceeding renal free water excretory capacity
Drug-induced	Desmopressin; oxytocin; cyclophosphamide; vincristine	Increased vasopressin activity or impaired renal free water excretion
Acute medical illness	Pneumonia; meningitis; acute pain; nausea	Non-osmotic AVP release (transient SIAD)

Abbreviations: AVP, arginine vasopressin; MDMA, 3,4-methylenedioxymethamphetamine; SIAD, syndrome of inappropriate antidiuresis.

Table 4. Strategies to prevent (proactive, reactive) and treat (rescue) overcorrection of plasma sodium concentration.

Strategy	Indications	Description
Proactive	Start immediately when plasma sodium concentration is <120 mmol/L in patients likely to have overly rapid correction and/or high risk for ODS	Desmopressin 1–2 µg s.c. or i.v. AND slow i.v. infusion of 3% NaCl (1–1.5 mL/kg over 6 hours or comparable dose given as bolus every 4–6 h)
Reactive	The increase in plasma sodium concentration is approaching the 24-hour limit but overcorrection has not yet occurred.	Two options: 1. 5% dextrose (initial rate 3 mL/kg/h) infusion. Monitor plasma sodium levels every 1–2 hours and add desmopressin if the trajectory is not or insufficiently changed. Stop dextrose as soon as it becomes clear that target plasma sodium levels are not exceeded within any 24 h period. 2. Desmopressin 1–2 µg s.c. or i.v. without additional 5% dextrose.
Rescue	Overly rapid correction of hyponatraemia has already occurred	Desmopressin 1–2 µg s.c. or i.v. AND dextrose 5% (initial rate 3 mL/kg/h) until plasma sodium reaches the target level. Re-check plasma sodium every 1–2 hours; stop dextrose as soon as target level is achieved. Adjust dextrose rate of infusion to make sure the volume exceeds urine output.

Abbreviations: ODS, osmotic demyelination syndrome.

Table 5. Equations useful for the diagnosis and treatment of hyponatraemic patients.

*Plasma osmolality = 2 × [Na^+] + BUN + [Glucose]
*Effective osmolality = 2 × [Na^+] + [Glucose]
$Corrected\ [Na^+] = measured\ [Na^+] + 2\ \times \frac{[glucose, mmol/L] - 5.5\ mmol/L}{5.5\ mmol/L}$
Electrolyte-free water excretion= $\dot{V} - \left[1\ \times \frac{(Na_U^+ + K_U^+)}{Na_P^+}\ \right]$
Change in plasma [Na+] with 1 litre infused = $\frac{infusate\ [Na^+] - serum\ [Na^+]}{Total\ Body\ Water}$

*These equations assume that BUN and glucose are measured in mmol/L. If measured in mg/dl, then BUN should be divided by 2.8 and glucose divided by 18 to convert to mmol/L. Effective osmolality is equivalent to plasma tonicity.

For corrected [Na^+], if glucose is measured in mg/dl, then replace 5.5 mmol/L in the equation with 100 mg/dl.

$\dot{V}$ = urine volume.

Table 6. Diagnosis of the syndrome of inappropriate antidiuresis.

Essential criteria • Plasma osmolality <275 mOsm /kg H_2O • Clinical euvolaemia • Urine osmolality >100 mOsm/kg H_2O • Urine sodium >30 mmol/L • Absence of adrenal or renal insufficiency • No recent us of diuretics
Supplemental criteria • Fractional uric acid excretion >12%, • Fractional sodium excretion >0.5% • Fractional urea excretion >55% • Plasma uric acid <0.24 mmol/L (4 mg/dL) • Plasma urea <3.6 mmol/L (<21.6 mg/dL) • Correction of hyponatraemia through fluid restriction.

Modified from[31, 38, 44]

Table 7. Differentiating the syndrome of inappropriate antidiuresis from cerebral salt wasting.

