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3

Diagnostic algorithm of hyponatremia

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Hyponatremia is the most common electrolyte disturbance and is associated with increased morbidity and mortality. It is driven by an excess of free water relative to total body sodium. While determining the underlying cause(s) of hyponatremia can be challenging, this can be facilitated by an algorithmic approach. Hypotonic hyponatremia is diagnosed by excluding translocational and pseudohyponatremia and confirmed by measuring plasma osmolality. Measuring urine osmolality and urine sodium concentration together with clinical history and examination, especially assessment of volume status, can determine the underlying cause. The most common cause of hyponatremia is the syndrome of inappropriate diuresis, characterised by inappropriate arginine vasopressin activity resulting a high urine osmolality and high urine sodium concentration. Further investigation can determine the underlying cause(s) of the syndrome of inappropriate antidiuresis. This review provides a diagnostic algorithm for hyponatremia, with a focus on biochemical parameters supplemented by clinical fluid status examination.

Introduction

Hyponatremia is defined as plasma sodium concentration below 135 mmol/L. It is the most common electrolyte disorder, affecting 1–2 % of the general population, with an increased prevalence in older adults and people with hypertension, diabetes, cardiovascular disease, cancer, and psychiatric disorders [1]. Hyponatremia is present in 15–30 % of hospitalised patients [2], and is associated with prolonged hospital stay, increased readmission within 90 days, and increased mortality [3]. Hyponatremia can present with a broad spectrum of symptoms, from subtle or asymptomatic (e.g. nausea, gait instability) to severe or life-threatening (e.g. seizures, coma) [4].

Determining the cause of hyponatremia can be difficult. People with hyponatremia often have multiple comorbidities and take numerous medications, and their hyponatremia is often multifactorial. Traditional diagnostic algorithms can be challenging to implement and may not always lead to accurate diagnosis. In one survey, 46 physicians were given 4 clinical cases of hyponatremia and provided with 10 published diagnostic algorithms to guide them, yet only 10 % of physicians were able correctly diagnose the cause of hyponatremia [5]. Weaknesses identified in the algorithms included the belief that mild hypovolemia could be distinguished from euvolemia by clinical examination supported by routine laboratory data, a tendency to diagnose the syndrome of inappropriate antidiuresis (SIAD) prior to excluding other causes of hyponatremia, and reliance on generalisations rather than robust data (e.g. hyperkalemia must be present to diagnose primary adrenal insufficiency) [5].

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This review provides a suggested approach for diagnosis of hyponatremia based on biochemistry and clinical assessment of volume status, according to best available evidence. Multiple diagnostic algorithms exist in the literature; however each has its limitations. Clinical history, medication history and examination are a critical part of diagnosis and provide important context for interpretation of biochemical assessments. However, fluid status assessment is often inaccurate, so it may not be appropriate to make treatment decisions based on fluid status assessment alone. Plasma and urine osmolality and urine sodium provide accurate information - but can have prolonged laboratory processing times and may not be immediately available to make preliminary management decisions. Furthermore, these measures are not static and can differ on serial measurements even if the pathophysiology is unchanged [6]. The algorithm we propose has a stronger emphasis on biochemistry supported by clinical assessment, which we believe provides the greatest diagnostic accuracy. Importantly, severely symptomatic hyponatremia is a medical emergency, and urgent treatment may be required prior to any assessment of its underlying cause. A list of suggested investigations to assist with determining the underlying cause of hyponatremia is provided in Table 1. Detailed discussion of the pathophysiology and treatment of hyponatremia is beyond the scope of this review.

Background pathophysiology

Hyponatremia is caused by a relative excess of free water compared to total body sodium. Plasma sodium concentration is regulated by changing the input and output of free water [4]. A positive fluid balance with increased water intake and/or reduced urine output results in a decrease in plasma sodium, whereas a negative fluid balance with reduced water intake and/or increased urine output results in a rise in plasma sodium.

The main mechanisms by which the body regulates water balance are thirst and arginine vasopressin (AVP) [7]. AVP, previously known as anti-diuretic hormone, is released by the posterior pituitary and acts in the nephron where it stimulates the synthesis and insertion of aquaporin-2 water-channels into the principal cells of the renal collecting duct. This results in reabsorption of free water from the filtrate, causing reduced water excretion via the production of low-volume concentrated urine. Under physiological conditions, AVP release can be stimulated by either increased tonicity detected by osmoreceptors in the anterior hypothalamus or reduced circulating blood volume detected by baroreceptors in the left atrium, carotid sinus, and aortic arch [4,8]. Many conditions that lead to reduced circulating blood volume can prompt “appropriate” release of AVP, such as hypovolemia from vomiting or diuretics, or hypotension in heart failure. When this persists despite decreasing plasma osmolality, hyponatremia can occur. “Inappropriate” production of AVP, independent of both osmotic and barometric triggers, can also result in hyponatremia and is known as SIAD (provided that important differentials like adrenal insufficiency are excluded).

