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Review

Hyponatremia, a diagnostic challenge: Clinical case analysis and decision-making tools

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Abstract

Introduction: Hyponatremia is the most common electrolyte disorder in clinical practice and is associated with morbidity and mortality, prolonged hospital stays, and increased healthcare resource utilization. Its variable presentation and association with multiple underlying conditions make timely recognition essential, particularly among hospitalized patients and individuals presenting in acute clinical care settings.

Objective: To analyze the pathophysiology, etiology, diagnosis, and management of hyponatremia, with an emphasis on optimizing clinical decision-making through structured diagnostic tools and the use of representative clinical cases.

Keywords: Hyponatremia, Plasma tonicity, Arginine vasopressin, Syndrome of inappropriate antidiuretic hormone secretion (SIADH), Cerebral salt-wasting syndrome (CSW).

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Methodology: A narrative review was conducted based on relevant scientific literature, integratingA structured, physiology-based approach improves etiological identification and reduces therapeutic errors. The integration of clinical, laboratory, and imaging tools allows for individualized treatment and the optimization of clinical outcomes, particularly in patients with acute or symptomatic presentations. physiological principles, current clinical evidence, and clinical practice guidelines. This approach was complemented by the presentation of clinical cases that illustrate different etiological mechanisms and enable the application of a systematic diagnostic approach in real-world settings.
Results: Hyponatremia is a heterogeneous disorder whose etiology is primarily related to disturbances in water balance mediated by vasopressin. A systematic approach based on plasma tonicity, urinary osmolality, and volume status allows for the differentiation of its main causes. The incorporation of tools such as point-of-care ultrasound (POCUS) and biomarkers improves diagnostic accuracy.
Conclusion: A structured, physiology-based approach improves etiological identification and reduces therapeutic errors. The integration of clinical, laboratory, and imaging tools allows for individualized treatment and the optimization of clinical outcomes, particularly in patients with acute or symptomatic presentations.

Hiponatremia, un reto diagnóstico: análisis de casos clínicos y herramientas para la toma de decisiones

Resumen

Introducción: la hiponatremia es el trastorno electrolítico más frecuente en la práctica clínica y se asocia con morbimortalidad, prolongación de la estancia hospitalaria y aumento en la utilización de recursos sanitarios. Su presentación variable y su relación con múltiples condiciones subyacentes hacen que su reconocimiento sea esencial en la atención médica.
Objetivo: analizar la fisiopatología, etiología, diagnóstico y manejo de la hiponatremia, con énfasis en optimizar la toma de decisiones clínicas mediante herramientas diagnósticas estructuradas y el uso de casos clínicos representativos.
Metodología: se desarrolló una revisión narrativa basada en literatura científica relevante, integrando principios fisiológicos, evidencia clínica actual y guías de práctica clínica. Esta se complementó con la presentación de casos clínicos que ilustran distintos mecanismos etiológicos y permiten la aplicación de un enfoque diagnóstico sistemático en escenarios reales.
Resultados: la hiponatremia es un trastorno heterogéneo cuya etiología se relaciona principalmente con alteraciones del balance hídrico mediadas por vasopresina. Un enfoque basado en la tonicidad plasmática, la osmolaridad urinaria y el estado de volumen permite diferenciar sus principales causas. La incorporación de herramientas como el ultrasonido a pie de cama (POCUS) y los biomarcadores mejora la precisión diagnóstica.
Conclusiones: un abordaje estructurado, sustentado en la fisiología, mejora la identificación etiológica y reduce errores terapéuticos. La integración de herramientas clínicas, paraclínicas y de imagen permite individualizar el tratamiento y optimizar los desenlaces clínicos, particularmente en pacientes con presentaciones agudas o sintomáticas.

Palabras clave: hiponatremia, tonicidad plasmática, arginina vasopresina, síndrome de secreción inadecuada de la hormona antidiurética (SIADH), síndrome de pérdida de sal cerebral (CSW).

Introducción

Hyponatremia, defined as a serum sodium concentration <135 mmol/L, is the most common electrolyte disorder, affecting 10-20 % of patients in the emergency department and up to 35 % of hospitalized patients [1–3]. It is classified into mild (130-135 mEq/L), moderate (125-129 mEq/L), severe (<125 mEq/L) and as acute (<48 hours) or chronic (>48 hours) [3, 4].

Hyponatremia represents a significant economic burden, with direct costs between USD 1.6 and 3.6 billion annually in the United States. In addition, it increases the risk of ICU admission and 30-day hospital readmission [5, 6]. Even mild hyponatremia has been associated with gait instability, falls, attention deficits, and an increased risk of fractures. It has also been associated with an increased risk of osteoporosis. The management strategy for hyponatremia depends on the clinical manifestations and the underlying cause [7, 8].

The aim of this review is to enhance understanding of the underlying physiological principles of hyponatremia and to strengthen knowledge for its evaluation.

A brief approach to sodium physiology

Sodium is the main cation in the extracellular fluid; therefore, changes in its concentration can lead to imbalances in plasma characteristics. Osmolarity is the concentration of dissolved osmoles per liter of plasma, whereas osmolality is the concentration of osmoles per kilogram of plasma water. Tonicity is defined as the osmotic concentration that is unable to move freely across the cell membrane (effective osmoles).

It is imperative that the concentration remains uniform both within and outside the body's cells, given that cell membranes are permeable to water due to the constitutive presence of aquaporins (with the exception of certain epithelial cells in the distal nephron). Consequently, the accumulation of effective osmoles within either intracellular or extracellular spaces serves as a driving force, prompting water to migrate into spaces with greater tonicity, thereby achieving equilibrium in terms of concentrations [7].

The Edelman equation facilitates the comprehension of the direct influence of exchangeable sodium (Na_E), exchangeable potassium (K_E), and total body water (TBW) on plasma sodium concentration (PNa) [9]:

Edelman's equation: $PNa = (Na_E + K_{E)} / TBW$

A decrease in NaE or an increase in TBW results in a reduction of PNa, thereby underscoring the significance of these two variables in the regulation of sodium concentration. Moreover, while the effect of K_E may appear less pronounced, its correction or alteration has substantial clinical implications, including the contribution of hypokalemia to hyponatremia and the increase in PNa when corrected [7, 10].

Several hormones are involved in sodium and water homeostasis, with the principal regulators being the antidiuretic hormone (ADH), cortisol, and aldosterone, as well as the renin- angiotensin-aldosterone system. The main effector organ is the kidney, which regulates urine production and concentration in response to these stimuli [4, 10, 11].