	Syndrome of inappropriate antidiuresis	**Cerebral salt wasting**
Plasma sodium concentration	Low	Low
Plasma urea concentration	Normal–low	Normal–high
Plasma uric acid concentration	Low	Low
Blood pressure	Normal	Low–orthostatic hypotension
Urine volume	Normal–low	High
Urine sodium concentration	>30 mmol/l	>>30 mmol/l*
Central venous pressure	Normal	Low

* In patients with cerebral salt wasting there is frequently a significant natriuresis (urinary sodium is often above 100 mmol/l) and the calculation of urinary sodium losses by multiplying urine volume by urinary sodium concentrations can aid management). Adapted from[55]

Table 8. Medications associated with the development of hyponatraemia according to mechanism of action.

Medications by Mechanism Of Action	Frequency
AVP release stimulants or potentiators	
• Anticonvulsants	
• Valproic acid	15% [225]
• Lamotrigine	(rare)
• Levetiracetam	(rare)
• Antidepressants	
• SNRI	7.4%[226]
• SSRI	5.6%[226]
• TCA	2.7%[226]
• MAOi	<1%[226]
• Others: mirtazapine, trazodone	≤1%[226]
• Antipsychotics	
• Haloperidol, chlorpromazine, thioridazine	(rare)
• Anticancer drugs	
• Vinka alkaloids: vincristine, vinblastine	
• Alkylating agents: cyclophosphamide	14%[227]
• Platinum compounds: cisplatin, carboplatin	20-40%[227]
• Targeted therapies: tyrosine kinase inhibitors	
• Others: methotrexate, IL-2, IFN	
• Other drugs: tramadol, opioids, NSAIDs, PPI, sulfonylureas (chlorpropamide, tolbutamine), amiodarone, nicotine, linezolid	Variable [228]
• Herbal supplements: ginkgo biloba, horsetail	(rare)[229]
AVP receptor potentiator & Reset Osmostat	
• Antiepileptics	
• Oxcarbazepine	46%[230]
• Carbamazepine	26%[230]
• Anticancer drugs	
• Alkylating agents: cyclophosphamide	14%[227]
AVP receptor activator	
• AVP analog: desmopressin, vasopressin, terlipressin	4%
• Receptor cross-talk	
• Oxytocin	
• MDMA	31%[231]
Natriuretic agents	
• Antibiotics: Bactrim	17-72%
• Diuretics:	
• Thiazides	4%[232]
• Loop diuretics	(rare)
• Anticonvulsants: Zonisamide	(rare)
• Anticancer drugs	
• Platinum compounds: cisplatin	20-40% [227]

Table 9. Clinical questions for guideline development systematic reviews.

Clinical question	Search criteria				Papers included (*n*)	Respective recommendation
	Population	**Intervention**	**Comparison**	**Outcome**		
Correction rate Question I: *What is the optimal correction rate (i.e. change in serum sodium concentration per unit time) during treatment of adult patients with hypotonic hyponatraemia?*	Adults presenting with hypotonic hyponatraemia	Targeted correction rate A (hypertonic saline for symptomatic patients)	Targeted correction rate B	(Time to) recovery from hyponatraemia (biochemical and/or symptoms), CNS status (myelinolysis, ODS, respiratory arrest, coma, GCS improvement, seizures, epilepsy, brain edema, brain damage), mortality, length of hospital stay	16 [68-73, 75-82, 84, 102]	**R 3.1**, **R 4.1**, **R 4.2**
Treatment of severe symptomatic hyponatraemia Question II: *What is the optimal use of hypertonic saline in treatment of hypotonic hyponatraemia in adult patients?*	Adults with hypotonic hyponatraemia	Hypertonic saline regimen A (bolus/infusion/timing etc)	No intervention, hypertonic saline regimen B (bolus/infusion/timing etc)	Improvement in severe symptoms of hyponatraemia, biochemical outcomes, overcorrection, mortality	11 [68, 86-95]	**R 3.1**, **R 3.2**, **R 5.2**, **R 5.3**
ODS Question IIIa: *What is the incidence of ODS in patients being treated for hypotonic hyponatraemia?* Question IIIb: *Can we identify risk factors or subgroups at risk for developing ODS while being treated for hypotonic hyponatraemia?* Question IIIc: *When biochemical overcorrection develops, is correction indicated? If yes; what is the best treatment option to relower overcorrection?*	**Population**	**Predictor**		**Outcome**		
	Adults being treated for hypotonic hyponatraemia	Clinical/biochemical parameters		(Incidence of) ODS	26 [68, 69, 73, 75-78, 80, 81, 84, 94-109] 0	**R 6.1**, **R 6.4**, **R 6.5**
	Population	**Intervention**	**Comparison**	**Outcome**	5 [101, 110-113]	**R 4.1**, **R 4.2**, **R 6.2**, **R 6.3**, **R 6.4, R 6.5**
	Adults being treated for hypotonic hyponatraemia in which overcorrection occurs	Intervention A (relowering)	No intervention, intervention B, intervention C etc (e.g. dextrose, desmopressin)	Reduction of risk/incidence of ODS symptoms, biochemical outcomes ("success": percentage of patients reaching target, or: rate), length of hospital stay, QoL, mortality		**R 6.2**, **R 6.3**, **R 6.5**