Diagnostic approach

1. Assess plasma osmolality

Total plasma osmolality is defined as the number of solute particles for a given mass of plasma (mOsm/kg), regardless of whether the solutes can cross biological membranes [4,8]. The main plasma solutes are sodium (and associated anions), glucose, and urea. Normal plasma osmolality ranges from 275 to 295 mOsm/kg. Plasma osmolality can be approximated using the equation:

$$Osmolality = 2(Na^+ + K^+) + glucose + urea.$$

Effective plasma osmolality, or tonicity, considers only solutes that cannot cross cell membranes (e.g. sodium and glucose) and therefore dictate the movement of water between the intracellular and extracellular space [8]. Plasma tonicity can be approximated using the equation:

$$Tonicity = 2(Na^+) + glucose.$$

Plasma tonicity is usually tightly regulated to prevent osmotic gradients which can lead to water shifts between the intracellular and extracellular space, with consequent cell swelling or shrinkage. Water shifts across the blood-brain barrier can result in

Table 1
Suggested initial investigations to determine the underlying cause of hyponatremia. Further investigations more specific to the underlying cause may be required following clinical assessment.

List of screening investigations in hyponatremia
Urea, electrolytes and creatinine (UEC)
Venous blood gas
Plasma osmolality
Urine osmolality
Urine sodium concentration
Glucose concentration
Lipid studies
Early morning cortisol level
Thyroid function tests

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potentially fatal cerebral edema if plasma sodium concentration rises too quickly, or osmotic demyelination if sodium concentration falls too quickly. "True" hyponatremia is hypotonic, associated with a low plasma osmolality $<$ 275 mOsm/kg. There are three possible explanations for hypertonic or isotonic hyponatremia.

Pseudohyponatremia

Pseudohyponatremia occurs when abnormally high concentrations of blood "solids" (proteins or lipids) interfere with accurate sodium measurement. This may be caused by endogenous (hypertriglyceridemia, paraproteinemia) or exogenous (intravenous immunoglobulin) agents. Pseudohyponatremia is a laboratory artefact affecting sodium concentration measured by automated "indirect" analysers which measure sodium concentrations per volume of plasma, where blood samples are diluted and the sodium concentration is calculated assuming a constant proportion of solids in the plasma [9]. Increased plasma solids lead to a lower sodium concentration result. "Direct" blood gas analysers that measure sodium in an undiluted sample will yield the true sodium concentration, so should be used instead in this setting [4].

Translocational hyponatremia

Translocational hyponatremia occurs when the presence of effective solutes in the bloodstream other than sodium and its associated anions attracts water from the intracellular to the extracellular space, resulting in a low plasma sodium concentration. The presence of these additional solutes generally results in a normal or even elevated plasma osmolality (i.e. isotonic or hypertonic hyponatremia). The most common osmolyte to consider is glucose (e.g. hyperglycemia in uncontrolled diabetes mellitus). Other osmolytes such as mannitol or glycine (irrigation fluids which can be absorbed during urological or gynecological procedures) [10], or radiocontrast media can also have this effect.

The Hillier equation can be used to approximate an anticipated sodium concentration (i.e. what the sodium concentration would be if glucose was normalised) based on the measured sodium and glucose concentrations [11]. This formula adds 2.4 mmol/L to the measured sodium concentration for every 5.5 mmol/L (100 mg/dL) rise in plasma glucose.

$$AnticipatedNa^{+} = MeasuredNa^{+} + 2.4 \times \frac{glucose - 5.5}{5.5}$$

Correction for glucose is necessary for significantly raised glucose concentrations, but for glucose levels $<$ 10 mmol/L (180 mg/dL), this formula alters measured plasma sodium concentration by $\leq$ 1 mmol/L. The Hillier equation can be computed via online calculators, or the anticipated sodium can be approximated with the equation (all in mmol/L):

$$AnticipatedNa^{+} = MeasuredNa^{+} + \frac{glucose}{3}$$

Elevated non-effective osmolytes

Elevated urea concentrations in renal impairment can also increase measured osmolality. Although acute rises in urea can stimulate AVP release [12], urea is not considered an effective solute as it can move freely across cell membranes, so does not cause persistent intracellular-extracellular water shifts and translocational hyponatremia [4]. Therefore, hyponatremia detected in this setting is "true" hyponatremia, despite a normal or elevated plasma osmolality, and the cause of the hyponatremia must lie elsewhere. Likewise, ethanol and toxic alcohols (e.g. ethylene glycol) are similarly considered ineffective osmolytes that contribute to measured osmolality, but do not cause hyponatremia. Calculation of the osmolar gap can provide a clue to the presence of a non-effective osmolyte, where an osmolar gap $>$ 10 mOsm/kg indicates the presence of unmeasured osmolytes.

$$Osmolar\,gap = serum\ osmolality_{measured} - serum\ osmolality_{calculated}$$

Therefore, the initial step in diagnosing hyponatremia is to establish whether hyponatremia is hypotonic by excluding pseudohyponatremia and translocational hyponatremia. Hypotonic hyponatremia can be confirmed by a low plasma osmolality (Fig. 1). Measurement of plasma glucose, lipids and protein may be informative while awaiting the osmolality result.

2. Assess urine osmolality

Once hypotonic hyponatremia is confirmed, the next step is to measure urine osmolality to infer AVP activity [13]. It is not currently recommended to measure AVP (or its surrogate marker copeptin) directly, as they do not reliably discriminate between different causes of hyponatremia [14]. Under physiological circumstances, hypotonic hyponatremia should result in complete suppression of AVP release, and therefore production of maximally dilute urine (urine osmolality $<$ 50–100 mOsm/kg) to offload excess water. Given that renal diluting capacity might be reduced on older people, this threshold has been proposed to be $<$ 200 mOsm/kg in this demographic [15]. Hence any urine osmolality above these values indicates AVP activity which is "inappropriate" given plasma hypotonicity, although it may be appropriate with regard to circulating plasma volume (see below). Provided kidney function is normal, urine volume is generally inversely proportional to urine osmolality and AVP activity, i.e. low urine osmolality is associated with high volume urine output, and vice versa [4]. In advanced kidney impairment, there is loss of concentrating ability and urine osmolality is the same as plasma osmolality (i.e. isosthenuria) [4]. In that setting, free water excretion is no longer dependent on AVP, but rather the number of solutes excreted in the urine, and therefore on solute intake.

