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Hyponatremia: An Overview

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ABSTRACT

Fluid and electrolyte imbalances occur more frequently and are the most common clinical problems encountered among hospitalized patients. Approximately 10% of all patients admitted to the emergency department have hyponatremia and 2% with hypernatremia [1,2]. It is very important to understand all details about sodium disturbances for better patient outcomes.[3] Recent studies conducted have reported that fluid and electrolyte imbalances are associated with increased morbidity and mortality among critically ill patients.

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INTRODUCTION:

Disorders of sodium and water balance occur frequently and this is the most common electrolyte imbalance seen in hospitalized patients. Approximately 10% of all patients admitted from the emergency department have hyponatremia and 2% with hypernatremia [1,2]. It is vital important to understand all details about sodium disturbances for better patient outcomes.[3]Sodium and water disorders occur frequently and mainly affect the neurologic system. The various factors that lead to disturbances in fluid and electrolyte homeostasis are severe burns, trauma, sepsis, brain damage, heart failure, and neurological problems. Studies reported that the complex interaction between respiratory and renal function is at the center of the electrolytic and acid-based environment in which the central and peripheral nervous systems function.[4]

SODIUM

Sodium is the major cation of extracellular fluid [ECF2 (1 mmol, or molar equivalent, corresponding to 23 mg of sodium)]. The mean body content of sodium in the adult male is 92 g, half of which (46 g) is located in the ECF at a concentration of 135–145 mmol/L, ~11 g is found in the intracellular fluid at the concentration of ~10 mmol/L, and ~35 g is found in the skeleton. Sodium is a very important electrolyte involved in the maintenance of normal cellular homeostasis and the regulation of fluid and electrolyte balance and blood pressure (BP).[5] Its role is crucial for maintaining ECF volume because of its important osmotic action and is equally important for the excitability of muscle and nerve cells and the transport of nutrients and substrates through plasma membranes. [6]

PHYSIOLOGY OF SODIUM REGULATION:

Electrolyte homeostasis can be maintained by balancing the intake primarily through ingestion and its loss mainly by urinary excretion. Sodium excretion is regulated by several controlling systems like perfusion pressure in kidneys, the sympathetic nervous system, and various hormones like angiotensin II, aldosterone, and vasopressin so that the sodium filtration fraction is normally 1% of the sodium filtered load.[7]