Abbreviations: CNS, central nervous system; ODS, osmotic demyelination syndrome; QoL = quality of life.

Table 10. Areas of uncertainty in the management of hyponatraemia.

Areas of uncertainty
• Bolus 3% hypertonic saline strategy: optimal volume balancing safety and efficacy; predictors of the need for repeated boluses; weight-based vs. fixed-volume approaches. • Biomarkers for predicting the risk of osmotic demyelination syndrome. • Patient-reported outcome measures as endpoints in clinical studies on hyponatraemia. • Randomised controlled trials comparing different treatment regimens for the syndrome of inappropriate antidiuresis. • The effect of prescribed correction rates on outcomes, rather than the association between achieved correction rates and outcomes.

Figure 1. Spectrum of symptoms according to severity and duration of hyponatraemia.

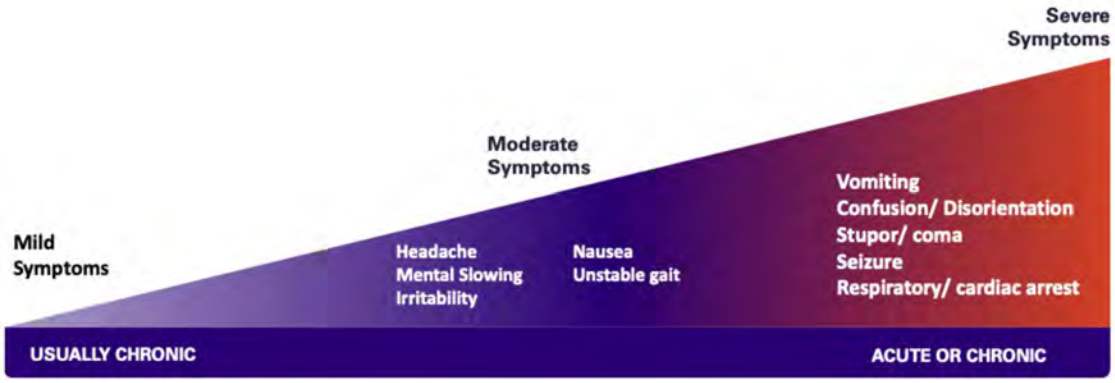


Figure 2. Diagnostic algorithm of aetiology of hyponatraemia.