ADH is produced in the hypothalamus as a precursor protein and stored in neurosecretory granules until a rise in serum tonicity or a reduction in effective arterial blood volume triggers its secretion into the circulation [12–15]. ADH has three types of receptors. In the kidney, it acts on V2 receptors, mediating antidiuresis by increasing the synthesis and insertion of aquaporin-2 water channels, thereby promoting greater water retention and urine concentration. Additionally, it enhances the expression of epithelial sodium channels (ENaC) and urea transporters (UT-A1), leading to increased sodium and urea reabsorption. This process increases the osmotic gradient in the renal interstitium, further concentrating the urine [15].

In acute hyponatremia, the brain may undergo edema, which increases intracranial pressure. In chronic hyponatremia, adaptive changes in brain osmolytes may protect against immediate injury; however, these adaptations increase vulnerability to rapid correction. Rapid correction of chronic hyponatremia may cause hypertonic stress in astrocytes, leading to osmotic demyelination syndrome [4, 10].

Classification

According to serum sodium concentration, hyponatremia is classified into mild (130-135 mEq/L), moderate (125-129 mEq/L), and severe (<125 mEq/L). Depending on the duration of presentation, it is further classified as acute (<48 hours) or chronic (>48 hours) [4, 16].

Based on effective arterial blood volume, hyponatremia may be classified as hypervolemic, euvolemic, or hypovolemic [17].

Hyponatremia and hyposmolality frequently, though not invariably, coexist. Hyponatremia with elevated plasma osmolality occurs when a substance that does not enter cells (e.g.,

glucose or mannitol) is added to the vascular space. Plasma osmolality may remain normal in severe hyperlipidemia or hyperproteinemia, in which a greater relative proportion of the plasma volume is occupied by lipids or proteins. Therefore, a comparison of the measured serum osmolality (SOsm) with the calculated serum tonicity (PTon) allows the identification of three possible conditions: isotonic hyponatremia (PTon $\approx$ SOsm); hypertonic hyponatremia (PTon $>$ SOsm); and hypotonic hyponatremia, otherwise known as true hyponatremia (PTon $<$ SOsm) [18].

Clinical manifestations

Hyponatremia can have significant clinical implications, especially in the central nervous system [19]. The severity of symptoms associated with hyponatremia is determined by the extent and rate of the decline in serum sodium levels. In chronic hyponatremia ($\geq$48 hours), symptoms are usually milder, as the brain has achieved complete adaptation to hypoosmolarity; conversely, in acute hyponatremia (<48 hours), more severe symptoms are present due to incomplete adaptation of the brain [2].

The symptoms of hyponatremia are not specific and may be attributable to the underlying condition causing the hyponatremia [3, 16]. Symptomatology is mainly related to the degree of cerebral edema and is divided into severe and moderate symptoms. The use of the term "asymptomatic" is avoided because even a patient with mild hyponatremia may present some symptoms such as impaired concentration. Severe symptoms include emesis, altered consciousness, seizures, cardiorespiratory arrest, cerebral edema, and death (3-5, 16-17). Seizures occur more frequently in patients with chronic hyponatremia with serum sodium <110 mEq/L and a history of seizures [20].

Moderate to mild symptoms include weakness, nausea, headache, and impaired concentration [4]. Symptoms are not always related to serum sodium levels; however, patients with severe hyponatremia are more likely to exhibit a greater number of manifestations. This was observed in a study of 298 patients with sodium <125 mEq/L, most of whom had chronic hyponatremia (96 %). These cases most commonly presented with nausea, vomiting, confusion, headache and less commonly, seizures [21]. Prolonged alterations in plasma sodium level may also have non-neurological effects, such as muscle sarcopenia, osteoporosis, cardiomyopathy, and hypogonadism [8, 22, 23].

Etiology

The spectrum of pathologies associated with hyponatremia is broad [2]. In the emergency department, hypotonic euvolemic hyponatremia accounts for 34 % of cases (with the syndro-

me of inappropriate antidiuretic hormone secretion (SIADH) as the main cause); hypotonic hypovolemic hyponatremia accounts for 24 % of cases (emesis or diarrhea: 10 %; diuretic use 14 %); hypotonic hypervolemic hyponatremia accounts for 11 % of cases; and the remaining 31 % of cases correspond to conditions such as alcohol abuse, primary polydipsia, and mixed etiologies [24].

Pragmatic approach

Because hyponatremia has many causes and symptoms, a systematic approach helps guide diagnosis. A diagnostic algorithm is proposed for the evaluation of patients with hyponatremia (see Annex 1).

The first step is to determine the effective serum tonicity using the following equation:

$$\textbf{Serum tonicity} = (2 \times [Na^{+}\ mEq/L]) + ([glucose\ mg/dL] \div 18)$$

This allows the identification of isotonic hyponatremia (280–295 mOsm/kg), hypertonic hyponatremia (>295 mOsm/kg), or hypotonic hyponatremia (true hyponatremia, <280 mOsm/kg) [4,7,11]. Once true hyponatremia has been identified, the second step is to assess the urinary osmolarity (OsmU) to determine if it is due to an ADH-dependent (urinary osmolarity >100 mOsm/kg) or ADH-independent mechanism (urinary osmolarity <100 mOsm/kg) [11]. Direct measurement of OsmU by osmometer is the method of choice; however, in resource-limited settings, this technique is not always available in clinical practice. Thus, it may be estimated using the following equation:

$$\text{Urinary osmolality} = (2 \times [\text{urine } Na^{+}\ mEq/L]) + (2 \times [\text{urine } K^{+}\ mEql/L]) + ([\text{urine urea nitrogen mg/dL}] \div 2.8) + ([\text{urine glucose mg/dL}] \div 18)$$

In instances where osmolality measurements are not available, a highly effective and straightforward approach to assess the renal response to hyponatremia involves the comparison of urinary sodium and potassium (UNa and UK) with serum sodium (PNa). The following comparison enables the determination of whether the patient is eliminating excess water. Specifically, if UNa + UK > PNa, the subject is reabsorbing water. Conversely, if UNa + UK < PNa, the subject is expelling water [18]. Urine density (UD) can also be used as an indirect method for estimating OsmU [25]. In clean urine samples, the OsmU value can be accurately approximated by multiplying the last two digits of the UD by 35 and by 32 in samples with proteinuria and/or glycosuria [26].