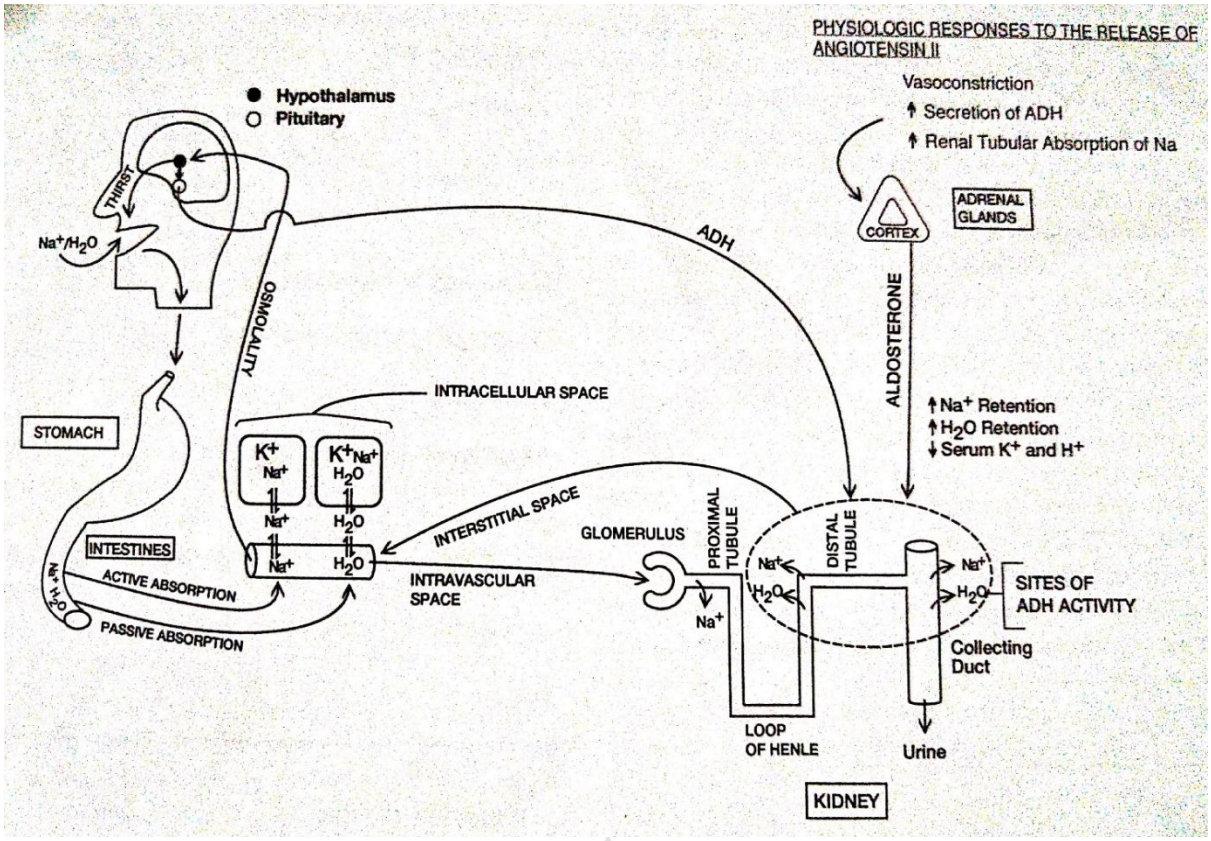

Figure No. 1: Physiology of sodium regulation.[8]

DYSNATREMIAS

Abnormalities of plasma sodium are probably the most common electrolyte disorders and they are associated with serious morbidity including a poorer long term neurologic outcome. [9]

HYPONATREMIA

Disturbances in serum sodium concentration are the main problem found in inpatients especially with intensive care unit patients having a prevalence rate of 15-30%. [3] Recent studies reported that many cases of dysnatremias were identified in ICU and the severity of dysnatremia is associated with poor outcome. [10-12]

Hyponatremia can be defined as a decrease in serum sodium concentration [<135 mEq/L].[3] Hyponatremia is a more common and important electrolyte imbalance that can be seen alone or, as a complication of other medical illnesses (eg, heart failure, liver failure, renal failure, pneumonia). [13]The normal serum sodium concentration is 135-145 mEq/L.

Hyponatremia is not a disease but rather a pathophysiologic process indicating disturbed water homeostasis. [14] Therefore, hyponatremia should be further classified to provide directions for diagnosis and treatment (Table 1). These classifications illustrate that hyponatremia is a very heterogeneous disorder. For understanding the current approach to hyponatremia, two sets of guidelines have been developed, one by professional organizations from within the United States ("United States guideline") and one from within Europe ("European guideline").[15-19]The United States guideline refrained from using a quality-of-evidence scoring system due to the limited evidence. Instead, the guideline was based on expert panel recommendations, which relied on a critical evaluation of relevant literature by the panel members. The European guideline did perform systematic reviews of the available evidence using the Grading of Recommendations Assessment Development and Evaluation scoring system. Both guideline committees were interdisciplinary, and the European guideline was endorsed by the European societies of nephrology, endocrinology, and intensive care. [15-19]

Table No. 1: Represent the classification and causes of hyponatremia

Classification	Criteria	Limitations of Clinical Utility
Moderate (125–129mmol/L) versus severe/profound[a] (<125 mmol/L)	Absolute SNa^+ concentration	Symptoms do not always correlate with the degree of hyponatremia
Acute versus chronic	Time of development (cutoff 48 h)	Time of development not always known
Symptomatic versus asymptomatic	Presence of symptoms	Many symptoms aspecific; chronic hyponatremia may be symptomatic
Hypotonic, isotonic, or hypertonic	Measured serum osmolality	Ineffective osmoles (e.g., urea, ethanol) are also measured
Hypovolemic, euvolemic, hypervolemic	Clinical assessment of volume status	Clinical assessment of volume status has low sensitivity and specificity