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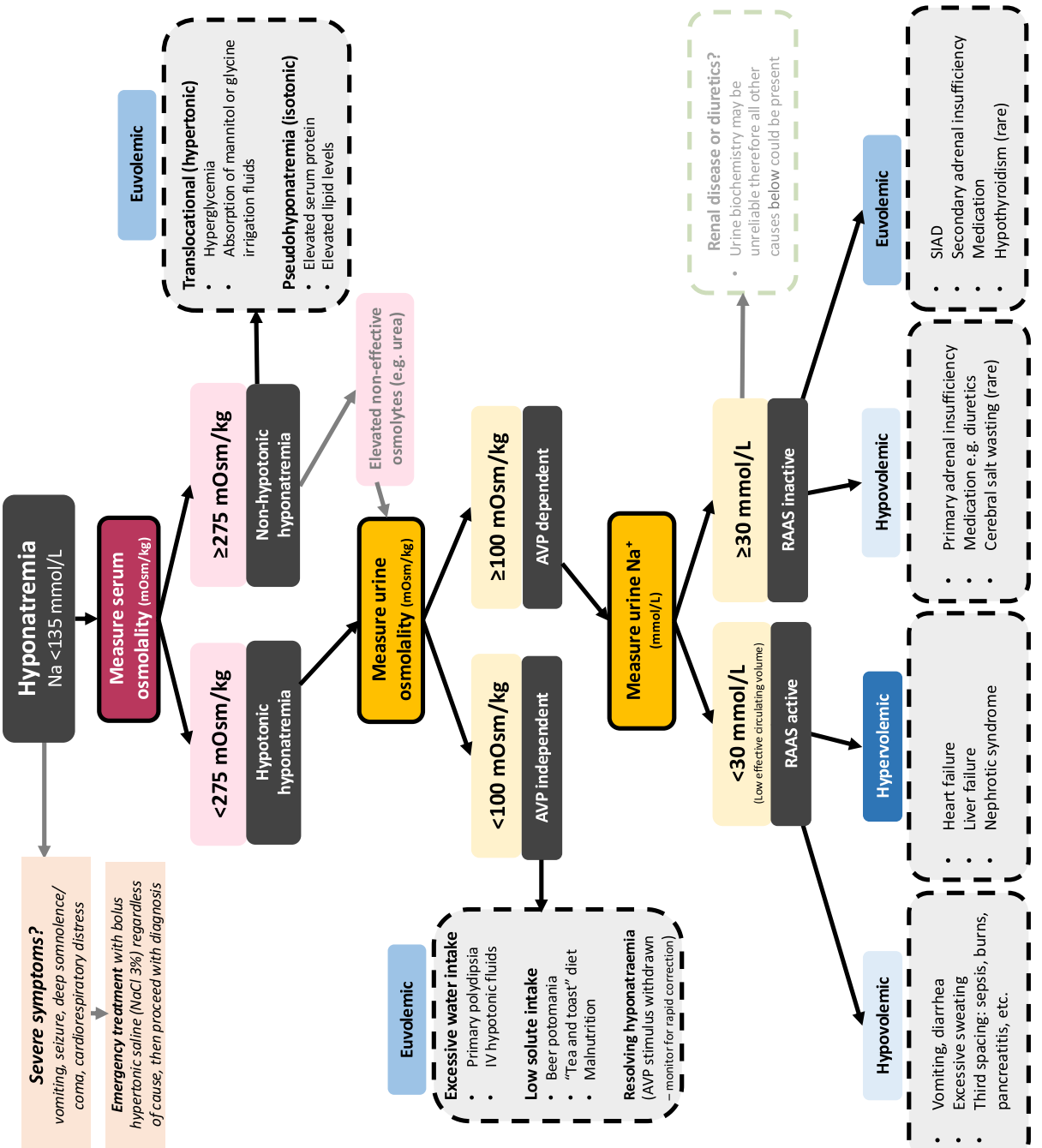

Fig. 1. Diagnostic algorithm of hyponatremia. The first step is to confirm the presence of trye hypotonic hyponatremia. Following this, assessment of urine osmolality and urine sodium concentrations is pertinent for diagnosing the underlying cause. Finally, the underlying cause should be confirmed with physical examination assessment of fluid status. Abbreviations: Na = sodium concentration; NaCl = sodium chloride; IV = intravenous; SVP = arginine vasopressin; RAAS = renin-angiotensin-aldosterone system; SIAD = syndrome of inappropriate antidiuresis.

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Urine osmolality < 100 mOsm/kg

Excessive water intake. Excessive water intake such as in primary polydipsia, water intoxication, or excessive intravenous hypotonic fluids, can result in hyponatremia if urine output is overwhelmed. Hyponatremia can also result from absorption of hypotonic irrigation fluids during urological surgery or colonoscopy [7]. Clinical features may include a history of excessive water intake, excessive exercise, or a history of mental illness or neurodevelopmental disorders that can be associated with primary polydipsia (inappropriate thirst) [16]. The kidneys can excrete very large quantities of urine, provided dietary solute intake is adequate. However, if hypotonic fluid input exceeds this capacity, the fluid intake is very rapid, or there is simultaneous inappropriate AVP activity, the excess free water results in hyponatremia [7,17]. Urine osmolality is typically maximally dilute, reflecting the suppression of AVP [18].