The third step is the estimation of extracellular fluid volume status, which is challenging because physical examination has low sensitivity and can lead to misdiagnosis. In recent years,

however, the multiparametric congestion assessment approach has gained relevance [27]. This approach integrates the use of serum biomarkers, such as N-terminal brain natriuretic peptide (NT-proBNP), produced by myocardiocytes in response to volume and/or pressure overload, and carbohydrate antigen 125 (CA-125), produced in serosae (such as the peritoneum or pleura) in response to increased hydrostatic tissue pressures [28]. Point-of-care ultrasound (POCUS), using the VExUS (venous excess ultrasound) protocol and the estimation of cardiac output from systolic volume, improves the performance of intravascular volume assessment. Tissue congestion can be determined using the LUS (lung ultrasound) protocol and the study of pleural effusion or ascites. The POCUS findings based on intravascular volume status are shown in table 1 [29].

In the setting of hypervolemic hypotonic hyponatremia (e.g., advanced heart failure or decompensated cirrhosis), hypoperfusion with a reduced effective circulating volume leads to non-osmotic arginine vasopressin (AVP) release; consequently, water retention provokes non-osmotic vasopressin release and hyponatremia, generating "sodium-avid kidneys", thus UNa will be <30 mEq/L. In contrast, a normal or increased effective arterial blood volume inactivates the renin-angiotensin-aldosterone system, resulting in UNa >30 mEq/L. In cases of hypovolemic hyponatremia, elevated urine sodium levels may be indicative of renal losses, which can be attributed to various factors such as diuretic use, salt wasting, or adrenal insufficiency. Conversely, decreased urine sodium levels may suggest extrarenal losses, which can be attributed to conditions such as gastroenteritis [7, 11].

Table 1. Classification of intravascular volume status according to POCUS findings

Volemia status	Ultrasound findings
Hypovolemia	- Inferior vena cava (IVC): Reduced diameter, collapsibility >50 %.
	- Low systolic volume: Decrease in LV outflow tract size and velocity-time integral (VTI).
	- Small cardiac chambers.
	- Pulmonary pattern: A lines (absence of B lines).
Hypervolemia	- Dilated IVC: Increased diameter, collapsibility <50 %.
	- Venous congestion: Pathological VExUS score (hepatic veins with pulsatile flow and diastolic reversal).
	- Presence of pleural effusion or ascites.
	- Pulmonary pattern: B lines or “pleural comets” (interstitial edema).
	- LV dysfunction: there may be systolic or diastolic dysfunction if the etiology is heart failure.

Source: Based on [28, 29].

Clinical cases

We present clinical cases of patients with true hyponatremia in whom a systemic approach allowed the identification of the etiological diagnosis. We propose common questions, each with different answers, and briefly review each scenario.

Case 1

A 47-year-old female patient with a medical history of stage 5 chronic kidney disease, presumably secondary to hypertension, had been receiving renal replacement therapy for 14 years. She received a renal transplant from a cadaveric donor 3 years ago. The graft functioned immediately, with a post-transplant creatinine of 0.6 mg/dL. Her maintenance immunosuppression regimen includes mycophenolate sodium 720 mg BID and standard tacrolimus 2 mg BID, without steroids. She is on prophylaxis with valganciclovir and trimethoprim–sulfamethoxazole (TMP-SMX).

The patient was admitted to the emergency department (ED) with a clinical picture of soft stools, devoid of mucus or blood, occurring three to five times per day. She exhibited asthenia, adynamia, hyporexia, and headache; the patient also presented with sudden loss of consciousness, devoid of abnormal movements. The patient exhibited no symptoms of chest pain or dyspnea, and a renal graft in the right iliac fossa without pain or increase in volume. The rest of the physical examination was described as normal. Simple cranial CT scan without lesions.

On admission, laboratories revealed severe hyponatremia, with sodium of 122.9 mmol/L (corrected to 124.6 mmol/L, seric glucose 206 mg/dL). The findings in the laboratory tests are summarized in table 2.

Table 2. Classification of intravascular volume status according to POCUS findings

	Day 1	Day 2	Day 3	Day 5	Day 6	Day 7
Sodium (mmol/L)	122.9		135		131.8	133
Potassium (mmol/L)	5.0		4.4	4.6	4.7	4.5
Chloride (mmol/L)	88.8		109	107	99.6	107
Magnessium (mg/dL)		1.4		1.54		2.0
Phosphate (mg/dL)		2.7				
Creatinine (mg/dL)	1.38	1.48	1.26	1.3	1.23.	1.15
Glucose (mg/dL)	206					
Uric acid (mg/dL)	2.5				3.0	

Table 2. Classification of intravascular volume status according to POCUS findings

	Day 1	Day 2	Day 3	Day 5	Day 6	Day 7
Urine osmolality (mOsm/kg)	320					
Urinary sodium (mmol/L)			82			
Urinary potassium (mmol/L)			38			

Source: Authors.

What diagnostic workup should be performed?

Serum tonicity of less than 280 mOsm/kg and a urinary osmolarity of 320 mOsm/kg were documented, which placed the patient within the diagnostic algorithm for ADH-dependent hypotonic hyponatremia. A hypovolemic origin associated with volume depletion due to diarrhea was initially considered, and rehydration with 0.9 % saline solution was initiated, resulting in a transient increase in serum sodium, followed by recurrence of hyponatremia despite diarrhea resolution. Urine samples were subsequently collected, revealing a urinary sodium concentration of 82 mmol/L. In the absence of diuretic use and with normal volume status, this prompted a shift in the diagnostic approach toward euvolemic hyponatremia. A TSH value of 3.98 μIU/mL, and a serum cortisol level measured before 8:00 a.m. of 20.2 μg/dL ruled out severe hypothyroidism and supported intact hypothalamic-pituitary-adrenal axis function [30].

What is the cause of hyponatremia in this patient?

In population-based studies, SIADH is the most common cause of hyponatremia, accounting for 35 %-45 % of cases [12, 13]. The causes are attributed to malignancy (18 %-48 %), medications (4 %-17.8 %), postoperative conditions (10 %), pulmonary disease (10.7 %-19 %), central nervous system (CNS) pathology (8.5 %-26 %), and other idiopathic causes (14.1 %-35.2 %). However, the prevalences vary widely across different studies [13].

SIADH was initially described by Schwartz and Bartter in 1967, who established diagnostic criteria that remain valid (table 3) [31]. These criteria can be used to appropriately diagnose most patients with stage 1-3 renal disease, as demonstrated in this case [13]. Additionally, other findings supporting the diagnosis have been described, such as serum uric acid levels $<$4 mg/dL during the period of hyponatremia induced by SIADH [32].