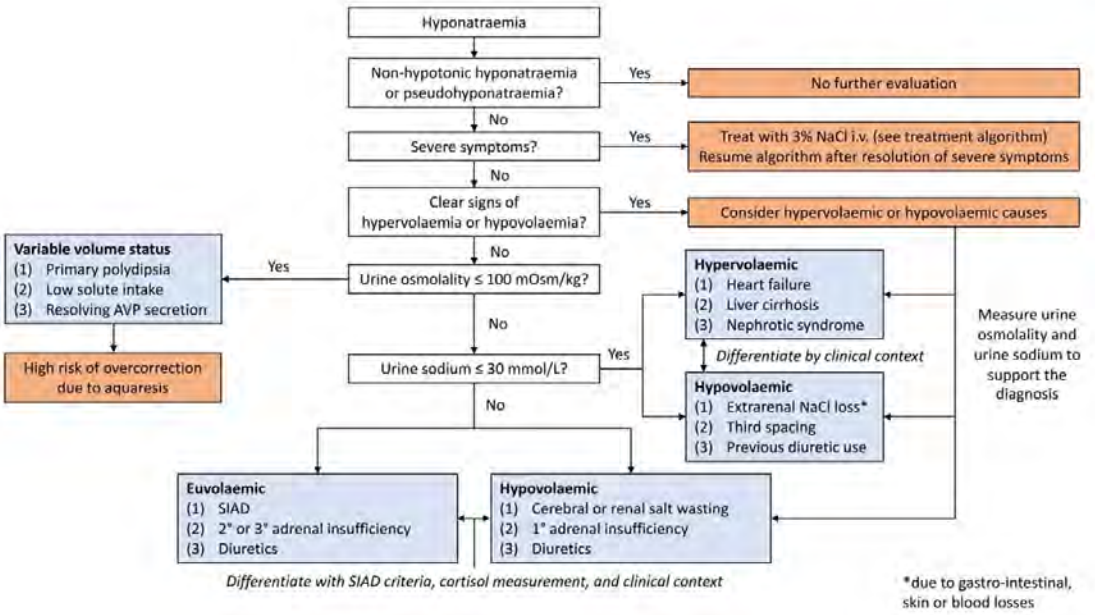


Figure 3. Treatment algorithm for the management of hyponatraemia based on symptoms and aetiology.

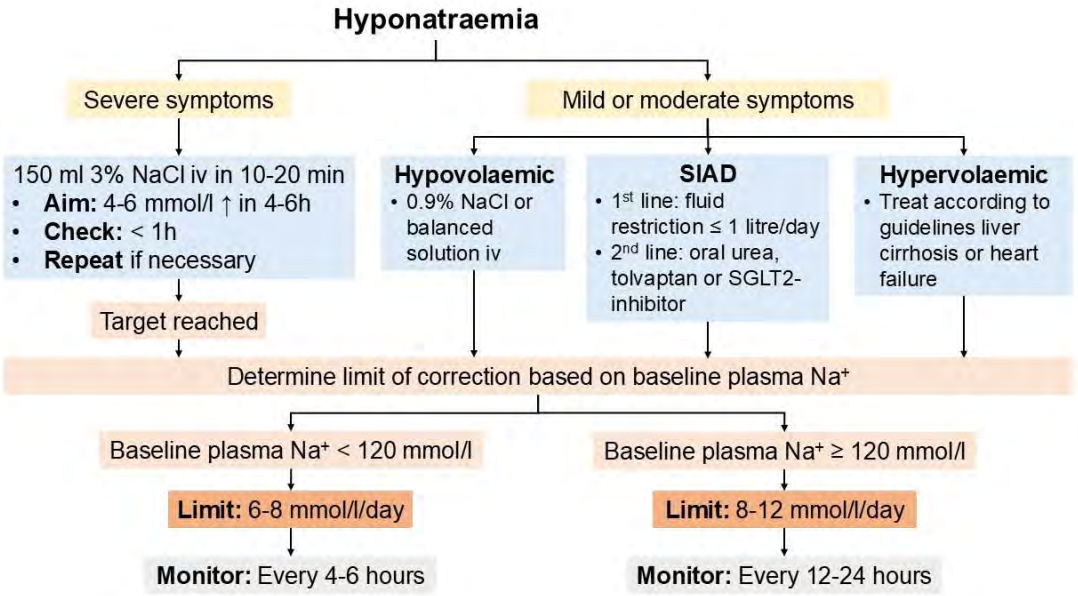


Figure 4. Algorithm for the management of acute hyponatraemia without severe symptoms

