

# Approach to Hyponatremia in the ICU: A Review Article

Alwatheq Alitelat, MD<sup>1</sup>; Awwab F. Hammad, MS<sup>2</sup>; Hebah Abuhayyeh, MS<sup>2</sup>,  
Tala Dabbah, MS<sup>2</sup>; Mohammad Abdeljawad<sup>3</sup>, MD ; Mazen O. Al-Qadi, MD<sup>4</sup>

**KEYWORDS** - Hyponatremia, Osmolarity, SIADH, Osmotic demyelination syndrome, Vaptans

## INTRODUCTION

Hyponatremia, defined as a serum sodium level below 135 mEq/L, is one of the most common electrolyte imbalances encountered in clinical practice [1]. The estimated prevalence of hyponatremia at initial presentation is 22% in acute hospital care, meanwhile, the prevalence of hyponatremia in the ICU is estimated to be between 21% and 30% [2-4]. Furthermore, the coexistence of hyponatremia with several disease states such as heart failure (17% of outpatients) and cirrhosis (49.4% of patients) has been documented [5,6]. Increasing age has also been proven as an independent strong risk factor for developing hyponatremia [2]. The exact incidence and prevalence of hyponatremia varies according to multiple factors such as the definition of hyponatremia, the frequency of testing, the healthcare setting, and the nature of the patient population [7].

Hyponatremia is clinically significant because it increases inpatient morbidity and mortality, especially in the intensive care unit (ICU). It has been reported as an independent risk factor for a poor prognosis [8]. Furthermore, severe hyponatremia (serum Na<125 mmol/L) has been shown to double the risk of in-hospital mortality (RR 2.10; P <0.001) [9].

In addition to its impact on patient health outcomes, hyponatremia significantly raises the economic burden by increasing hospital costs in general, as well as ICU admission rates and length of stay [10-13].

<sup>1</sup> Intern Doctor, Al-Nadeem Governmental Hospital, Madaba, Jordan

<sup>2</sup> Medical Student, School of Medicine, The University of Jordan, Amman, Jordan

<sup>3</sup> Intensive Care Unit, School of Medicine, The University of Jordan, Amman, Jordan

<sup>4</sup> University of North Carolina at Chapel Hill; Marsico Lung Institute, University of North Carolina at Chapel Hill; Department of Medicine, University of North Carolina at Chapel Hill

Financial support/ funding source: None-  
Conflict of interest: No conflict of interest.

Corresponding Author:  
Mazen O. Al-Qadi, MD  
Division of Pulmonary and Critical Care  
Medicine and Pulmonary Hypertension  
Program, Department of Medicine,  
University of North Carolina at Chapel Hill,  
North Carolina, Chapel Hill USA

E-mail: alqadim@upmc.edu

## PATHOPHYSIOLOGY

Hyponatremia is characterized by excessive free water relative to total sodium content. Serum sodium is a major determinant of serum osmolarity, as shown in the serum osmolarity equation:

$$\text{Osmolarity} = 2(\text{Na}) + \text{glucose}/18 + \text{BUN}/2.8$$

Because urea moves freely across the cell membrane, it does not affect water movement between compartments and, therefore, is not a part of serum tonicity:  $\text{tonicity} = 2(\text{Na}) + \text{glucose}/18$ .

Serum osmolarity is maintained in the range of 275 - 295 mOsm/kg; thirst is stimulated to increase water intake if serum osmolarity reaches 295 mOsm/kg. Serum sodium is tightly regulated by the thirst response, antidiuretic hormone (ADH), and the kidneys. The normal physiologic response to hyponatremia is to enhance renal water excretion (i.e., to dilute the urine). This results in low urine osmolarity (<100 mOsm/L) and the correction of hyponatremia. Renal water excretion, however, depends on three major factors: normal kidney function, the absence of antidiuretic hormone (ADH), and normal thyroid and adrenal functions. In patients with hyponatremia, in the absence of renal insufficiency or endocrinopathy (i.e., hypothyroidism or adrenal insufficiency), the presence of diluted urine (U. Osm < 100 mOsm/L) signifies the absence of ADH; this can be seen in low solutes intake or excessive water intake.

Concentrated urine (U. Osm > 100 mOsm/L) in patients with hyponatremia indicates elevated ADH. Importantly, elevated ADH is 'appropriate' in the presence of reduced effective arterial blood volume (EABV), such as hypovolemia, congestive heart failure, or cirrhosis. Pain, medications, stress, hypoxia, and malignancy can result in an 'inappropriate' elevation of ADH (i.e., SIADH). Furthermore, nausea generally causes inappropriate ADH secretion, while vomiting causes volume depletion and appropriate ADH secretion. Urine volume is reduced in SIADH, and hyponatremia only develops when water intake exceeds the urine electrolytes free water clearance. This can be due to abnormal thirst response in SIADH.