Table 3. Diagnostic criteria for SIADH by Schwartz and Bartter (1967)

• Low serum osmolality (<275 mOsmol/kg H_2O).
• Elevated urinary osmolality (>100 mOsmol/kg H_2O, inappropriately concentrated).
• Clinical euvolemia (absence of signs of hypovolemia or hypervolemia).
• Elevated urinary sodium excretion (>30 mEq/L with normal intake of salt and water).
• Absence of other potential causes of euvolemic hypoosmolality (glucocorticoid insufficiency, hypothyroidism).
• Normal renal function and absence of diuretic use.

Source: Based on [31].

Furthermore, patients with SIADH may develop worsening hyponatremia with intravenous normal saline due to a "desalination" effect. With a fixed urinary osmolarity, for instance, 180 mEq/L, infusion of 1 liter of 0.9 % saline (154 mEq/L) results in only about 800 mL being excreted to maintain osmotic balance, while the remaining 200 mL is retained, exacerbating hyponatremia [33]. Finally, measuring plasma vasopressin and copeptin levels has been proposed; however, previous studies have shown limited utility in the differential diagnosis of hyponatremia, except in cases of primary polydipsia [7, 21, 34]. The main causes of SIADH include malignancies (particularly lung, CNS, and GI tumors); CNS disorders (e.g., trauma, stroke, infection, inflammation); medications (e.g., selective serotonin reuptake inhibitors (SSRIs), chemotherapy, antiepileptics); pulmonary diseases (e.g., pneumonia, chronic obstructive pulmonary disease (COPD), and mechanical ventilation); and other triggers such as pain, nausea, surgery, or idiopathic cases [12]. These should be systematically evaluated when the etiology is unclear.

In the presented case, a chest CT was performed, which showed a miliary distribution pattern and cylindrical bronchiectasis, leading to suspicion of tuberculosis, which was confirmed by identification on bronchoalveolar lavage samples.

What is the pathophysiology of hyponatremia in this case?

SIADH results from excessive ADH activity relative to osmotic requirements [7]. Additionally, to counteract the expansion of extracellular fluid volume, aldosterone suppression occurs alongside increased levels of atrial natriuretic peptide, leading to urinary sodium loss, a phenomenon referred to as "pressure natriuresis". Excessive ADH activity may arise from non-osmotic release of pituitary ADH, unregulated ectopic production of ADH from a non-pituitary source (paraneoplastic), or abnormal renal sensitivity to ADH in the rare case of nephrogenic SIADH [15].

What is the treatment?

Treating the underlying cause may suffice; however, chronic or non-reversible SIADH requires specific interventions [12]. The first-line treatment involves restricting fluid intake to less than 1000 mL per day. Alternatively, the Fürst Equation ((UNa + UK)/pNa) can be used to determine the restriction level: if the ratio is less than 0.5, fluid intake is restricted to 1000 mL/ day; if it is between 0.5 and 1, intake is limited to 500 mL/day; and if the ratio exceeds 1, it predicts a lack of response to fluid restriction [35]. A urinary osmolality >500 mOsm/L or a urinary volume <1500 mL/day also predict a poor response to fluid restriction [13].

For second-line treatment, tolvaptan has demonstrated short-term efficacy in increasing serum sodium levels [36]. Another therapeutic option is the administration of urea, which has comparable effects to fluid restriction [13]. Salt tablets have limited evidence and are reserved for scenarios where other second-line therapies are unavailable [13, 37]. Finally, in recent years, two clinical trials have been conducted with SGLT2 inhibitors, yielding promising and safe results [38, 39].

Final diagnosis: The patient presented with euvolemic hypotonic hyponatremia associated with SIADH related to pulmonary tuberculosis.

Case 2

An 84-year-old female with a history of hypertension and prediabetes, receiving treatment with losartan, metformin, amlodipine, and atorvastatin, without chronic use of diuretics, was admitted after experiencing several days of unspecified clinical symptoms, including dizziness. She experienced syncope with craniofacial trauma. On physical examination, vital signs were stable, with left periorbital ecchymosis but no neurological deficits; the remainder of the examination was described as normal. A simple cranial CT scan was performed, revealing no lesions. Severe hyponatremia was noted on admission, with a sodium level of 111 mEq/L. Laboratory findings are summarized in table 4.

Table 4. Laboratory findings

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Sodium (mmol/L)	111	115	118	124	129	135
Potassium (mmol/L)		4.1				4.2
Chlorum (mmol/L)	84	86				104
Creatinine (mg/dL)	0.4			0.5		
Urinary sodium (mEq/L)				66.9		

Table 4. Laboratory findings

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Urinary potassium (mEq/L)				10.6		
TSH (mUI/L)	2.4					
Cortisol (ng/dL)					18	
Uric Acid (mg/dL)					2	

Source: Authors.

What diagnostic workup should be performed?

Serum tonicity was <280 mOsm/kg, so hypotonic hyponatremia was considered, with ADH-dependent mechanism by urine osmolarity of 175 mOsm/kg; TSH was normal, and there was no hypoglycemia or hypotension. POCUS revealed signs of intravascular volume depletion. Sodium in an isolated urine sample greater than 30 mEq/L and associated with hypouricemia suggests the possibility of SIADH; however, it is, by definition, an euvolemic condition. Additionally, this patient had hypochloremia and an adequate response to medical management with SSN 0.9 %. This is not expected in SIADH, a condition characterized by a fixed osmolar excretion that for this patient was 77.5 mEq/L and would worsen with the administration of an iso-osmolar solution.

What is the cause of hyponatremia in this patient?

Cerebral salt-wasting syndrome (CSW) was included in the differential diagnosis. Pharmacological origin was ruled out, since the patient was not receiving diuretics, osmotic agents, intravenous contrast media, or another possible causal agent [40].After documentation of a normal 8:00 am cortisol level, a contrasted brain MRI was performed, confirming subarachnoid hemorrhage.

What is the pathophysiology of hyponatremia in this case?

The differential diagnosis between CSW and SIADH can be challenging due to the similarity of their clinical manifestations. CSW is characterized by renal sodium loss leading to hypovolemia and hyponatremia (figure 1). At this point, two issues must be considered: the mechanisms of salt wasting and hyponatremia. Cerebral disease may cause salt wasting through disruption of neural input to the kidneys or the release of a central natriuretic factor:

- The sympathetic nervous system promotes sodium, uric acid, and water reabsorption in the proximal tubule, as well as renin release. Thus, impaired sympathetic neural input

could explain the reductions in proximal sodium and urate reabsorption, as well as the impaired release of renin and aldosterone. The failure of serum aldosterone to rise in response to volume depletion would explain the absence of potassium wasting despite increased distal sodium delivery [41].

- Brain natriuretic peptide (BNP) is released in patients with brain injury [42]. It impairs renal tubular sodium reabsorption and inhibits renin release [43]. BNP may also reduce autonomic outflow via effects at the level of the brainstem [44].