SNa, 125mmol/L is defined as "severe hyponatremia" by the United States guideline, and as "profound hyponatremia" by the European guideline.[15-19]

Hyponatremia can be classified into Acute and chronic. Acute severe hyponatremia occurs when serum [Na^+] falls rapidly below120 mEq/l in less than 48 Hrs. Chronic hyponatremia occurs when serum [Na^+] falls slowly during a period of 48 Hrs or more. With a **Mild** decrease in serum sodium level, the symptoms include nausea, malaise, lethargy, altered level of consciousness, headache. With a serum sodium level less than 125mEq/L (**Moderate**), the symptoms are seizures, coma. With very low serum sodium levels less than 115mEq/L (**Severe**), the symptoms are neurological symptoms resulting in intracerebral osmotic fluid shifts and cerebral oedema. Hyponatremia can also be classified according to the volume status as below as:

- Hypovolemic hyponatremia**:** Means a decrease in total body water with a greater decrease in total body sodium.

- Euvolemic hyponatremia**:** Means normal body sodium with an increase in total body water.

- Hypervolemic hyponatremia**:** Results as a result of an increase in total body sodium with a greater increase in total body water.

Based on effective osmolality, hyponatremia can be further classified as follows:

- Hypotonic hyponatremia

- Isotonic hyponatremia

- Hypertonic hyponatremia

The primary underlying mechanisms to identify hyponatremia are:

1. Urine osmolality

A urine osmolality more than 100mOsm/Kg indicates the impaired ability of the kidney to dilute the urine and this helps to differentiate between the associated conditions with impaired free-water excretion and primary polydipsia.

2. Serum osmolality

This helps to differentiate between true and pseudo hyponatremia. Pseudohyponatremia refers to any secondary conditions like hyperlipidemia or hyperproteinemia or due to

hypertonic hyponatremia associated with elevated glucose, mannitol, glycine (post urologic or post gynecologic procedure), sucrose, or maltose (contained in IgG formulations).

3. Urinary sodium concentration

This aims to differentiate between hyponatremia secondary to hypovolemia with urine sodium less than 25mEq/L and SIADH with urine sodium greater than 20-40mEq/L.

Additional tests to be performed are serum uric acid levels which will be decreased in SIADH and salt-wasting conditions. Thyroid-stimulating hormone (TSH) and serum cortisol also should be measured if hypothyroidism and hyperadrenalism are suspected. Other tests to be considered are serum albumin, triglycerides, and serum protein electrophoresis. Certain imaging studies like CT scanning, chest radiography are also performed in some patients to confirm any underlying etiologic factors like SIADH or cerebral salt wasting.[20]

GENERAL APPROACH TO TREATMENT

The United States and European guidelines recommend the various diagnostic and treatment algorithms for the management of hyponatremia. The United States guidelines are based on acute v/s chronic hyponatremia and subdivided the classification of acute hyponatremia into severe and mild to moderate based on duration. [21-22]

The European guidelines adhered primarily to the presence and severity of symptoms rather than duration.[23]Treatment of hyponatremia depends on 1] presence of neurological symptoms and 2] the cause for the hyponatremia. Symptomatic hyponatremia is a medical emergency.

Proper diagnosis of hyponatremia is essential as its presence can increase the mortality of 9 – 27% [24] and the management of hyponatremia is based on its cause, duration, and severity. Rectification of serum sodium should be done without delay in symptomatic patients, especially those experiencing seizures. The presence of hyponatremia in less than 48hours with the symptoms greatly suggests the benefit of managing acute cerebral edema over the risk of treatment-associated adverse effects.[25-26]]