Urine sodium can be used to differentiate appropriately elevated ADH secondary to low EABV (U. Na <20 mOsm/L) from inappropriately elevated ADH (U. Na >30 mOsm/L). However, it will not always differentiate between the two states if there is ongoing salt wasting.

## CLINICAL MANIFESTATIONS OF HYPONATREMIA

Hyponatremia can be classified according to severity into mild (Na 130-135 mEq/L), moderate (Na 125-129 mEq/L), and severe (Na <125 mEq/L). It may also be acute in onset (<48 hours) or chronic (>48 hours) [14]. Hyponatremia can manifest in various ways, and it is crucial to distinguish between the signs and symptoms of acute and chronic clinical presentations. Acute hyponatremia is characterized by the onset of symptoms with sodium levels dropping to 125 mmol/l or less within 48 hours. Typically, patients with a history of excessive thirst or access to electrolyte-free water sources, such as hypotonic IV solutions, may exhibit symptoms of low serum sodium levels. However, accurately diagnosing this condition can be difficult due to the patient's nonspecific symptoms and lack of baseline readings [19]. This can make it challenging to distinguish between acute and chronic forms of the condition.

The symptoms of hyponatremia include nausea, vomiting, cognitive impairment, confusion, seizures, noncardiogenic pulmonary edema, coma, and death. The severity of the symptoms depends on the level of sodium in the blood [19]. Both chronic and acute forms of hyponatremia can impact the brain [14]. Acutely, it can result in cerebral edema, which can manifest as visual changes, focal neurologic changes, encephalopathy, respiratory depression, seizures, or even death due to brain herniation [20]. The severity of symptoms is determined by the magnitude and onset of the drop in sodium concentration. If the drop is significant, less than 120 mmol/L, and occurs rapidly within a few hours, it can be life-threatening. [26].

In cases of chronic conditions, brain cells undergo a process called adaptation [14]. During this process, the neuroactive substance glutamate is lost, leading to a decrease in the release of excitatory neurotransmitters. This can result in gait instability and reduced reflexes, increasing the risk of falls in chronically hyponatremic patients [26].

When correcting hyponatremia, it is important to do so slowly to prevent the negative consequences of rapid correction. The main concern with rapid correction is its effect on the brain. When brain cells suddenly experience an increase in extracellular tonicity due to adaptation, it can lead to osmotic demyelination syndrome (ODS) [14] [26]. The severity of symptoms associ-

ated with this syndrome can be devastating. If symptoms do occur, they typically manifest several days after initial improvement. Symptoms include quadriparesis, dysarthria, dysphagia, pseudobulbar palsy, seizures, locked-in syndrome, coma, and even death [26].

## DIAGNOSTIC APPROACH TO HYPONATREMIA

**DIAGNOSIS** - Diagnosing and treating hyponatremia may pose a challenge for healthcare professionals. A careful review of the history, physical examination, and laboratory tests is crucial to establish the underlying cause of hyponatremia [16]. The history should explore electrolyte-rich fluid loss, nutritional habits (e.g., low solutes or excessive water intake), medications, and pain. [17,18]. Assessment of circulatory blood volume by physical examination is insensitive and can be helpful only in severe cases of volume depletion (e.g., resting tachycardia, postural hypotension, etc).

Evaluation of hyponatremia should always start by assessing serum osmolarity; 'true' hyponatremia is associated with low serum osmolarity. Because the serum is 93% water (contains solutes such as sodium) and 7% lipids and proteins, expansion of the nonaqueous serum (electrolytes exclusion) by hyperlipidemia or hyperproteinemia results in falsely low serum sodium measurement when dilution of samples is required before analysis (e.g., indirect potentiometry). This 'pseudohyponatremia' is usually present with normal serum osmolarity.