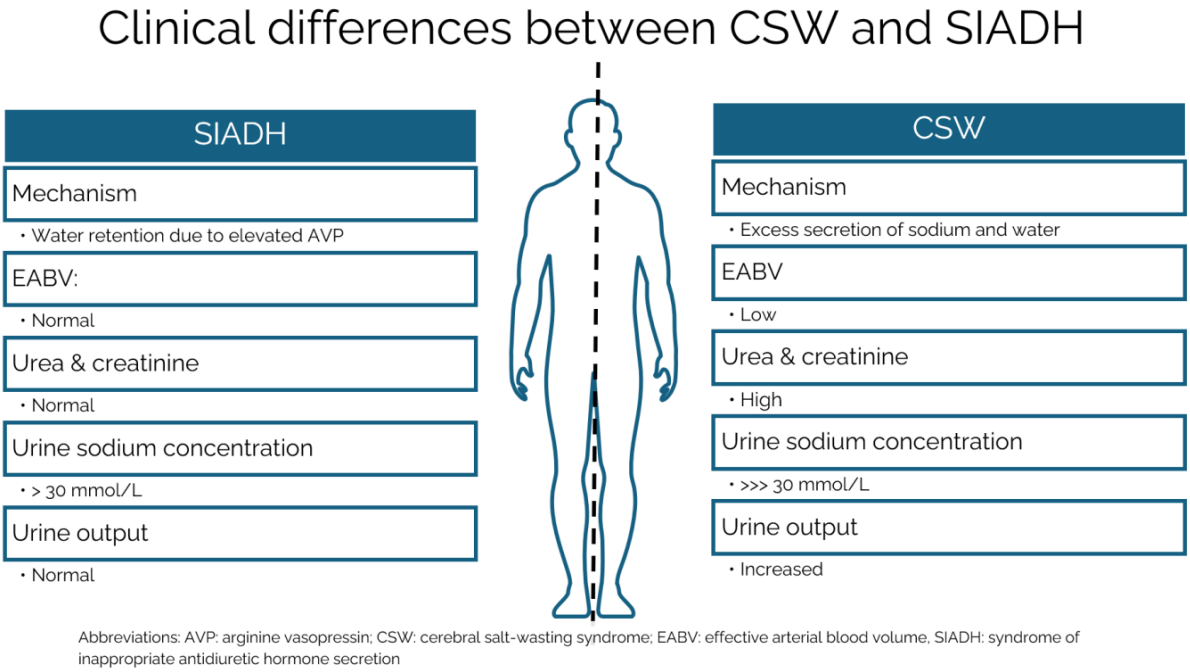

Figura 1. Differences between CSW and SIADH

Source: Authors, based on references [40–42, 44].

What is the pathophysiology of hyponatremia in this case?

Treatment includes water replenishment and dietary sodium chloride supplementation [45]. Some authors have reported the use of fludrocortisone [46]. In this case, the patient received water and sodium chloride supplementation, showed clinical improvement, and was discharged with normal serum sodium levels.

Final diagnosis: Hypotonic hypovolemic hyponatremia secondary to CSW.

Case 3

A 54-year-old man presented with a 3-week history of persistent vomiting, adynamia, altered mental status, and progressive lower limb weakness with impaired gait. He was hypotensive and somnolent, with dry mucous membranes, hyporeflexia, and generalized weakness, without focal or meningeal signs. Intravenous hydration was initiated. Initial tests revealed moderate hyponatremia and elevated azotemia. Lumbar puncture showed albuminocytologic dissociation, supporting a diagnosis of Guillain-Barré syndrome (GBS) in the clinical context. Therapeutic plasma exchange was initiated. Laboratory results are summarized in table 5.

Table 5. Laboratory findings

	Day 1	Day 2	Day 3	After starting hormone therapy	Day 2
Sodium (mEq/L)	126	126	126	130	136
Potassium (mEq/L)	3.7				3.8
Chlorum (mEq/L)	98	104			108
Creatinine (mg/dL)	1.8	1.4	1.3		1.0
Glucose (mg/dL)	86				
Urine osmolarity (Osm/kg)	350				
Urinary sodium (mEq/L)			40		
Glucose (mg/dL)	5				

Source: Authors.

The patient showed improved consciousness and hydration but remained borderline hypotensive and developed renal dysfunction. Hyponatremia persisted despite adequate hydration and absence of other electrolyte losses, raising suspicion of SIADH. Fluid restriction was initiated but failed to correct sodium levels, prompting nephrology consultation.

What diagnostic workup should be performed?

Serum osmolality was 257 mOsm/kg, and urine osmolality was 350 mOsm/kg. Despite initial dehydration, hyponatremia persisted after adequate hydration, with urine sodium at 40 mEq/L. These findings were consistent with ADH-dependent hyponatremia, classified as moderate. SIADH was initially suspected, as it is frequently linked to neurologic disorders, such as Guillain-Barré syndrome, in up to 26 % of cases [12, 47]. However, hypothyroidism and adrenal insufficiency must always be ruled out. In this case, serum cortisol at 8:00 a.m. was markedly decreased (1.5 μg/dL).

What is the cause of hyponatremia in this patient?

Given that two pituitary axes appear to be affected, a brain MRI was performed, revealing an infiltrative process in the pituitary gland. Assessment of the hypothalamic-pituitary axis was completed and revealed an ACTH level of 6.8 pg/mL (normal range 10-60 pg/mL). There was no evidence of involvement of the gonadal, prolactin, or growth hormone axes. A serum cortisol level at 8:00 a.m. of <3.0 μg/dL, along with a low or low-normal ACTH level, is suggestive of secondary adrenal insufficiency (SAI) [48].

SAI results from dysfunction of the hypothalamic-pituitary axis, impairing cortisol production [49]. Its prevalence ranges from 150 to 280 cases per million, and common causes include hypothalamic or pituitary tumors, infiltrative diseases, and cranial irradiation [48, 50, 51].

Diagnostic tools to confirm SAI vary among different centers due to the lack of a gold standard for diagnosis. Evaluating the hypothalamic-pituitary-adrenal (HPA) axis response is essential and can be done using various methods. The ACTH1-24 stimulation test (short Synacthen test) is the most widely used due to its safety and simplicity. It involves administering 250 μg of synthetic ACTH and measuring serum cortisol at 30 and/or 60 minutes; values <16.35 μg/dL or <18.15 μg/dL, respectively, confirm the diagnosis [48]. In this patient, a serum cortisol level of 10 μg/dL at 60 minutes confirmed adrenal insufficiency.

