Clinical Approach to Altered Serum Sodium levels

Ashish K Duggal*, Pushpa Yadav**, AK Agarwal***, BB Rewari****

Disorders of sodium and water balance are very common and are seen in the emergency department almost every day worldwide. Sodium is the principal solute in the extracellular compartment and hence the plasma osmolality largely depends on the serum sodium concentration. Plasma osmolality in turn is regulated tightly within a narrow range of 275 - 290 mosm/kg by various mechanisms. A decrease or increase in the serum sodium level will have an effect on the plasma osmolality and this can have deleterious effects on the whole body – in particular, the central nervous system. Severe hypo- and hypernatraemia are associated with significantly high mortality and morbidity. Moreover, inappropriate treatment may result in treatment related complications such as osmotic demyelination syndrome. This article discusses the pathophysiology and management of both hyponatraemia and hypernatraemia with special emphasis on preventing treatment related complications.

Hyponatraemia

Hyponatraemia is defined as a decrease in the serum sodium concentration to a level below 136 mmol/l. Although plasma osmolality is closely related to serum sodium concentration, hyponatraemia can be associated with low, normal, or high osmolality. Osmolality or tonicity refers to the contribution to osmolality of solutes such as sodium, glucose, and urea that cannot freely move across the cell membrane thereby reducing transcellular shifts in water. Plasma osmolality can be measured by osmometry, or can be calculated by the following formula:

\[ P_{osm} = 2 \left[ \frac{[Na](meq/l)+[glucose](mg/dl)+BUN(mg/dl)}{18} \right] + \frac{2.8}{2} \]

Plasma osmolality is preserved within the normal range by the hormone arginine vasopressin, also known as the antidiuretic hormone (ADH). Osmoreceptors near the hypothalamus sense plasma osmolality and modulate vasopressin release. Vasopressin functions at the distal collecting duct of the kidney to increase water reabsorption in the otherwise relatively impermeable section of the nephron. Thirst is another crucial but less sensitive mechanism for maintaining plasma osmolality. Furthermore, because the cell membranes are freely permeable to water, all body fluids are in osmotic equilibrium. As a result, plasma sodium concentration not only reflects the plasma osmolality but also the intracellular osmolality. Any change in the serum sodium concentration not only changes the tonicity of the extracellular fluid, but also causes water to shift into or out of cells as the tonicity of the two compartments equilibrates. This shift has important implications because the CNS manifestations of hypo- and hypernatraemia are the result of these water fluxes.

Hyponatraemia is the most common electrolyte abnormality found in hospitalised patients. It has an incidence of around 1% and the frequency increases with increasing age. In acute (< 48 hrs) and symptomatic hyponatraemia, the mortality rates may be as high as 17.9%. Hyponatraemia is more commonly caused by an excess free water rather than sodium depletion. There is convincing evidence that hyponatraemia is not only a marker of serious underlying disease, but when severe, can itself be the cause of major neurologic damage and death.

Classification of hyponatraemia

Hyponatraemia can be classified according to the plasma osmolality into hyperosmolar, iso-osmolar and hypo-osmolar states. Table I lists the various causes of hyponatraemia according to the classification.

<table>
<thead>
<tr>
<th>Hyperosmolar Hyponatraemia</th>
<th>Iso-osmolar Hyponatraemia</th>
<th>Hypo-osmolar Hyponatraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td>Pseudohyponatraemia</td>
<td>Post-TURP</td>
</tr>
<tr>
<td>Hypertonic mannitol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Medical Officer, ** Senior Physician and Associate Professor, *** Consultant, Professor and Head, **** Senior Physician and Assistant Professor, Department of Medicine, Dr RML Hospital, New Delhi - 110 001.
Hypovolaemic Hyponatraemia

Renal sodium loss
- Diuretic agents
- Osmotic diuresis (glucose, urea, mannitol)
- Adrenal insufficiency
- Salt-wasting nephropathy
- Bicarbonaturia (renal tubular acidosis, disequilibrium stage of vomiting)
- Ketonuria

Extra-renal sodium loss
- Diarrhoea
- Vomiting
- Blood loss
- Excessive sweating (e.g., in marathon runners)
- Fluid sequestration in “third space”, i.e.,
  - Bowel obstruction
  - Peritonitis
  - Pancreatitis
  - Muscle trauma
  - Burns

Hypervolaemic Hyponatraemia

Congestive heart failure
- Cirrhosis
- Nephrotic syndrome
- Renal failure (acute or chronic)
- Pregnancy

Hyponatraemia can occur with increased plasma osmolality (> 290 mosm/kg) as a result of increased concentration of an effective solute in the extra-cellular fluid compartment. This creates an osmotic gradient that drives water from the cells into the extra cellular space leading to a lower, diluted sodium concentration. This can be seen in severe hyperglycaemia during uncontrolled diabetes. Quantitatively, the measured sodium decreases approximately 1.5 meq/l for every 100 mg/dl rise in serum glucose concentration12. This formula is based on the presumption that the volume of distribution of glucose is 45% of the total body water. But in many patients admitted in the hospital, the body composition may be altered and this formula cannot be used. The following formula is a more generalised formula to predict changes in serum sodium12:

\[ \text{Change in sodium} = 5.5 \times (1 - V)/2 \times \text{C change in glucose} \]

where V is the volume of distribution of glucose as a fraction of total body water.

