Approach to a Patient with Hyponatremia in ICU

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Introduction

Hyponatremia, defined as a serum sodium concentration <135 mmol/L, is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. It occurs in up to 30% of hospitalized patients and can lead to a wide spectrum of clinical symptoms, from subtle to severe or even life threatening. Hyponatremia is a powerful prognostic factor in patients with heart failure and cirrhosis. Additionally, it is associated with increased cost, prolonged length of stay, and increased mortality in hospitalized patients.

Definitions

Based on serum sodium concentration

- Mild hyponatremia – serum sodium concentration between 130 and 135 mEq/L
- Moderate hyponatremia – serum sodium concentration between 125 and 129 mEq/L
- Profound hyponatremia – serum sodium concentration <125 mEq/L

Based on rate of development

- Acute hyponatremia – hyponatremia that is documented to exist for < 48 hours
- Chronic hyponatremia – as hyponatremia that is documented to exist for at least 48 hours

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Based on symptoms

Moderately symptomatic hyponatremia – presence of moderately severe symptoms of hyponatremia like nausea without vomiting, confusion and headache

Severely symptomatic hyponatremia – presence of moderately severe symptoms of hyponatremia like vomiting, cardiorespiratory distress, abnormal somnolence, seizures and coma (Glasgow Coma Scale ≤8)

Causes of Acute Hyponatremia (<48 Hours)

- Postoperative phase
- Post-resection of the prostate, post-resection of endoscopic uterine surgery
- Polydipsia
- Exercise
- Recent thiazides prescription
- 3,4-Methylenedioxymethamphetamine
- Colonoscopy preparation
- Cyclophosphamide (IV)
- Oxytocin
- Recently started desmopressin, terlipressin, vasopressin therapy

Diagnosis of Hyponatremia

The management of hyponatremia requires an approach that identifies the underlying cause of the electrolyte disorder. One approach to this involves the sequential assessment of serum osmolality, urine osmolality, volume status and urinary [Na^+].

Assessment of serum osmolality

Sodium is the predominant solute in the extracellular fluid compartment and, as such, the primary determinant of serum osmolality. A decrease in serum [Na^+] (i.e., hyponatremia) generally, but not always, reflects a state of hypo-osmolality. The presence of an increased concentration of solutes that do not cross the cell membrane (such as glucose, mannitol or glycine) can lead to the development of translocational hyponatremia as a result of the movement of water from the cells to the extracellular space. Such patients can have normal, or even high, serum osmolality. Another setting in which hyponatremia is associated with a normal serum hypo-osmolality occurs in the presence of high levels of lipids or proteins.

This is designated as pseudohyponatremia and is the result of the increased proportion of serum volume taken up by these substances. The serum osmolality remains normal in pseudohyponatremia and can be used to eliminate this diagnosis.

Assessment of urine osmolality

Once the presence of hypotonicity has been established, the urinary osmolality may be used to differentiate between patients who do and do not have a disorder in the renal diluting mechanism. A urine osmolality below 100 mOsm/kg reflects a normal diluting mechanism, the hyponatremia resulting from a level of water intake that exceeds normal urinary diluting capacity (psychogenic polydipsia). This can also be observed in infants fed dilute formula and patients with a low solute intake. In contrast, a urine osmolality exceeding 100 mOsm/kg reflects impairment to the renal diluting mechanism at a time when the urine should be maximally dilute in the setting of serum hypotonicity; this most commonly is a consequence of persistent vasopressin in the circulation.

Assessment of urinary sodium concentration and volume status

In patients whose urine osmolality is greater than 100 mOsm/kg, assessment of volume status is necessary to identify the underlying etiology of the hyponatremia. In hypovolemic patients with hyponatremia, urinary [Na^+] greater than 20 mmol/L is indicative of renal sodium losses, whereas a urinary [Na^+] below 20 mmol/L reflects extra renal sodium losses. Patients with hypervolemic hyponatremia (due to heart failure, cirrhosis and nephrotic syndrome) characteristically also have a sodium retaining disorder in addition to the water retention reflected in the decrement of sodium serum. Thus, their urinary sodium is <20 mmol/L. Less commonly, hypervolemic hyponatremia is seen in patients with advanced renal failure who cannot conserve sodium, and therefore may have a urinary [Na^+] >20 mmol/L. In euvolemic hyponatremia there is an excess of total body water relative to a normal amount of total body sodium. These patients characteristically have a urinary sodium >20 mmol/L, as this reflects their sodium intake.