Low solute intake. Renal water excretion is dependent on solute excretion and therefore solute intake. Where urine is maximally dilute with urine osmolality < 50–100 mOsm/kg, 100 mmol of solutes (e.g. urea, potassium) is required to excrete > 1 litre of water. In high income countries a normal diet provides ~900 mOsm per day (mostly from protein or salt), allowing excretion of 18 L of urine per day if required (assuming urine osmolality of 50 mOsm/kg). If solute intake is low relative to water intake, such as chronic alcoholism or malnutrition (e.g. "beer potomania" or "tea and toast" diet), the available solutes are insufficient to excrete the volume of water ingested, resulting in hyponatremia [19]. Hence with low solute intake, urine volumes becomes the limiting factor for water excretion, and hypotonic hyponatremia occurs despite maximally dilute urine (and suppressed AVP). Clinical features of low solute intake may include cachexia, weight loss, known eating disorder, social isolation or alcohol abuse.

Correction of hyponatremia. Low urine osmolality and increasing urine volumes in hyponatremia could also be a sign that normal physiology is restored, and hyponatremia is starting to self-correct whereby excess free water is excreted in the urine. Hyponatraemia may have originally occurred due to any cause. Low urine osmolality can occur with resolution of transient SIAD (e.g. improvement in pain or nausea), cessation of diuretic, or following treatment of an underlying cause (e.g. glucocorticoids for adrenal insufficiency). In these situations, it is important to monitor plasma sodium concentration closely, due to the risk of overcorrection (see below).

Urine osmolality > 100 mOsm/kg

In the setting of hypotonic hyponatremia, a urine osmolality of > 100 mOsm/kg indicates that AVP is present. This AVP is inappropriate with respect to hypotonicity. The next step is to determine whether this AVP is appropriate with respect to circulating blood volume. If the patient is hypovolemic (i.e. reduced circulating volume), the AVP secretion is "appropriate" due to hypotension, and fluid replacement is the logical treatment. AVP may also be "appropriately" elevated in the setting of reduced *effective* circulating volume because of heart failure, cirrhosis or nephrotic syndrome, despite overall hypervolemia (expanded extracellular fluid). If the patient is euvolemic, AVP secretion is inappropriate with respect to both tonicity and volume (i.e. SIAD), and fluid restriction is the first-line treatment. Therefore, making the distinction between hypovolemia and euvolemia is critical, given the difference in therapeutic approach. However, clinical distinction between euvolemia and (especially mild) hypovolemia can be difficult, which is why we favour, in line with the European guidelines [4], the assessment of urine sodium as the next step, to help distinguish between these causes.

Assess urine sodium concentration

A urine osmolality of > 100 mOsm/kg reflects the presence of AVP activity. Urine sodium can be used as a surrogate marker of renin-angiotensin-aldosterone system (RAAS) activity (i.e. of volume status). If the RAAS is activated by hypovolaemia or decreased effective circulating volume, aldosterone will act in the distal nephron to reabsorb sodium from the renal filtrate, thereby conserving sodium and water, resulting in a low urine sodium concentration [20]. In the absence of interference by diuretics or renal impairment, urine sodium concentration can help distinguish hyponatremia due to decreased effective arterial volume (urine sodium < 30 mmol/L), from dilutional disorders due to intravascular volume expansion (urine sodium ≥30 mmol/L) [21,22].

Urine sodium concentration < 30 mmol/L

Hypovolemia. In hypovolemic states, stimulation of osmoreceptors and baroreceptors triggers physiological AVP release, resulting in urine osmolality > 100 mOsm/kg. Renal sodium conservation occurs, resulting in urine sodium concentration < 30 mmol/L [4], except for in renal sodium wasting due to diuretic therapy [23]. Causes of hypovolemic hyponatremia include gastrointestinal sodium loss due to vomiting or diarrhea, or transdermal sodium loss due to excessive sweating. Patients often replace these gastrointestinal or transdermal losses with hypotonic fluids such as water, further exacerbating hyponatremia. Treatment of hypovolemic hyponatremia involves replacing volume with isotonic (normal) 0.9 % saline, and addressing the underlying cause to present further sodium loss.

Hypervolaemia - Heart failure, cirrhosis, nephrotic syndrome. Heart failure, cirrhosis and nephrotic syndrome can cause hyponatremia with reduced effective arterial volume but increased extravascular volume ("hypervolemic hyponatremia"). The estimated prevalence of hyponatremia in both chronic heart failure and chronic liver disease is ~20–30 % [24–26]. In these conditions, hyponatremia is dilutional, caused by retention of both water and salt, but an excess proportion of water. Free excess water accumulates because, despite extravascular fluid overload, there is reduced effective arterial volume - due to reduced cardiac output in heart failure, hypoalbuminemia and splanchnic vasodilation in liver failure, or proteinuria and hypoalbuminaemia in nephrotic syndrome. Activation of both AVP and the RAAS system results in production of concentrated urine (urine osmolality > 100 mOsm/

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Table 2
List of medications that can cause hyponatremia.