Less common causes of hyperosmolar hyponatraemia include hypertonic mannitol, sorbitol, maltose and radiocontrast administration13, 14. This is also known as translocational hyponatraemia.

Iso-osmolar hyponatraemia

Hyponatraemia can occur with a normal plasma osmolality (275 - 290 mosm/kg). This occurs as a result of either pseudohyponatraemia, by massive absorption of irrigant solutions that do not contain sodium, as during transurethral resection of the prostate, and by accumulation of cations in the extracellular space other than sodium.
Pseudohyponatraemia is a laboratory artefact and occurs with severe hypertriglyceridaemia and paraproteinaemia. It occurs because the large non-aqueous molecules such as lipids or proteins occupy a greater proportion of the serum and there is a corresponding decrease in total sodium content per unit volume of serum. This is a laboratory artefact, which is now fairly obsolete with the use of modern instruments that use sodium ion specific electrodes.

Irrigating fluids used during TURP and endoscopic hysterectomies are hypotonic or isotonic glycine, mannitol, or sorbitol. Hyponatraemia is caused primarily by retention of near-isotonic fluid in the extracellular space. The plasma osmolality may be normal in case of isotonic solutions such as 5% mannitol, or hypo-osmolar if the solution used is hypotonic such as 1.5 percent glycine or 3.3% sorbitol. Whether the symptoms derive from the presence of retained solutes, the metabolic products of such solutes, hypotonicity, or the low serum sodium concentration remains unclear.

**Hypo-osmolar hyponatraemia**

Most cases of hyponatraemia are associated with a low plasma osmolality (< 275 mosm/kg) reflecting a net gain of free water. Patients can be classified according to the total body volume state of the patient.

**Hypovolaemic hyponatraemia** occurs when there is loss of both water and sodium, but sodium loss exceeds that of water. As a result of hypovolaemia, vasopressin release and the thirst mechanism are activated leading to increased water retention, thus further aggravating the hypo-osmolar state. Causes of water and sodium loss could be:

1. Renal causes, which include:
   a. Salt wasting nephropathies such as polycystic kidney disease and chronic pyelonephritis in which there is loss of sodium in excess of water.
   b. Hypoaldosteronism.
   c. Use of thiazide diuretics. Although thiazide diuretics are not the most common cause of hyponatraemia, they are the most common causes of severe symptomatic hyponatraemia causing neurological sequelae. Mild asymptomatic hyponatraemia frequently occurs with diuretic use, but does not require a change in therapy. Few patients, particularly elderly females who are volume depleted are at greater risk of developing severe hyponatraemia. It typically develops within three days to three weeks of initiation of therapy. Multiple mechanisms are involved in the pathogenesis of diuretic-induced hyponatraemia. Diuretic-induced volume depletion impairs renal diluting capacity and diuretics block reabsorption in the thick ascending limb in the loop of Henle. Diuretic-induced hypokalaemia and hypomagnesaemia may also contribute to hyponatraemia.

2. Extra-renal causes include: loss of sodium and water from the gut as in diarrhoea and vomiting, or third space collection as in severe burns, pancreatitis, and peritonitis. In this case, sodium and water loss causes both water and sodium reabsorption by the kidneys, but the amount of water reabsorbed is more than the amount of sodium reabsorbed because of the baroreceptor-mediated ADH release and decreased GFR, and increased proximal tubular reabsorption because of hypovolaemia. So there is a relative deficiency of sodium.

**Euvolaemic hyponatraemia** occurs when there is free water gain and negligible sodium loss. These individuals make up the largest single group of hospitalised hyponatraemic patients. In these cases, there is either decreased water excretion or increased water intake. Causes include:

1. Adrenal insufficiency. Hyponatraemia in primary adrenal deficiency is related both to hypocortism and hypoaldosteronism. The water retention is primarily ADH dependent which is related to reduction in blood pressure and cardiac output. ADH secretion may also be directly increased by CRH secretion, which is also increased in primary adrenal insufficiency.