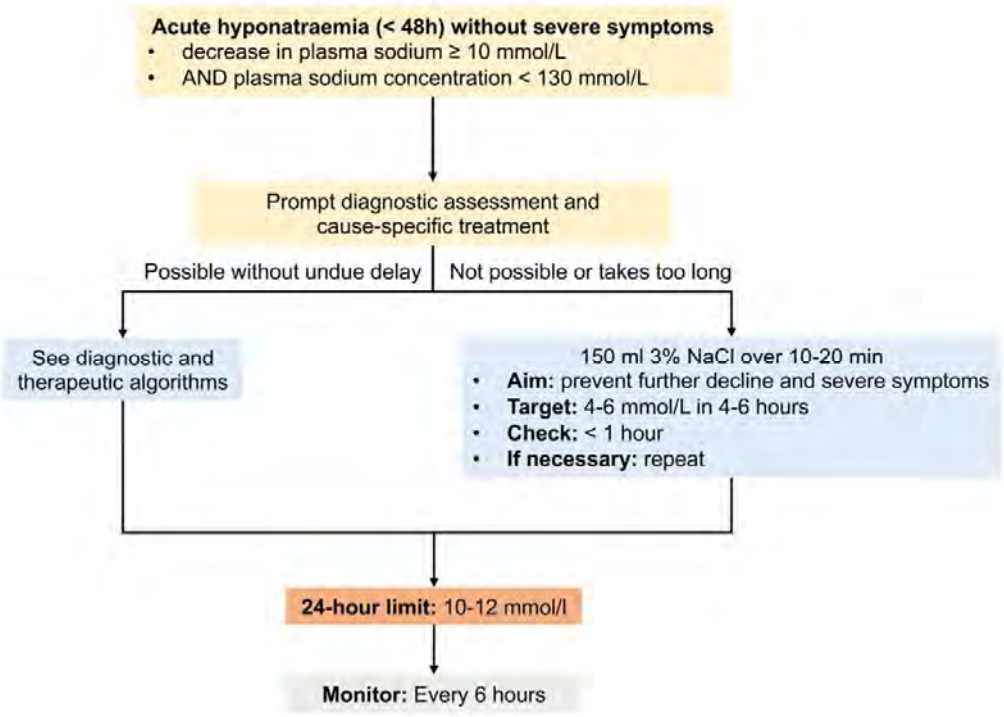
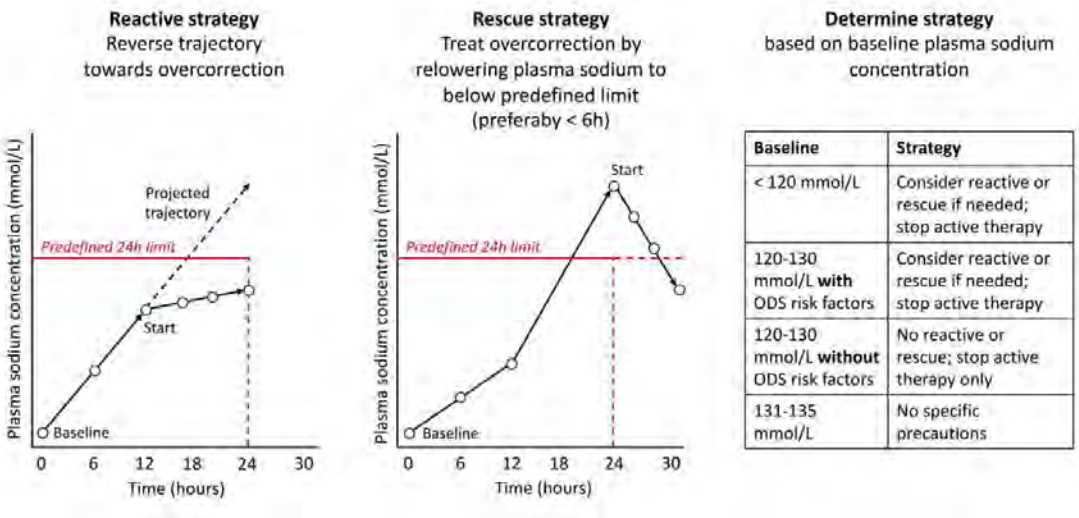


Figure 5. Reactive and rescue approaches to prevent or treat overcorrection.