Mechanism	Medication Examples
SIAD	Psychotropics: TCAs, SSRIs/SNRIs, MAOI, phenothiazides
	Antiepileptics: carbamazepine, sodium valproate, lamotrigine
	Opioids
	Chemotherapy: cyclophosphamide, vincristine
	NSAIDs
	MDMA
	Proton pump inhibitors
Inhibit free water reabsorption	Loop diuretics
	Thiazides
Renal salt wasting	Trimethoprim-sulfamethoxazole
AVP analogue	Desmopressin
Unknown	Aminoglycosides
	Antihypertensives: Angiotensin II receptor blockers, beta-blockers
	Potassium-sparing diuretics
	Antiepileptics: gabapentin, phenytoin
	Lipid-lowering therapy: statins, ezetimibe

Abbreviations: SIAD = syndrome of inappropriate antiduresis; TCA = tricyclic antidepressants; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-noradrenaline reuptake inhibitor; MAOI = monoamine oxidase inhibitor; NSAID = non-steroidal anti-inflammatory drugs; MDMA = 3,4-methylenedioxymethamphetamine; AVP = arginine vasopressin.

kg) with renal sodium conservation (urine sodium < 30 mmol/L) [4]. Treatment of hypervolemic hyponatremia mainly involves fluid restriction, disease-specific treatment and possibly loop diuretics.

Urine sodium concentration $\geq$ 30 mmol/L

Urine sodium ≥ 30 mmol/L indicates the absence of RAAS activity. Hyponatremia where AVP is active (urine osmolality > 100 mOsm/kg) and RAAS is inactive (urine sodium ≥ 30 mmol/L) can be caused by euvolaemic hyponatraemia (e.g. SIAD, secondary adrenal insufficiency), or mineralocorticoid deficiency (e.g. primary adrenal insufficiency). Cerebral salt wasting, a rare and somewhat controversial entity, and diuretic use also present with urine sodium > 30 mmol/L and hypovolaemia. Finally, vomiting with metabolic alkalosis can cause an increased urine sodium > 30 mmol/L despite hypovolemia because increased urine bicarbonate excretion leads to obligate urine sodium loss.

Syndrome of inappropriate antidiuresis. SIAD is the most common cause of hyponatremia, responsible for 35–40 % of hyponatremia cases admitted to hospital [27–29]. It is a condition of excess AVP activity occurring despite hypo-osmolality and the absence of hypovolaemia. Excess AVP activity results in water retention, production of concentrated urine (urine osmolality > 100 mOsm/kg, urine sodium > 30 mmol/L) and hyponatremia [30]. Patients with SIAD are typically clinically euvolemic, but have excess total body water, which is difficult to detect clinically. Importantly, SIAD is a diagnosis of exclusion, where glucocorticoid deficiency and severe hypothyroidism must be excluded [4,21].

SIAD can be caused by malignancies, CNS disorders, lung disorders, medications [e.g. carbamazepine, selective serotonin reuptake inhibitors (Table 2)], stress (e.g. pain, nausea, post-operative state), or rarely genetic defects in the vasopressin-2 receptor (nephrogenic SIAD) [30,31] (Table 3). It is important to investigate for an underlying cause of SIAD, as often the best treatment for SIAD is to address the underlying cause (if identifiable and modifiable). In cases where there are no clinical diagnostic clues, imaging with computed tomography (CT) of the brain and chest, and consideration of CT abdomen/pelvis is recommended [32]. In young people with recurrent and unexplained SIAD, positron emission tomography may be considered to investigate further for occult malignancy [32]. SIAD may have multiple contributing causes, or be idiopathic with no cause found [16 % of patients in one study [33]]. Idiopathic SIAD is more common in older people [15].

Other features consistent with SIAD are persistent oliguria, and decreasing plasma sodium concentration in response to isotonic fluid administration. Sometimes this is used as a diagnostic test in situations of uncertainty to differentiate SIAD from hypovolaemia, by administering 1–2 litres of 0.9 % normal saline with close monitoring of plasma sodium concentration and urine output [30]. If the hyponatremia is caused by hypovolemia it should improve, however in SIAD, administration of normal saline will lead to water retention and further dilution of plasma sodium - which can be dangerous in some patients. As such, administration of isotonic fluids is not recommended if SIAD is suspected. SIAD is also associated with reduced plasma uric acid levels and elevated copeptin levels [4,30], however currently these parameters are mainly used in research settings rather than routinely in clinical practice, as these markers do not discriminate SIAD from other causes of hyponatraemia.

The first-line treatment of SIAD is fluid restriction [4,34], however this is not always effective. Urine osmolality > 500 mOsm/kg or urine output < 1500 mL/day are predictors of non-responsiveness to fluid restriction [21]. Second-line treatments of SIAD aim to increase water output through various mechanisms, including AVP V2-receptor antagonists (e.g. tolvaptan), oral urea, and sodium-glucose co-transporter 2 inhibitors [32].

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Table 3
List of causes of the syndrome of inappropriate antidiuresis.