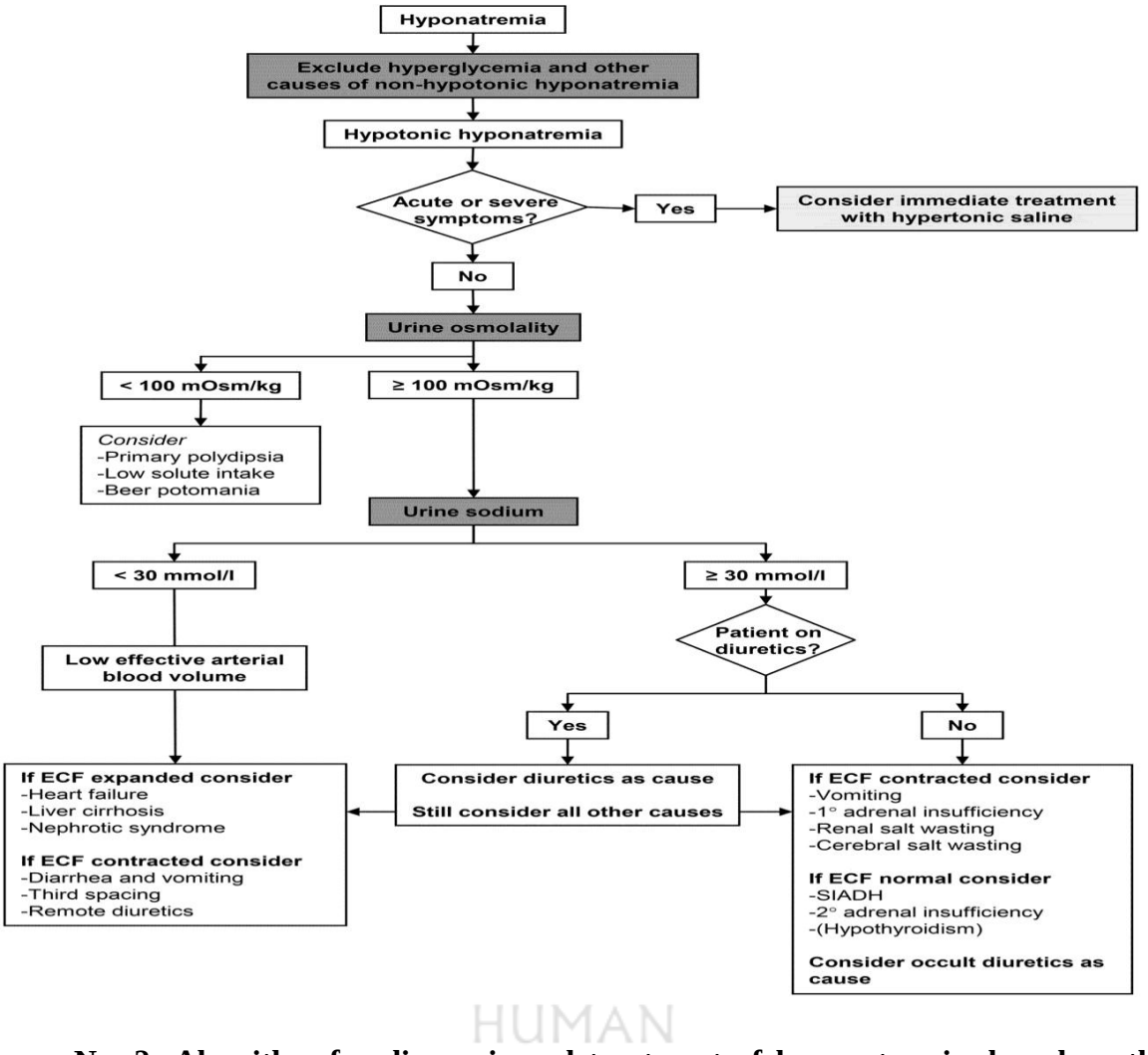

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Figure No. 2: Algorithm for diagnosis and treatment of hyponatremia, based on the clinical practice guidelines on hyponatremia.

Acute hyponatremia

Many factors predispose to acute hyponatremia, especially with more water intake. [26] Hypertonic saline is the more effective and life-saving treatment for cerebral edema caused by hyponatremia, as the high extracellular sodium concentration immediately removes water from the intracellular space. [27].Hypertonic sodium chloride with or without a loop diuretic is usually started at a rate of 1–2 ml/kg/hr to raise sodium concentration by 1–2 mEq/L/hr.This rapid correction of hyponatremia should be limited to the initial phase of management. The overall correction of sodium should not exceed 8–12 mEq/L for 24 hours, as the risk of osmotic demyelination rises above this limit.