What is the pathophysiology of hyponatremia?

Cortisol inhibits ADH secretion; its deficiency leads to increased hypothalamic secretion of corticotropin-releasing hormone (CRH), which in turn stimulates ADH release [7, 52]. The loss of cortisol's direct inhibitory effect on ADH, along with reduced vascular responsiveness to catecholamines, promotes vasodilation and decreases effective arterial blood volume, further enhancing ADH secretion [7, 12, 53, 54].

In animal models, glucocorticoid deficiency results in elevated AVP levels and increased aquaporin-2 expression after water loading, whereas animals with normal adrenal function do not exhibit these changes [12, 55]. This mechanism contributes to hyponatremia, observed in up to 85-90 % of cases, and manifests with biochemical characteristics almost identical to those of SIADH, although responsive to hormone replacement [7, 12, 54]. Symptomatology will depend on the associated hormonal deficits [56, 57]. Stressors such as infections, hypoglycemia, nausea, vomiting, or neurologic conditions may trigger ADH release and worsen hyponatremia in these patients [12, 53].

What is the treatment?

In this case, treatment with hydrocortisone and levothyroxine was initiated. In the absence of adrenal crisis, the hydrocortisone dose is 15–25 mg/day, divided into 2–3 doses to mimic the circadian cortisol rhythm. The dose should be adjusted based on symptoms and clinical response [4, 48]. Although rare, osmotic demyelination has been reported following steroid initiation, underscoring the need for close monitoring during treatment [12, 52]. With hormone supplementation, both the initial symptoms and hyponatremia resolved completely. The patient was discharged with multidisciplinary outpatient follow-up.

Final diagnosis: Hypotonic euvolemic hyponatremia secondary to hypopituitarism (secondary adrenal insufficiency and hypothyroidism) caused by an infiltrative pituitary pathology.

Case 4

A 69-year-old man with a history of hypertension, type 2 diabetes mellitus, and prior myocardial revascularization presented with progressive dyspnea and reduced urine output. On examination, he had a blood pressure of 105/60 mmHg, heart rate of 90 bpm, respiratory rate of 24 breaths/min, temperature of 36 °C, and oxygen saturation of 92 % on 2 L/min via nasal cannula. Additional findings included lower limb edema, jugular venous distension, and basal rales. Ultrasound confirmed signs of intravascular congestion (figure 2). Admission tests revealed severe hyponatremia (119 mEq/L) and impaired renal function.

He was transferred to intensive care for further management. A central venous catheter was placed, and venous and arterial gases confirmed a central venous oxygen saturation of 57 % and a V-A CO_2 difference of 12 mmHg, with a serum hemoglobin of 11.3 g/dL. Inotropic support with levosimendan was initiated, and a loading dose of furosemide (1.0 mg/kg) was administered. Two hours later, diuresis reached 270 mL, and maintenance therapy with IV furosemide was started.

Thereafter, 24-hour diuresis increased to 3.6 L, urinary sodium rose to 120 mEq/L, and both clinical and ultrasound markers of congestion improved. Serum sodium levels normalized by day 5, and the patient was transferred to the general ward for ongoing heart failure management. Laboratory results are summarized in table 6.

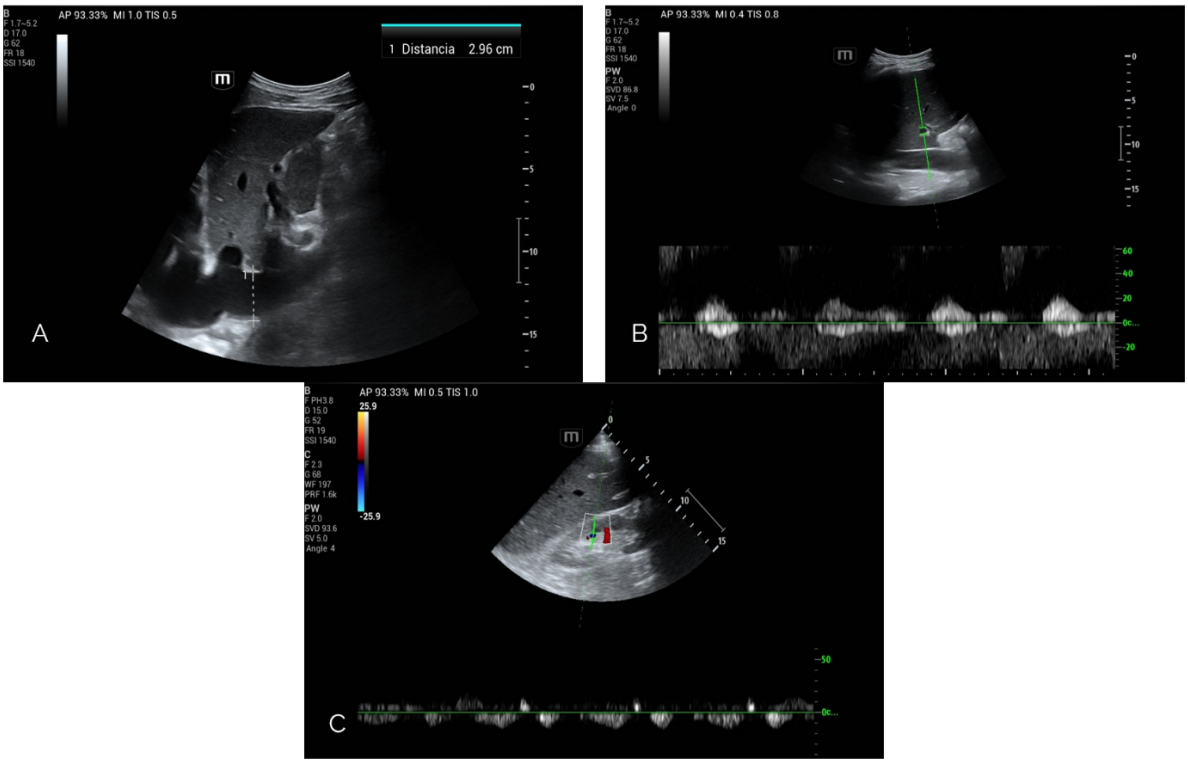

Figura 2. Point of care ultrasound findings

Note. Panel A: Subcostal view showing a dilated IVC with increased diameter; Panel B: Portal vein with pulsatile flow (hepatic expiratory flow reversal); Panel C: Doppler intrarenal vein.
Source: Authors' own clinical images.