Causes of SIAD	Examples
Malignancy	Lung: small cell lung cancer, mesothelioma
	Oropharyngeal
	Gastrointestinal tract: pancreatic cancer, gastric cancer, duodenal cancer
	Genitourinary tract: bladder cancer, prostate cancer, endometrial cancer
	Hematological: leukemia, lymphoma
	Sarcoma
CNS disorders	Infections: meningitis, encephalitis
	Bleeding: intracranial hemorrhage, subdural hematoma
	Mass effect: brain tumours, hydrocephalus, stroke
	Brain trauma
Lung disorders	Infections: pneumonia, tuberculosis, pulmonary abscess
	Asthma
	Cystic fibrosis
	Pleural: pleural effusion, pneumothorax
Medications	See Table 2
Stress	Pain
	Nausea/vomiting
	Extreme exercise
	General anesthesia, post-operative state
Genetic (very rare)	Gain of function mutations in the AVP V2 receptor (also known as "nephrogenic SIAD")
Idiopathic	

Abbreviations: CNS = central nervous system; AVP = arginine vasopressin; SIAD = syndrome of inappropriate antidiuresis.

Adrenal insufficiency. Adrenal insufficiency is an important cause of hyponatremia to screen for, as it is readily treatable and potentially dangerous if missed. Primary adrenal insufficiency is more commonly assocuetd with hyponatremia than secondary [32], due to concurrent glucocorticoid and mineralocorticoid deficiency. Mineralocorticoid deficiency due to lack of aldosterone production results in renal sodium loss. In addition, hypovolemia due to renal sodium loss and hypotension from glucocorticoid deficiency stimulate AVP release which in turn triggers renal water retention, further contributing to hyponatremia [4,21]. Moreover, cortisol deficiency leads to increased hypothalamic secretion of corticotrophin-releasing hormone, an AVP secretagogue. Therefore, biochemical changes in primary adrenal insufficiency are similar to SIAD with high urine osmolality $>$ 100 mOsm/kg and high urine sodium $>$ 30 mmol/L, but in contrast to SIAD, patients are usually volume deplete. Primary adrenal insufficiency is often associated with hyperkalemia due to renal conservation of potassium, with low urine potassium concentration [21]. Other features of primary adrenal insufficiency can include fatigue, hypotension, dizziness, nausea, muscle and abdominal pain [35].

Secondary adrenal insufficiency is hypocortisolism due to deficiency of adrenocorticotropic hormone (ACTH) from the anterior pituitary. Cortisol suppresses AVP production in the posterior pituitary, so lack of cortisol effectively stimulates AVP, leading to hyponatremia [35,36]. Unlike in primary adrenal insufficiency, mineralocorticoid function is intact, so there is no renal salt wasting, hypovolemia, or hyperkalemia. Patients with secondary adrenal insufficiency tend to be euvolemic, closely resembling those with SIAD [21]. In an observational study examining 1323 hospital admissions with hyponatremia, of 573 patients initially diagnosed as SIAD, 22 patients (3.8 %) actually had secondary adrenal insufficiency, evidenced by low plasma cortisol concentrations [28] – reinforcing the importance of proactive screening.

Adrenal insufficiency should be screened for with early morning plasma cortisol and ACTH level. A low plasma cortisol $<$ 140 nmol/L with an ACTH concentration $>$ 2-fold above the upper limit of the reference interval for the specific assay is highly diagnostic of primary adrenal insufficiency [37], whereas ACTH is reduced or inappropriately normal in secondary adrenal insufficiency. Patients with a low plasma cortisol level [one paper suggests a threshold of plasma cortisol $<$ 300nmol/L [28]] should have further testing with an $ACTH_{1-24}$ stimulation test ("short synacthen test"). The exact cortisol cut off below which a short synacthen test is necessary depends on assay characteristics and ideally, local validation. The short synacthen test is the most commonly used test for diagnosing primary adrenal insufficiency [37], however in early secondary adrenal insufficiency the short synacthen test may be normal and provide false reassurance. Pituitary imaging should be considered in newly identified secondary adrenal insufficiency. If a patient is unwell and adrenal insufficiency is suspected, empirical treatment with intravenous hydrocortisone should proceed prior to formal diagnostic workup, with close monitoring of serum sodium to identify and manage potential rapid correction of sodium, which may occur due to glucocorticoid-induced water diuresis.

Hypothyroidism. Hypothyroidism is often listed as a potential cause of hyponatremia, however this is increasingly disputed. Recent data suggest the prevalence of hyponatremia in severe hypothyroidism is similar to the general hospital population – ~20 % of cases [38]. In severe hypothyroidism (e.g. myxedema coma), low-output cardiac failure may drive non-osmotic AVP release and hyponatremia. Hyponatremia may occur with hypothyroidism because of comorbid adrenal insufficiency given the association between primary adrenal insufficiency (Addison's) and autoimmune hypothyroidism (Hashimoto's), or secondary adrenal insufficiency and secondary hypothyroidism in pituitary disease. It is important to replace glucocorticoids prior to treating severe hypothyroidism to avoid precipitating adrenal crisis.

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Cerebral salt wasting. Cerebral salt wasting (CSW) is a rare, and disputed, cause of hyponatraemia following cerebral insult (e.g. traumatic brain injury, stroke). It is postulated to be caused by release of natriuretic peptides (e.g. B-type natriuretic peptide (BNP), formerly known as brain natriuretic peptide) and/or altered stimualtion to the kidney by the sympathetic nervous system suppressing the RAAS, leading to renal salt and water loss and hyponatremia [39,40]. In most patients, hyponatraemia following cerebral insult is due to SIAD or adrenal insufficiency [41]. The main differentiating factor between CSW and these more common causes is volume status, with hypovolemia a feature of CSW.