The change in serum sodium following administration of 1litre of IV fluid can be calculated by Madras and Adrogue as follows:

$$\text{Change in plasma sodium} = \frac{Infuse\ [Na+]\text{-}plasma\ \{Na+]}{Total\ body\ water + 1}$$

$$\text{Change in plasma sodium} = \frac{Infuse\ [Na^{+}] + Infuse\ [k^{+]} - plasma\ [Na^{+}]}{Total\ body\ water + 1}$$

These equations are an accurate prediction of changes in serum sodium in almost all clinical settings[28-29]. The accuracy of these formulas was assessed by the retrospective study on patients administered hypertonic saline (3%NS) for treating hyponatremia. [30]Even though these formulas are accurate, recently hypertonic saline as a fixed-dose has been started giving for such conditions. Both the guidelines support this approach for the following reasons with slightly different specifications,

1. In patients with cerebral edema, rapid partial correction in serum Na^{+}should is achieved properly.

2. Potential calculation errors can be avoided as a fixed bolus does not requires calculations in patients with acute problems.

3. It also avoids the risk of overcorrection which usually occurs with continuous infusion of hypertonic saline.[31]

Some other studies also show the advantages of giving 500ml 3%NaCl over 6 hours in patients with hyponatremic encephalopathy (S.Sodium -130mmol/L and neurological symptoms) and found to improve the symptoms without causing osmotic demyelination syndrome(ODS). [32,33] The correction will be different in some patients who had chronic hyponatremia based on severity (Sodium) frequently,110 mmol/L) and the duration of the symptom.[34]

Chronic hyponatremia

Fluid restriction (<1L/day) is the fundamental principle for the treatment of chronic hyponatremia excluding hypovolemic hyponatremia.[35]. Apart from fluid restriction,

pharmacological therapy is required to increase renal free water excretion. [36,37]The treatment with diuretics, urea, vasopressin receptor antagonist [vaptans], or demeclocycline is usually used (Table 2).

Table No. 2: Comparison of the United States and European guidelines

Subject	United States Guideline	European Guideline
Acute or symptomatic hyponatremia	Severe symptoms: Bolus 3% NaCl (100 ml over 10 min × 3 as needed)	Severe symptoms: Bolus 3% NaCl (150 ml over 20 min 2–3 times as needed)
	Moderate symptoms: Continuous infusion 3% NaCl (0.5–2 ml/kg per h)	Moderate symptoms: Bolus 3% NaCl (150 ml 3% over 20 min once)
Chronic hyponatremia		
SIAD	Fluid restriction (first line)	Fluid restriction (first line)
	Demeclocycline, urea, or vaptan (second line)	Urea or loop diuretics + oral NaCl (second line)
		Do not recommend or recommend against vaptan[a]
		Recommend against lithium or demeclocycline
Hypovolemic hyponatremia	Isotonic saline	Isotonic saline or balanced crystalloid solution
Hypervolemic hyponatremia	Fluid restriction	Fluid restriction
	Vaptans[b]	Recommend against vaptan
Correction rates	Minimum: 4–8 mmol/L per d, 4–6	No minimum

Subject	United States Guideline	European Guideline
	mmol/L per d (high risk of ODS)	
	Limits: 10–12 mmol/L per d, 8 mmol/L per d (high risk of ODS)	Limit: 10 mmol/L per d
Management of overcorrection	Baseline S_{Na}≥120 mmol/L: probably unnecessary	Start once limit is exceeded
	Baseline S_{Na}<120 mmol/L: start relowering with electrolyte-free water or desmopressin after correction exceeds 6–8 mmol/L per d	Consult an expert to discuss infusion containing electrolyte-free water (10 ml/kg) with or without 2 μg desmopressin iv

- *↵a "Do not recommend" when S_{Na}<130 mmol/L, "recommend against" when S_{Na}<125 mmol/L.*
- *↵b In liver cirrhosis, restrict to patients where the potential benefit outweighs the risk of worsened liver function.*