Classification of Hyponatremia

Hyponatremia is classified according to serum osmolality:

- Hyperosmolality hyponatremia (hypertonic hyponatremia) – serum osmolality >295 mOsm/kg
- Isoosmolality hyponatremia (isotonic hyponatremia) – serum osmolality 280–295 mOsm/kg
- Hyperosmolality hyponatremia (hypotonic hyponatremia) – serum osmolality <280 mOsm/kg

Hypotonic hyponatremia is further classified according to extracellular fluid volume status:

- Hypovolemic hyponatremia
- Hypervolemic hyponatremia
- Euvolemic hyponatremia

Syndrome of Inappropriate Antidiuresis (SIAD)

SIAD is a diagnosis of exclusion. It fits the category of hyponatremia with a urine osmolality >100 mOsm/kg, urine sodium concentration ≥30 mmol/L and normal extracellular fluid volume, but formal diagnosis requires exclusion of other possible causes of hyponatremia. One such possible cause is adrenal insufficiency. Hyponatremia due to hypothyroidism is very rare other than in myxoedema coma, when there is also a decrease in cardiac output and glomerular filtration rate.

Diagnostic criteria for SIAD

Essential criteria

- Effective serum osmolality <275 mOsm/kg
- Urine osmolality >100 mOsm/kg at some level of decreased effective osmolality

- Clinical euvolemia
- Urine sodium concentration >30 mmol/L with normal dietary salt and water intake
- Absence of adrenal, thyroid, pituitary or renal insufficiency
- No recent use of diuretic agents

Supplemental criteria

- Serum uric acid <4 mg/dL
- Serum urea <21.6 mg/dL
- Failure to correct hyponatremia after 0.9% saline infusion
- Fractional sodium excretion >0.5%
- Fractional urea excretion >55%
- Fractional uric acid excretion >12%
- Correction of hyponatremia through fluid restriction

Causes of SIAD

Malignant disease. Carcinoma of lung, orophraynx, gastrointestinal tract, genitourinary tract, lymphoma, sarcoma and neuroblatoma.

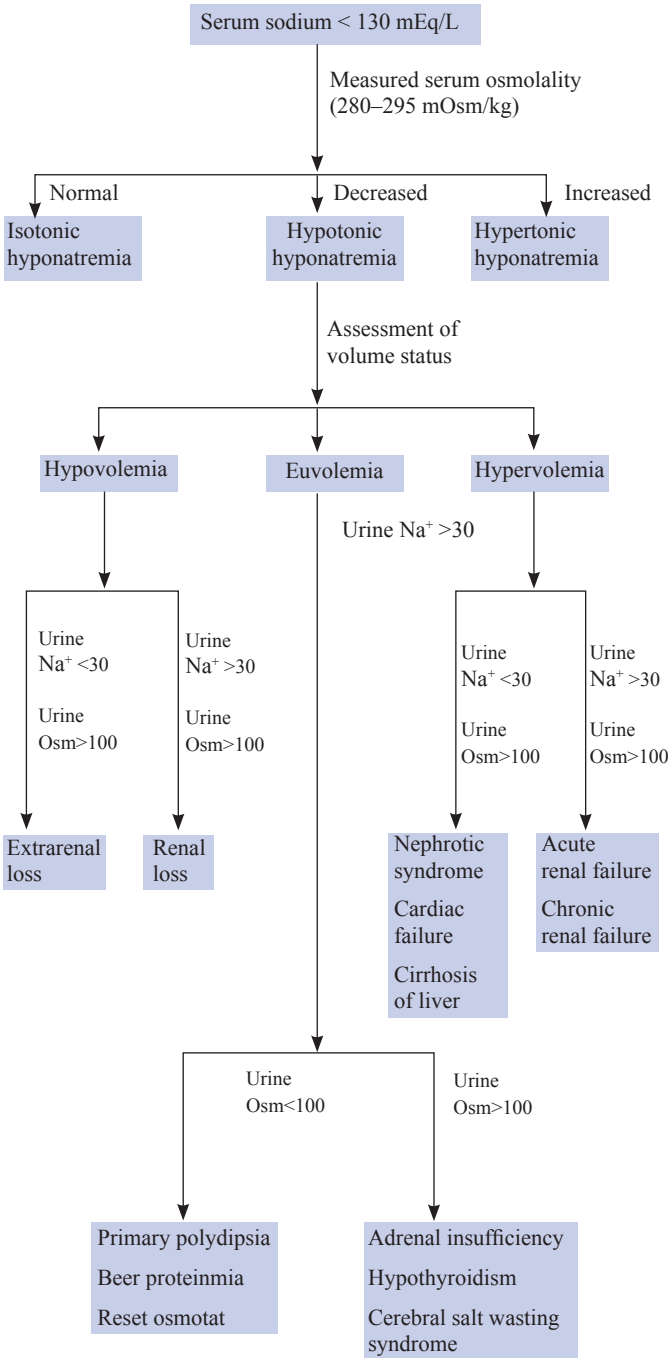
Pulmonary disorder. Infection (bacterial pneumonia, viral pneumonia, tuberculosis, aspergillosis, pulmonary abscess, asthma and cystic fibrosis).