Kidney disease

Urine osmolality and urine sodium can be difficult to interpret in patients with renal impairment or on diuretic therapy. Renal regulation of water and sodium excretion is compromised, so urine osmolality and urine sodium concentration are no longer reflective of hormonal activity [4]. In oliguric or anuric kidney disease, urine output is relatively fixed, so fluid intake in excess of urine output and other insensible losses will cause hyponatremia [21]. Furthermore, kidney disease can also contribute to hyponatremia independently. Proteinuria with resultant hypoalbuminemia in renal failure can result in arterial underfilling, which can trigger baroreceptor-mediated AVP release and resultant hyponatremia [29]. Any diagnostic algorithm must be used with caution in patients with renal impairment.

Diuretics

Diuretics result in renal sodium loss, so urine sodium is often $>$ 30 mmol/L. Thiazide diuretics are a common cause of hyponatremia. Thiazide-induced hyponatremia has been associated with a genetic predisposition, with around half of those affected having a single nucleotide polymorphism in the *SLCO2A1* gene that encodes a prostaglandin transporter in the collecting duct, resulting in increased water absorption despite AVP suppression (akin to a "nephrogenic antidiuresis") [42]. Volume status assessment in the context of diuretics can vary depending on the dose, and how recently they were administered. Often people with heart, liver or kidney impairment on diuretics have reduced intravascular circulating volume which can trigger physiological AVP release, further contributing to hyponatremia.

Several biochemical markers are being studied to help determine the underlying cause of hyponatremia in people on diuretics. One study suggested that fractional uric acid excretion may have better diagnostic utility for diagnosing SIAD in people on diuretic therapy, where fractional uric acid excretion $>$ 12 % had a positive predictive value (PPV) of 100 % for SIAD [23]. Another study assessed the utility of the apparent strong ion difference (aSID; defined as $serumNa^+ + K^+ - Cl^-$), supplemented with the urine chloride and potassium score ($urineCl^- - K^+$) and fractional uric acid excretion in diagnosing thiazide-associated hyponatremia. They reported that aSID $>$ 42 mmol/L had a PPV of 79.1 %, whereas aSID $<$ 39 mmol/L excluded thiazide-associated hyponatremia with a negative predictive value of 76.5 %. In cases where aSID was between 39 and 42 mmol/L, urine chloride and potassium score $<$ 15 mmol/L had a PPV of 100 %, and fractional uric acid excretion $<$ 12 % had a PPV of 85.7 % for thiazide-associated hyponatremia [43]. However, these results need to be confirmed in a broader population before these parameters can be recommended in routine clinical practice.

3. Assess fluid status

Clinical volume status assessment can be difficult and is not always reliable, particularly in patients with multiple comorbidities [21]. Nonetheless, accurate volume status assessment can add important context in determining the underlying cause of hyponatremia (Table 4).

Clinical signs of hypovolemia include postural hypotension, tachycardia, dry mucous membranes, decreased skin turgor and reduced jugular venous pressure. Some studies suggest that point-of-care ultrasound of the inferior vena cava may provide a more accurate assessment of volume status [44]. As discussed earlier, hypovolemic hyponatremia can be caused by gastrointestinal sodium loss due to vomiting or diarrhea, transdermal sodium loss due to excessive sweating, or renal sodium loss due to diuretic therapy or primary adrenal insufficiency.

Hypervolemia can be associated with pulmonary edema, peripheral edema, ascites and elevated jugular venous pressure. Causes of hypervolemic hyponatremia include heart failure, liver failure, and renal failure. There may be associated orthopnea or paroxysmal nocturnal dyspnea in cardiac failure; the presence of jaundice, signs of portal hypertension, or a history of alcoholism or viral hepatitis in liver failure; or oliguria or uremic symptoms in renal impairment.

Clinical examination consistent with euvolemia can be indicative of SIAD, secondary adrenal insufficiency, extreme hypothyroidism, or low solute /excessive water intake as the underlying cause of hyponatremia.

Areas of ongoing research - Copeptin

Copeptin is a glycoprotein which is cleaved from the AVP precursor pre-pro-vasopressin, and can be used as a surrogate marker of AVP activity. However, its utility in hyponatremia diagnosis is still debated. A prospective observational study involving 106 patients with hyponatremia found that the copeptin/urine sodium ratio was able to accurately differentiate between hypovolemia and euvolemia, where a cut-off of 30pmol/mmol had a sensitivity of 85 % and specificity of 87 % [14]. The combination of plasma copeptin $<$ 3pmol/L with urine osmolality $<$ 200 mOsm/kg was diagnostic for primary polydipsia in 100 % of cases [14]. In another prospective observational study involving 298 patients with profound hyponatremia (Na $<$ 125 mmol/L), plasma copeptin $<$ 3.9pmol/L diagnosed primary polydipsia with high specificity (91 %) [45]. The copeptin/urine sodium ratio was lower in patients with SIAD

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Table 4
Summary of different causes of hyponatremia according to fluid status, including clinical features and additional supporting investigations.