Vaptans: The mechanism of action of vaptans are by blocking the vasopressin type2 receptors in collecting duct principal cells and thus inducing diuresis[37,38,39]Tolvaptan, satavaptan, lixivaptan and conivaptan are some of the vaptans that are currently available and they are the main therapy for patients with hyponatremia with excess vasopressin.[40]But most studies had reported that in patients with SIADH, heart failure, or liver cirrhosis vaptans are not recommended. Both US and European guidelines also do not recommend vaptan for acute or severely symptomatic hyponatremia. Some studies reported the adverse effects of vaptans like an overcorrection, liver toxicity, etc European guidelines completely disagree with vaptan therapy. [41]

Urea: The best alternative approach for vaptans is urea for patients having chronic hyponatremia due to SIAD [42]. Urea induces an osmotic diuresis, which increases the renal free water excretion.[43,44]Some animal experimental studies reported that urea had reduced demyelination, microglial activation, and changes in BBB, and increased astrocyte activity.

While in a comparison study in animals with urea and hypertonic saline, the neurological scores and survival rates were more in animals treated with urea. [45]

NEUROLOGICAL COMPLICATIONS

The neurologic indisposition in patients with hyponatremia is Hyponatremic Encephalopathy (HNE). The various signs and symptoms associated with HNE are brain alterations due to hypo-osmotic conditions. These signs and symptoms usually depend on different factors like cause, the severity of hyponatremia, sex, age, and speedy onset.[45] The clinical manifestations of HNE due to acute hyponatremia will differ from the symptoms of chronic conditions, which are depicted in the table. In acute hyponatremia, when the electrolyte content in the brain reaches the maximum depletion (~18%), and the organic osmolytic extrusion not completed, brain edema will occur invariably. Some studies reported that when the rate of SNa drops to less than 0.5mEq/L/Hr over 24 Hrs, the condition will probably be uncomplicated but other neurologic events, as well as death, can occur when the SNa drops to less than 0.1mEq/L/Hr.[47]

Preadolescents are more susceptible to having severe HNE. This is because drastic symptoms are associated with brain edema.[48,49] This can be as a result of the brain and skull development as this attains its maximal size only at the age of 16 years and thus the brain edema occurs during hyponatremia is more prone to younger adults.

Certain studies found some female predisposition to HNE but need more studies to prove the interdependence. [50,51,52]

Hypernatremia and hypoxia are found to have a complex interrelation reported by various experimental and clinical studies.[53,54] This occurs when the brain parenchyma swells and compresses the blood vessels contributing to brain hypoxia which in turn causes neurogenic pulmonary edema which again results in decreased oxygen deficiency in the brain.[55]

Table No. 3: Symptoms of HNE *[56,57,58,59]*

Acute severe	Chronic
Headache	Fatigue
Seizure	Gait and attention deficit
Coma	Falls and bone fracture
Death	
Respiratory arrest	
Noncardiogenic pulmonary edema	

Management of HNE

For managing HNE, the goal of the treatment should always be to reverse severe neurological manifestation that is always secondary to hyponatremia. The basis for severe HNE includes altered mental status, seizures, focal neurological damage, coma, and other signs or symptoms of brain herniation. Therefore the cornerstone of the treatment should be the reduction of intracranial pressure by decreasing brain water content.[60,61] This can be attained by rapid infusion of hypertonic saline with a recommended and well-accepted bolus dose of 100 to 300 ml of 3% sodium chloride. The boluses must be repeated until symptoms of brain edema revert with recurrent sodium monitoring.[62]

CONCLUSION:

Abnormalities in fluid and electrolyte balance in particularly ill and hospitalized patients can lead to several life-threatening consequences among which hyponatremia is found to be a common water balance disorder that often poses a diagnostic or therapeutic challenge. Care should be taken to assess and identify the signs and symptoms in patients admitted to the emergency department. Two guidelines are formulated and updated for the classification, diagnosis, and treatment of hyponatremia. Physicians must have enough knowledge about fluid and electrolyte physiology that could help them to understand the underlying mechanism of the respective disorders to provide maximum care. Caution should be taken while administering fluid and medications for the correction of electrolyte imbalances.

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