Disorder of central nervous system. Infection (meningitis, encephalitis, brain abscess, AIDS, malaria), vascular and masses (brain tumor, head trauma, stroke, subdural hematoma and subarachnoid hemorrhage), Guillain–Barré syndrome, multiple sclerosis, hydrocephalus and cavernous sinus thrombosis.

Drugs

- Antidepressants (SSRIs, tricyclic antidepressant, MAOI and venlafaxine)
- Anticonvulsants (carbamazepine, oxcarbazepine, sodium valproate, lamotrigine)
- Antipsychotics (phenothiazides, butyrophenones)
- Anticancer (ifosfamide, melphalan, cyclophosphamide, methotrexate and pentostatin)
- Vasopressin analogues (desmopressin, oxytocin, terlipressin and vasopressin)
- Miscellaneous (opiates, levamisole, interferon, NSAIDs, clofibrate, nicotine, amiodarone and proton pump inhibitors)

Approach to Hyponatremia



Extrarenal loss

- Vomiting
- Diarrhea

- Third space
- Burn
- Pancreatitis
- Traumatic

Renal loss

- Diuretic excess
- Minerlocortical deficiency
- Salt-losing nephropathy
- Bicarbonaturia
- Renal tubular acidosis
- Ketonuria

Management

The key to effective management of hyponatremia is establishing the type and its cause so that the cause can be removed, if possible, and the management will be appropriate. The treatment of hyponatremia is determined by three major factors: severity of hyponatremia, that is, the presence or absence of severe central nervous system (CNS) symptoms such as lethargy, delirium, seizure, and coma; onset of hyponatremia, acute or chronic; and volume status.

Treatment of hyponatremia

The correct treatment of hyponatremia in acute illness depends first and foremost on the correct diagnosis.

Unfortunately, occasionally a physician believes that all types of hyponatremia means a decrease in total body sodium concentration and therefore the treatment is isotonic saline administration. Only hypovolemic hyponatremia is appropriately treated by volume expansion with isotonic saline. Therefore, when hypovolemic hyponatremia is the suspected diagnosis, a trial of volume expansion with isotonic saline is certainly appropriate.

Acute hyponatremia

Acute symptomatic hyponatremia can be a very serious clinical situation. In hyponatremia, the water equilibrates across the brain cell membrane and leads to cell swelling. Acute hyponatremia can lead to severe brain swelling, herniation and cardiopulmonary arrest. There are, however, adaptive changes that occur in the brain over time. Within the first 1–3 hours, extracellular fluid moves into the cerebrospinal fluid and then into circulation. A slower process of adaptation then occurs in which brain cells extrude potassium and organic solutes, thereby decreasing intracellular osmolality and reducing brain edema as water moves out of cells. In acute hyponatremia with neurological symptoms, the treatment of choice is 3% hypertonic saline at 100 ml/h. For each 100 mL of 3% hypertonic saline, the serum sodium concentration will increase by approximately 2 mEq/L. The duration of hypertonic saline treatment of acute symptomatic hyponatremia should be based on the improvement in the patient's symptoms and signs. Patients with acute hyponatremia may be lethargic, disoriented, agitated and have anorexia and nausea. Physical findings include abnormal sensorium, pathological reflexes, Cheyne–Stokes respiration, hypothermia and seizures. In case of severe symptoms, such as seizures, obtundation and coma, 3% sodium chloride may be infused at 4–6 mL/kg/h. A loop diuretic, for example, furosemide, may be added to this treatment, as it may cause hypotonic urine. Urinary electrolytes, however, should be replaced to avoid extracellular fluid volume (ECFV) depletion and electrolyte disturbances such as decreased plasma potassium, magnesium and calcium. The consensus is that correction of hyponatremia should be limited to less than 12 mEq/L in 24 hours and less than 18 mEq/L in 48 hours. There are high-risk patients, however, with severe malnutrition, alcoholism or advanced liver disease in whom the rate of correction of hyponatremia should be below these limits. Patients with too rapid correction of hyponatremia develop osmotic demyelination syndrome (central pontine myelinosis).The patients demonstrate improved neurological symptoms initially, but one to several days later, new and progressive neurological symptoms emerge and can lead to permanent neurological deficits or even death.