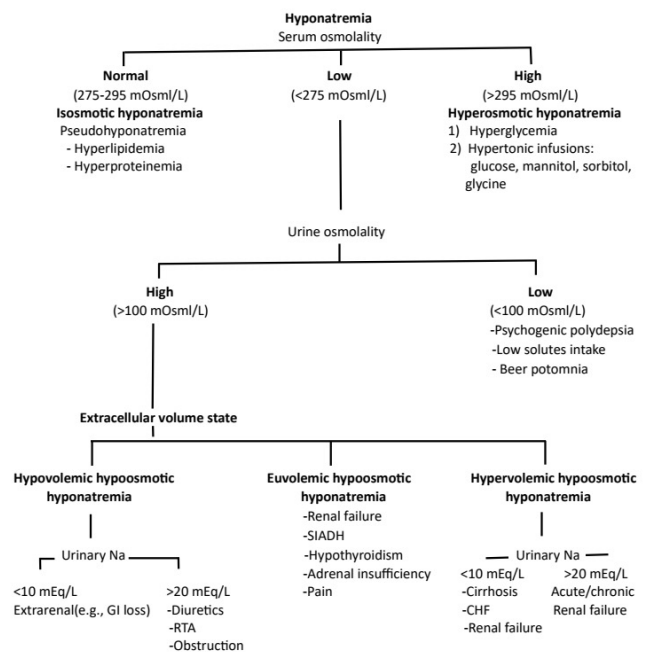
When serum osmolarity is elevated due to the presence of osmotically active molecules (e.g., hyperglycemia), fluid shift into the intravascular space results in lower measured serum sodium, this is referred to as dilutional or translocational hyponatremia. [Table 1]. Before determining extracellular fluid volume, measuring urine osmolarity is essential to determine the presence of ADH [19]. Diluted urine (U. Osm < 100 mOsm/L) narrows the differential diagnosis to low solute intake (tea and toast syndrome), and excessive water intake (e.g., psychogenic polydipsia or beer potomania). In contrast, concentrated urine with U. Osm >100 mOsm/L confirms elevated ADH. The next step is to determine if elevated ADH is appropriate (e.g., due to low EABV) from inappropriate ADH. Low urine sodium (U. Na <20 mmol/L) could be an indication of appropriately elevated ADH secondary to low EABV; however, this could also be a result of low sodium intake. In addition, high urine sodium can be due to IV fluid and does not exclude hypovolemia.

**Table 1.** Diagnostic criteria and interpretations.

Diagnostic Criteria	Interpretation
<b>Serum Osmolality (mOsm/kg H<sub>2</sub>O)</b>	
<b>hYPERTONIC (&gt;295)</b>	Severe hyperglycemia with dehydration; mannitol
<b>iSOTONIC (280-295)</b>	Hyperglycemia; pseudohyponatremia
<b>hYPOTONIC (&lt;280)</b>	SIADH; heart failure; cirrhosis
<b>Urine osmolality (mOsm/kg)</b>	
<b>High(&gt;=100)</b>	Vasopressin-dependent cause of hyponatremia
<b>Low(&lt;100)</b>	Vasopressin-independent cause of hyponatremia
<b>Urine sodium (mmol/L)</b>	
<b>High (&gt;=30)</b>	Diuretics, cerebral and renal salt wasting, SIADH,  Primary adrenal insufficiency, Hypopituitarism
<b>Low (&lt;30)</b>	Heart or liver failure, polydipsia, non-Renal Sodium  loss, true volume depletion
<b>Serum uric acid</b>	
<b>Low</b>	SIADH, renal salt wasting, acute volume expansion

H<sub>2</sub>O :water; kg :kilogram; L : liter; mmol : millimole; mOsm: milliosmole; SIADH: syndrome of inappropriate antidiuretic hormone secretion

**Figure 1.** Hyponatremia management approach



A thorough medical history should include a careful review of medications (e.g., diuretics, antidepressants, etc), recent symptoms (pain, nausea, vomiting, diarrhea, etc), and chronic medical illnesses (e.g., cirrhosis, CHF, etc). A physical examination can help identify hypervolemia secondary to cirrhosis or CHF (e.g., JVD, ascites, peripheral edema) and severe hypovolemia (tachycardia, postural orthostasis, etc). Laboratory tests are required; while elevated levels of BUN, creatinine, and BUN-to-creatinine ratio may suggest hypovolemia, it is important to note that high protein intake and glucocorticoids can also affect these levels.

Measuring urinary sodium excretion is a more useful test. In cases of hypovolemic hyponatremia, urine sodium is less than 20 to 30 mmol/L unless the kidneys are the cause of hyponatremia [22]. For individuals taking diuretics, higher urinary sodium excretion and fractional uric acid excretion can identify hypovolemia [23]. In uncertain cases, confirming the diagnosis through volume expansion (i.e., desalination) can be helpful. For those with hypovolemic hyponatremia, a 0.5 to 1 L infusion of isotonic (0.9%) NaCl can be initiated; this method should reduce the release of ADH, causing the excretion of diluted urine (U. Osm <100 mOsmol/L) and correct hyponatremia quickly. Because sodium excretion in the urine is regulated by aldosterone (not ADH), in patients with SIADH (high urine osmolality), infusion of the isotonic fluid (0.9% saline) causes excretion of the sodium load in hypertonic urine and reabsorption of the free water, leading to worsening of hyponatremia [24].

The diagnosis of SIADH can be established in hypotonic hyponatremia (P. Osm <275 mOsmol/L), concentrated urine (U. osm >100 mOsmol/L) with normal renal function, high urine sodium concentration (>20-30 mmol/L), and the absence of thyroid, adrenal, or kidney disease. It is not recommended to use vasopressin levels for the diagnosis of SIADH. Additionally, routine imaging should not be used for the routine evaluation of the condition [15].