2. Hypothyroidism.

3. Syndrome of inappropriate ADH secretion (SIADH), the most common cause of hyponatraemia in hospitalised patients. Vasopressin is released from the posterior pituitary or an ectopic site inappropriately resulting in decreased free water excretion. In SIADH, there is no
overt hypervolaemia inspite of water retention because only one-third of the water is distributed in the extracellular space. However, there is a modest expansion of the intravascular volume, which results in an increased RPF and GFR. It also results in reduced proximal tubular absorption of sodium, which further contributes to hyponatraemia. Once a steady state is reached, urinary sodium excretion becomes equal to dietary sodium intake. Diagnostic criteria of SIADH are:

a. Hypo-osmolar hyponatraemia
b. Clinical euvoilaemia
c. Inappropriately concentrated urine > 100 mosmol/kg
d. Normal adrenal, cardiac, thyroid, hepatic and renal functions.

Causes of SIADH can be categorised into four major groups: malignancy, pulmonary disease, CNS disease and pharmacological use (Table I).

4. Psychogenic polydipsia or compulsive water drinking is found predominantly in the psychiatric population, particularly in individuals with schizophrenia. These patients often drink over 15 lit of water a day, overwhelming their kidneys’ maximum capacity to excrete free water. This leads to dilutional hyponatraemia with urine osmolality less than 100 mosmol/l.

5. Reset osmostat is a chronic condition where vasopressin osmoreceptors have a lower threshold to trigger vasopressin release. This has been associated with quadriplegia, psychosis, tuberculosis, and chronic malnutrition.

6. Beer potomania is seen in chronic alcoholism. Chronic alcoholics, who already have low dietary sodium and nutritional stores, ingest large quantities (4 - 5 l) of low sodium beer with minimal food intake, can have hyponatraemia. Although the kidneys produce maximally dilute urine, the amount of daily dietary solute intake is so low that the kidneys are unable to maintain isoosmolality leading to water retention and hyponatraemia.

Hypervolaemic hyponatraemia: Here free water gain exceeds sodium gain, resulting in hyponatraemia. This is seen mainly in the setting of increased total body water as occurs in oedematous states such as CHF, hepatic cirrhosis, nephrotic syndrome, and renal failure. In these conditions, although the total body water is increased, the effective arterial volume is decreased. Intravascular volume depletion triggers secretion of ADH, renin-angiotensin, norepinephrine, and thirst. So the intake and retention of water exceeds the intake of sodium leading to dilutional hyponatraemia.

Clinical features

The signs and symptoms of hyponatraemia depend not only on the absolute serum sodium levels but also on the rate of serum sodium decline. While chronic hyponatraemia defined as hyponatraemia for more than 48 hrs may be asymptomatic, acute hyponatraemia of duration < 48 hrs, may result in severe neurological dysfunction. Those at extremes of age are less tolerant to hyponatraemia.

Symptoms of hyponatraemia are listed in Table II.

Table II: Clinical features of hyponatraemia.

<table>
<thead>
<tr>
<th>Serum sodium</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 125 mmol/l</td>
<td>Usually asymptomatic</td>
</tr>
<tr>
<td>120 - 125 mmol/l</td>
<td>Gastrointestinal:</td>
</tr>
<tr>
<td></td>
<td>- Anorexia</td>
</tr>
<tr>
<td></td>
<td>- Nausea</td>
</tr>
<tr>
<td></td>
<td>- Vomiting</td>
</tr>
<tr>
<td>&lt; 120 mmol/l</td>
<td>Neuromuscular:</td>
</tr>
<tr>
<td></td>
<td>- Muscle cramps</td>
</tr>
<tr>
<td></td>
<td>- Generalised weakness</td>
</tr>
<tr>
<td></td>
<td>- Seizures</td>
</tr>
<tr>
<td>&lt; 110 mmol/l</td>
<td>Neurologic:</td>
</tr>
<tr>
<td></td>
<td>- Confusion</td>
</tr>
<tr>
<td></td>
<td>- Disorientation</td>
</tr>
<tr>
<td></td>
<td>- Agitation</td>
</tr>
<tr>
<td></td>
<td>- Delirium</td>
</tr>
<tr>
<td></td>
<td>- Lethargy</td>
</tr>
<tr>
<td></td>
<td>- Stupor</td>
</tr>
</tbody>
</table>

The neurological manifestations are most likely related to
diffuse cerebral oedema, which results from movement of water from extracellular fluid into brain cells. In severe cases, death can result from tentorial herniation and brain stem compression32.