Table 6. Laboratory findings

	Day 1	Day 2	Day 3	Day 4	Day 5
Sodium (mEq/L)	119	122	128	131	136
Potassium (mEq/L)	5.2			4.5	4.2
Chlorum (mEq/L)	96				
Creatinine (mg/dL)	1.5	2.0	2.7		1.8
Blood ureic nitrogen (BUN) (mg/dL)	36	40	44		36
Urine osmolarity (mOsm/kg)	525				
Urinanry sodium (mEq/L)	12	30	85	94	133
Serum glucose (mg/dL)	94				
Albumin (g/dL)	3.7				

Source: Authors.

What diagnostic workup should be performed?

The serum tonicity was 243 mOsm/kg, consistent with hypotonic hyponatremia, with an ADH-dependent mechanism by urine osmolarity of 525 mOsm/kg. In this instance, the clinical signs of tissue congestion were evident. POCUS revealed signs of intravascular congestion (figure 2). In the absence of prior diuretic use, a urinary sodium level of less than 30 mEq/L is indicative of extrarenal sodium loss. In such cases, conditions such as cirrhosis, heart failure, and nephrotic syndrome should be ruled out.

What is the cause of hyponatremia?

No clinical, laboratory, or imaging findings were indicative of liver disease. Urine sediment was negative for proteinuria and hematuria, while pro-BNP was markedly elevated (6229 pg/mL). Transthoracic echocardiography revealed a left ventricular ejection fraction of 28 %, and a progressive rise in azotemia was noted. These findings supported a diagnosis of hypotonic hypervolemic hyponatremia secondary to acute decompensated heart failure (HF), consistent with a Stevenson B hemodynamic profile and cardio-veno-renal syndrome. Management included intravenous furosemide and restriction of water and sodium intake.

What is the pathophysiology of hyponatremia?

Hypotonic hyponatremia in HF is mainly due to a state of water overload, with water retention, leading to dilutional hyponatremia [19]. Reduced cardiac output decreases effective arterial volume, triggering non-osmotic ADH release, which promotes water reabsorption and dilutional hyponatremia [58].

Additionally, there is an activation of the renin-angiotensin-aldosterone axis, which, among its effects, leads to increased renal sodium avidity (UNa <30 mEq/L); in the distal nephron, neurohumoral activation impairs free water excretion [4]. ADH further enhances water retention by increasing collecting duct permeability [58]. Moreover, reduced glomerular filtration and impaired proximal sodium reabsorption decrease tubular flow, further limiting water excretion. Heightened sympathetic tone shifts splanchnic blood into the systemic circulation, exacerbating venous congestion and dilutional hyponatremia [58].

What is the treatment?

Treatment of fluid overload in patients with acute decompensated HF is based on loop diuretics. Initial furosemide dosing depends on prior use: 40 mg IV if diuretic-naïve or 1–2 times the home dose if previously treated. In acute congestion, gut edema and reduced perfusion may impair absorption, making IV administration the preferred route [59].

If loop diuretics are insufficient, sequential nephron blockade is recommended. Adding thiazides or MRAs (mineralocorticoid receptor antagonists) can enhance natriuresis, although they should be used cautiously in patients with stage 3b or higher chronic kidney disease (CKD) [59]. Acetazolamide, when added to other diuretics, provides potent diuresis and may promote renal vasodilation via increased sodium delivery to the macula densa—a mechanism similar to SGLT2 inhibitors, potentially offering nephroprotection [27].The use of hypertonic saline in combination with furosemide is an alternative option in cases of diuretic resistance [60].

Other strategies used in acute congestion (such as vasopressin receptor 2 antagonists [vaptans], neprilysin inhibitors, intravenous albumin, inotropic agents, and extracorporeal ultrafiltration) are beyond the scope of this review.

With decongestive therapy and optimized management of heart failure, the initial symptoms and hyponatremia were completely resolved. The patient was discharged with outpatient multidisciplinary follow-up.

Final diagnosis: Hypotonic hypervolemia hyponatremia secondary to acute decompensated heart failure, classified as a Stevenson B hemodynamic pattern, associated with cardio-veno-renal syndrome.

Case 5

A 22-year-old man with no significant medical history was brought to the emergency department after experiencing a generalized tonic-clonic seizure at an electronic music event. According to his peers, he consumed .ecstasy"(MDMA; 3,4-methylenedioxymethamphetamine) along with large volumes of water. On examination, vital signs were stable; there were no signs of dehydration. His Glasgow Coma Scale score was 13/15, and he exhibited hyperreflexia without other neurological deficits. Laboratory results are summarized in table 7.

Table 7. Laboratory findings

	Day 1	Day 2	Day 3
Sodium (mmol/L)	118	126	131
Potassium (mmol/L)	3.6	3.7	3.8
Chlorum (mmol/L)	92	92	98
Glucose (mg/dL)	92		
Creatinine (mg/dL)	0.7		

Table 7. Laboratory findings

	Day 1	Day 2	Day 3
Urinary sodium (mEq/L)	62		32
Urinary potassium (mEq/L)	28		
TSH (mIU/L)	1.4		
Cortisol (ng/dL)	24		
Urine osmolarity (mOsm/kg)	521		
Urine toxicology	MDMA +		

Source: Authors.

What diagnostic workup should be performed?

Hypotonic hyponatremia was identified, with serum osmolality of 244 mOsm/kg and a urine osmolality of 521 mOsm/kg, indicating an ADH-dependent mechanism. The absence of clinical signs of hypovolemia or hypervolemia suggested an euvolemic state. An endocrinologic evaluation excluded hypothyroidism and adrenal insufficiency, thereby supporting a diagnosis of SIADH [11]. Given the clinical context and history of recent MDMA use, drug-induced SIADH was considered the most likely etiology.

What is the pathophysiology of hyponatremia in this case?

The mechanisms underlying MDMA-induced hyponatremia remain theoretical. It is believed that MDMA, due to its serotonergic structure, stimulates vasopressin release, triggering SIADH and increased thirst, which promotes polydipsia. However, recent studies have reported elevated oxytocin—but not copeptin—levels, suggesting oxytocin may exert vasopressin-like renal effects via structural homology. Hyperthermia and excessive water intake further contribute to hyponatremia development [61].

What is the treatment?

This is a case of acute severe symptomatic hyponatremia, for which immediate administration of hypertonic saline (3 %) was indicated. The patient received an initial 100 mL bolus over 10 minutes, which was repeated due to persistent neurological symptoms. Asubsequent rise in serum sodium of 5 mEq/L was observed, aligning with the recommended correction target of 4–6 mEq/L in the first 6 hours. Additionally, the Fürst index was <0.5, supporting the indication for free water restriction. As an alternative, urea therapy was considered a safe and effective option for managing drug-induced SIADH [11, 61].