Congestive heart failure and cirrhosis can cause an increase in extracellular fluid (ECF) volume and hypervolemic hyponatremia. Excess volume can be detected through physical examination. In addition, echocardiography can help assess the diameter of the inferior vena cava; similarly, direct measurement of the central venous pressure can be used to rule out intravascular volume depletion. [15]

**MANAGEMENT OF HYPONATREMIA** - Treatment of hyponatremia in the ICU necessitates a delicate balance between swift correction in acute cases and cautious management in chronic cases to prevent neurological complications like cerebral edema and osmotic demyelination syndrome (ODS). Patients with malnutrition, alcoholism, and prolonged use of diuretics are at higher risk of developing ODS. The treatment options span a spectrum depending on factors such as the underlying cause, severity of hyponatremia, symptoms of CNS dysfunction, and extracellular fluid volume status [26].

Asymptomatic patients with mild hyponatremia generally do not require urgent intervention [14]. The approach to correcting symptomatic hyponatremia involves increasing sodium levels by 1-2 mmol/L/h until symptoms improve, with a recommended increase of no more than 6-8 mmol/L in 24 hours to prevent ODS [14] [19] Patients exhibiting severe manifestations necessitate the administration of hypertonic (3%) saline, delivered at a calculated rate of approximately 1 mL/kg/hour during the initial treatment phase. [14] When hypertonic saline is administered, simultaneous DDAVP 'clamp' ensures more predictable slow correction of serum sodium.

In instances of seizures or impending brain herniation, a more aggressive approach is advised, involving a higher rate of 2-3 mL/kg/hour or rapid infusion of a 50-mL bolus, followed by a controlled infusion of 200 mL over 4-6 hours, utilizing 3% saline. Upon successful resolution of severe symptoms, discontinuation of 3% saline is recommended. Subsequent therapeutic interventions should be discerningly initiated, considering the nuanced factors of the patient's volume status and the underlying causative factors of hyponatremia. [14]. The underlying cause of hyponatremia should be addressed appropriately. For those with SIADH, the recommended course of action is to implement fluid restriction. Salt tablets or urea will increase solute excretion and urine volume and will facilitate the correction of hyponatremia.

In the case of hypovolemia, isotonic saline is administered. Conversely, individuals with hypervolemia are prescribed a regimen comprising both sodium and fluid restriction. The use of loop diuretics assists in promoting the excretion of water and sodium. Simultaneously, efforts should be directed towards optimizing the treatment of the underlying hypervolemic disorder. Diuretics are prescribed to correct volume overload in patients with hypervolemic hyponatremia. However, the use of diuretics depletes

sodium and predisposes patients to dilutional hyponatremia. Volume contraction also increases water intake by stimulating thirst and can lead to worsening hyponatremia.

Therefore, diuretics should be used cautiously in those patients; serum sodium should be closely monitored during diuresis. Discontinuing or reducing the dosage of diuretics, lifting salt restriction, and prescribing limited fluid intake are the basic tools for managing patients with heart failure and diuretic-induced hyponatremia. It is advisable to avoid thiazide diuretics in such cases, and in selected instances, vasopressin receptor antagonists may be considered as part of the treatment strategy. [14] A cautious approach towards avoiding hypertonic saline is advised.

Management of hyponatremia with  $U. Osm < 100$  mOsm/L as seen in beer potomania can be challenging as profound water diuresis is expected when solutes are presented. This carries a risk of rapid correction of hyponatremia. Therefore, careful monitoring of urine output is essential in such patients. In mild cases, fluid restriction and close monitoring of serum sodium is the safest approach.

In conclusion, several strategies play crucial roles in managing hyponatremia, including water restriction, salt supplementation, saline, and hypertonic saline administration in combination with desmopressin (DDAVP). Careful monitoring of patients in the intensive care unit is usually recommended in severe cases to ensure slow correction of hyponatremia and avoid the devastating complications of over-correction.

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## AUTHORS' CONTRIBUTION

Mazen O. Al-Qadi: Study conception and design, Leading the project, and mentoring team members. Alwatheq Alitelat: Manuscript writing including Abstract, Diagnosis, and monitoring and drafting the manuscript. Awwab F. Hammad: Manuscript writing including Introduction. Hebah Abuhayyeh: Manuscript writing including Management. Tala Dabbah: Manuscript writing including Clinical manifestations. Mohammad Abdeljawad: Critical review of the manuscript.

## DISCLAIMER

This article was made possible by the support of the American people through the United States Agency for International Development (USAID). The contents are the sole responsibility of the authors and do not necessarily reflect the views of USAID or the United States Government.

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