Chronic hyponatremia

Correction of chronic hyponatremia with hypertonic saline is generally only necessary if the patient is symptomatic. In asymptomatic patients with euvolemic or hypervolemic hyponatremia in which no specific intervention is available (e.g., SIAD), fluid restriction is generally the treatment of choice. The daily fluid intake must, however, be severely restricted to less than 24 hours urine output and insensible losses. There may, however, be patients with chronic hyponatremia who

will not tolerate or comply with this degree of daily fluid restriction. In these patients, several approaches have been used in the past. Demeclocycline causes arginine vasopressin resistant nephrogenic diabetes insipidus and has been used to treat chronic hyponatremia by administering divided doses ranging from 600 to 1200 mg/day. The demeclocycline doses should only be increased every 3–4 days.

Formulas for Estimating the Rate of Correction

Various formulae have been proposed to aid in predicting the increment in serum sodium concentration that would accompany the infusion of either isotonic saline or hypertonic saline in order to avoid over and rapid correction; the Adrogue–Madias formula is the one most widely used. However, it is not clear how accurately these calculations predict correction rates in clinical use. Therefore, a close monitoring of serum sodium concentration as well as the urinary electrolyte content is an essential element in the management of patients with hyponatremia, as there is no perfect formula for predicting the rate and amount of hypertonic saline to correct, but not to overcorrect, hyponatremia.

Adrogue–Madias formula

Change in serum sodium with 1 L of infusate containing Na= infusate Na^+- serum Na^+/ total body water (TBW)+1

Change in serum sodium with 1 L of any infusate containing Na and K= (infusate Na^+ infusate K^+) - serum Na^+/total body water (TBW)+1

The estimated total body water (in liters) is calculated as follows:

0.6 × weight in kg (nonelderly men)

0.5 × weight in kg (nonelderly women)

0.5 × weight in kg (elderly men)

0.45 × weight in kg (elderly women)

Vasopressin receptor antagonist

Antidiuretic hormone (ADH), also called vasopressin, interacts with various receptor, V1 and V2 receptor; V1 receptor is further classified in V1a and V2b. Drug that blocks V2 receptor in the renal tubule increases water excretion, making them attractive as therapy for hyponatremia status. These drugs exert their aquatic effects by causing a decrease in transcription and insertion of aquaporin-2 channels into apical collecting duct membrane. As a result, the water permeability of the collecting duct is decreased even in the presence of circulating ADH.

Conivaptan. It is a combined V1a and V2 receptor antagonist that has been approved for treatment of euvolemic and hypervolemic hyponatremia. It inhibits the cytochrome P450 3A4 system. Its use has been limited to no more than 4 days of intravenous infusion over 30 minutes, followed by continuous infusion of 20–40 mg/day. No dose adjustment is required in hepatic and renal impairment.

Tolvaptan. It is an oral selective V2 receptor antagonist that has been approved for the treatment of euvolemic and hypervolemic hyponatremia. It inhibits the cytochrome P450 3A4 system. The dose of tolvaptan is 15–60 mg once daily.

Key Points

Vaptans should not be used to treat hyponatremia associated with severe symptoms; hypertonic saline solution is the treatment of choice in this setting

- Establish the cause of hyponatremia
  - Vaptans are potentially indicated for euvolemic or hypervolemic hyponatremia only and contraindicated for hypovolemia or euvolemic disorders that reverse quickly (e.g., glucocorticoid deficiency)
- Avoid fluid restriction during the first 24–48 hours after initiation
- Measure serum sodium at baseline and every 6–8 hours for the first 24 hours and followup urine output closely
  - Adjust fluid restriction based on rate of correction
  - The development of high-volume aquaresis suggests that the patient may be at risk of over-rapid correction

- Goal of correction is the same as other treatments for chronic hyponatremia
  - Maximum correction limits of 12 mmol/L per 24 hours and in the aggregate 18 mmol/L per 48 hours apply; these are limits, not goals
  - An increase of 6 mmol/L per 24 hours will improve CNS symptoms and abrogate risk of deterioration while limiting risk of exceeding correction limits; little, if any, benefit accrues with faster rate of correction
  - Increase oral or parenteral water intake if the rate of correction appears to be exceeding the goal
- Urine osmolality can be a helpful tool during vaptan therapy and should be measured before and after the drug initiation of drug to see adequate response
- Depending upon urine osmolality one should
  - increase the drug dose if urine osmolality remains high
  - limit fluid intake if urine osmolality is low

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Answers to Image Quiz on Page no. 26

1. Intercostal drain on right side
2. Internal jugular venous sheath with pulmonary artery catheter
3. Prosthetic mitral valve
4. Percutaneously implanted aortic valve (Core valve)
5. Temporary pacemaker lead
6. Metallic sternal sutures from previous cardiac surgery
7. Surface ECG electrodes and attached cables