The patient showed progressive neurological improvement and normalization of sodium levels. In cases of acute hyponatremia, such as this one, rapid correction with hypertonic saline is generally safe and necessary, as the brain has not yet undergone osmotic adaptation. Unlike chronic hyponatremia—where rapid correction increases the risk of osmotic demyelination—acute presentations (<48 hours) carry a higher risk of cerebral edema and neurological deterioration if not promptly treated. Thus, aggressive correction in symptomatic acute hyponatremia is both appropriate and potentially life-saving [7].

Final diagnosis: Drug-induced SIADH.

Conclusion

Hyponatremia is the most common electrolyte disorder in clinical practice and is associated with increased morbidity, mortality, and healthcare burden. As a syndromic diagnosis, it requires thorough evaluation of underlying causes and individualized management. Initial assessment should focus on clinical severity, plasma osmolality, and volume status, guided by clinical history, urinary sodium levels, and tools such as point-of-care ultrasound.

Importantly, hyponatremia reflects a pathophysiological disturbance—primarily of water balance—rather than an isolated laboratory abnormality. Its etiology often involves dysregulation of hormonal pathways governing water and sodium homeostasis. A structured, algorithmic approach improves diagnostic accuracy, facilitates identification of causes such as SIADH, cerebral salt wasting (CSW), or heart failure, and reduces the risk of inappropriate therapy.

Clinical vigilance is critical, especially in acute or symptomatic cases, where timely and appropriate intervention can improve outcomes. Careful correction is essential to avoid complications such as osmotic demyelination syndrome, underscoring the importance of gradual and closely monitored sodium normalization.

Author's contribution

Machado-Gómez: Study concept and design, acquisition, analysis, and interpretation of data, manuscript's drafting, and English translation; Guzmán-Bedoya: Study concept and design, acquisition, analysis, and interpretation of data, manuscript's drafting, and English translation; Sánchez-Ríos: Study concept and design, acquisition, analysis, and interpretation of data, and manuscript's drafting. English translation; Bernal-Barbosa: Study concept and design, acquisi-

tion, analysis, and interpretation of data, critical manuscript revision for important intellectual content, study supervision.

Ethical

This report was written following Helsinki's declaration. For this type of case report, ethical approval is not required.

Conflict of interest

None of the authors declare conflicts of interest.

Financial statement

None.

Consent for publication

Informed written permission was obtained from the patient.

Use of artificial intelligence (AI)

The authors declare that they did not use artificial intelligence in the preparation or writing of this article.

Data statement

All data and materials relevant to the presentation of this case are included in this manuscript.

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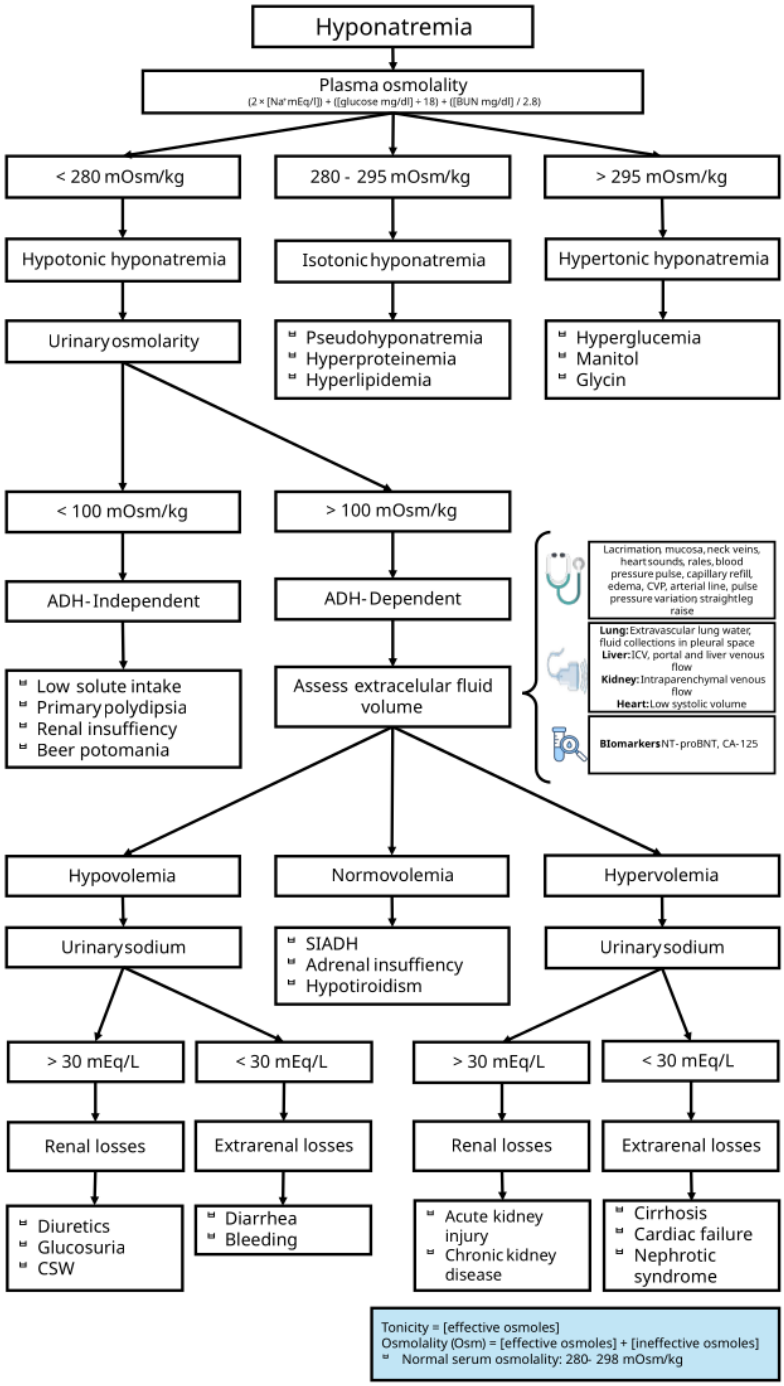
Annex 1. Diagnostic approach to hyponatremia



ADH: antidiuretic hormone (arginine vasopressin); CA 125: carbohydrate antigen 125; CPV: central venous pressure; CSW: cerebral salt-wasting syndrome; EABV: effective arterial blood volume; IVC: inferior vena cava; NT-proBNP: N-terminal brain natriuretic peptide; RAAS: renin-angiotensin-aldosterone system; SIADH: syndrome of inappropriate antidiuretic hormone.

Source: Based on [4, 7, 18, 26–29].