Baseline	Strategy
< 120 mmol/L	Consider reactive or rescue if needed; stop active therapy
120-130 mmol/L **with** ODS risk factors	Consider reactive or rescue if needed; stop active therapy
120-130 mmol/L **without** ODS risk factors	No reactive or rescue; stop active therapy only
131-135 mmol/L	No specific precautions

Figure 6. Causes of the syndrome of inappropriate antidiuresis.

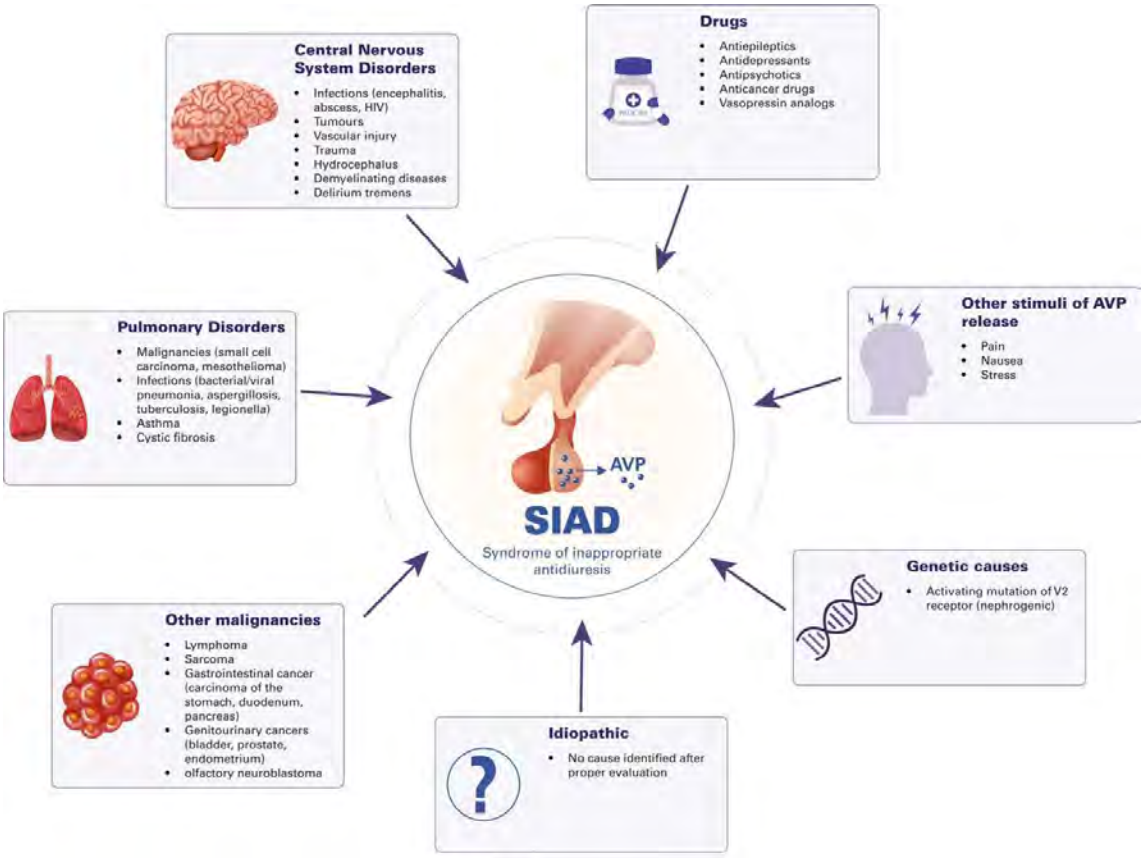


Figure 7. Meta-analysis of the incidence of osmotic demyelination syndrome in patients treated for hyponatraemia.