Cause	Signs/Symptoms	Investigations
Hypovolemic hyponatremia		
Gastrointestinal disease	Vomiting, diarrhea, high water intake	• Positive stool culture • Urine Na < 30 mmol/L
Exercise-associated hyponatremia	Vigorous endurance exercise (e.g. marathon)	• Urine Na < 30 mmol/L
Primary adrenal insufficiency	Fatigue, postural dizziness, hypotension, hyperpigmentation, nausea	• Hyperkalemia • Low morning cortisol • Abnormal short synacthen test • Elevated ACTH level • Urine Na > 30 mmol/L
Diuretic therapy	History of diuretic use, especially thiazides	• Variable urine Osm • Urine Na > 30 mmol/L
Euvolemic hyponatremia		
SIAD	Malignancy, respiratory illness, CNS disease Small volume concentrated urine Falling Na level with IV fluid administration	• Urine Osm > 100 mOsm/kg • Urine Na > 30 mmol/L • Normal cortisol and TFTs • Low plasma uric acid levels* • High copeptin levels*
Secondary adrenal insufficiency	Fatigue, postural dizziness, hypotension, nausea	• Low morning cortisol • Abnormal SST • Low ACTH level • Urine Na > 30 mmol/L
Hypothyroidism (rare)	Fatigue, cold intolerance, weight gain, constipation	• Low free T3/free T4 (± high TSH) • Urine Osm > 100 mOsm/kg • Urine Na > 30 mmol/L
Low solute intake	Alcohol excess, malnutrition, cachexia	• Vitamin and mineral deficiencies • Urine Na < 30 mmol/L
Primary polydipsia	Excessive water intake, thirst	• Urine Osm < 100 mOsm/kg • Urine Na < 30 mmol/L
Hypervolemic hyponatremia		
Heart failure	Dyspnea, bilateral lung crepitations, reduced exercise tolerance	• Abnormal echocardiogram • Elevated BNP • Pulmonary edema on CXR
Liver cirrhosis	Ascites, jaundice, dyspnea	• LFT derangement • Cirrhosis on abdominal imaging
Renal failure	Oliguria	• Reduced eGFR • Elevated urine PCR

Abbreviations: Na = sodium; ACTH = adrenocorticotropic hormone; T3 = triiodothyronine; T4 = thyroxine; Osm = osmolality; LFT = liver function tests; GFR = glomerular filtration rate
* Used mainly in research settings

compared to hyponatremia of other etiologies ($p < 0.0001$), with a moderate specificity of 61 % [45]. One area where copeptin may be useful is in identifying rare nephrogenic SIAD, a genetic disorder of increased sensitivity to AVP, where a low copeptin without polydipsia may prompt confirmatory *AVPR2* gene testing [46,47]. Overall, the diagnostic utility of copeptin in the work-up of hyponatremia requires further research, and at this stage should not be used routinely in clinical practice.

Reassessment of urine biochemistry to detect overcorrection of hyponatremia

Overly rapid rise in plasma sodium concentration can cause life-threatening neurological complications including osmotic demyelination syndrome (ODS) [48]. International guidelines recommend that correction of chronic hyponatremia > 24 h duration (or hyponatremia with unknown duration) be limited to < 10 mmol/L in a 24-hour period, with more stringent targets in people at increased risk of ODS [4,21]. Risk factors for ODS include plasma sodium < 105 mmol/L, hypokalemia, chronic alcoholism, liver disease, and malnutrition [4,21,48].

It is vital to recognise the signs of impending overcorrection of hyponatremia. The most common feature is rapid water diuresis, evidenced by increasing urine volume. This is reflected biochemically as declining urine osmolality, and urine sodium < 20 mmol/L. Clinically, this occurs most commonly when the stimulus to AVP secretion is no longer present [e.g. offending medications (including thiazide diuretics) are ceased, an intercurrent illness resolves, or euvolemia is restored]. When this occurs, there is a change from small volume concentrated urine to large volume dilute urine. Rapid excretion of excess free water leads to a rapid rise in plasma sodium concentrations, requiring close monitoring of plasma sodium concentrations, and may require intervention to prevent overcorrection.

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Summary

Hyponatremia is a common but complex condition. Accurately diagnosing the underlying cause(s) can be difficult, particularly in those with multiple comorbidities. Plasma osmolality measurement is required to confirm the presence of hypotonic hyponatremia, which can be associated with neurological sequelae. Urine osmolality, urine sodium concentration, and clinical volume status assessment can then infer AVP and aldosterone activity to aid in determining the cause. A structured algorithmic approach can improve the diagnosis and hence treatment of hyponatremia, as correctly identifying the underlying cause is a prerequisite to effective treatment, and can avoid iatrogenic adverse treatment outcomes. While definitive data to support this intuitive concept are lacking, dedicated specialist care has been shown to improve mortality outcomes in hyponatremia, likely at least in part, due to more accurate diagnosis [49].

Research Agenda

- Improved accuracy of current hyponatremia diagnostic algorithms is required, with reduced reliance on clinical fluid status assessment which can be unreliable.
- Rapid processing or point of care measures for plasma and urine osmolality and sodium concentrations will improve the utility of diagnostic algorithms which depend on these measures
- Further research assessing methods for identifying the underlying cause of hyponatremia in patients with renal impairment or on diuretic therapy is needed.
- The clinical utility of biomarkers such as copeptin or uric acid concentration in differentiating the syndrome of inappropriate antidiuresis from other causes of hyponatremia needs to be explored further.

Practice Points

- Hyponatremia is the most common electrolyte disorder and is associated with increased morbidity and mortality.
- Hyponatraemia frequently occurs secondary to other pathology, so it is critical to investigate for an underlying cause, as this may direct treatment.
- Diagnosing the underlying cause of hyponatremia can be difficult, particularly in cases with multiple contributing causes, or patients with renal disease or on diuretics.
- Urine osmolality and urine sodium concentration, together with clinical history and assessment of fluid status are key in identifying the underlying cause of hyponatremia.

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