Brain adaptation to hyponatraemia

During hyponatraemia, the brain cells exposed to hypotonic plasma swell because fluid shifts into the brain cells resulting in cellular swelling. The swelling occurs within the confines of the rigid skull leading to reduction in cerebral blood flow. The early adaptation of the brain cells to hyponatraemia is by loss of water into the CSF. This is followed by extrusion of sodium and potassium from the brain cells. This constitutes the early adaptive response34, 35. The late adaptive response occurs with the extrusion of organic osmolytes such as myoinositol, glycerophosphatylcholine, glutamate, glutamine, creatinine, and taurine35, 36. Organic osmolytes account for approximately one-third of the solute loss in chronic hyponatraemia36. If adaptation of the brain is incomplete, raised intracranial tension develops which may eventually lead to death.

Risk factors for developing acute cerebral oedema during hyponatraemia are mentioned in Table III28.

Table III: Risk factors for developing acute cerebral oedema during hyponatraemia.

<table>
<thead>
<tr>
<th>Acute cerebral oedema</th>
<th>Osmotic demyelination syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young menstruating women</td>
<td>Alcoholics</td>
</tr>
<tr>
<td>Elderly women on thiazides</td>
<td>Malnourished patients</td>
</tr>
<tr>
<td>Children</td>
<td>Hypokalaemic patients</td>
</tr>
<tr>
<td>Psychiatric polydipsic patients</td>
<td>Burn victims</td>
</tr>
<tr>
<td>Hypoxaemic patients</td>
<td>Elderly women on thiazide diuretics</td>
</tr>
<tr>
<td></td>
<td>Liver transplant patients</td>
</tr>
</tbody>
</table>

Osmotic demyelination syndrome (ODS) is associated with rapid correction of hyponatraemia37-39. The adaptive response of the brain creates a potential problem for therapy. A rapid increase in the plasma sodium concentration can lead to osmotic demyelination syndrome, previously known as central pontine myelinolysis. This rapid cellular dehydration originally was identified in the pons, but now has been identified in other areas of the brain40. Because of the organic solute loss that occurs during adaptation, the brain cells become hypotonic to the extracellular fluid during correction of hyponatraemia. As a result, water is drawn from the brain cells and brain volume shrinks. Since there is a delay in the reaccumulation of organic osmolytes, there is a higher concentration of inorganic ions as compared to the organic osmolytes. This probably has a role in the pathogenesis of myelinolysis35. Table III enlists the various risk factors for development of ODS28, 41. The clinical manifestations of ODS may be delayed for 2 - 6 days after the elevation of serum sodium and include dysarthria, dysphagia, paraparesis or quadriplegias, and rarely even seizures or coma37, 42, 43. Demyelinating lesions can be detected by MRI and appear as areas of increased signal activity on T2-weighted images and as areas of decreased signal intensity on T1-weighted MRI scans28. ODS is associated with a very poor prognosis and there is no effective therapy, although plasmapheresis and IV immunoglobulins have been tried with variable success44.

Management of hyponatraemia

The treatment of hyponatraemia requires a proper assessment of the patient so as to determine the cause of hyponatraemia. The two primary goals of therapy are to initiate the treatment of the underlying condition and to restore the normal serum osmolality without causing an iatrogenic complication. Mild asymptomatic hyponatraemia

Journal, Indian Academy of Clinical Medicine • Vol. 7, No. 2 • April-June, 2006 95
slowly these patients fare better.  

- Chronic hyponatraemia along with associated risk factors is associated with permanent neurologic sequelae than acute hyponatraemia.
- Patients with chronic hyponatraemia are more likely to develop ODS as compared to those with acute hyponatraemia.

Based on these evidences, certain guidelines can be made for treatment of severe hyponatraemia. Hypertonic saline is clearly indicated in patients who are both severely symptomatic and their serum sodium concentration is less than 120 meq/l. Patients with milder symptoms and serum sodium < 105 meq/l may also be given hypertonic saline.

Figure 1 shows a suggested algorithm for the diagnosis and management of hyponatraemia.

Hyperosmolar and iso-osmolar hyponatraemia patients do not require immediate correction of hyponatraemia; instead, reversal of the underlying disorder, such as hyperglycaemia is sufficient.

**Hypo-osmolar hyponatraemia:** Treatment of hypo-osmolar hyponatraemia depends on the volume status of the patient, severity of hyponatraemia, and the duration of hyponatraemia.

In patients with severe symptomatic hyponatraemia, urgent treatment is necessary to prevent the complication of cerebral oedema.

---

**Fig. 1: Algorithm for management of Hyponatraemia.**
In hypervolaemic patients, water and sodium restriction are usually enough but in some very severe cases (presence of seizures or coma) hypertonic (3%) saline along with a loop diuretic may be used. This helps in removing the excess of free water. These patients are however usually chronically hyponatraemic and care should be taken so as to avoid rapid or over-correction.

Euvolaemic patients can be subdivided into 2 groups: those with concentrated urine (Uosm > 100 mosm/kg), and those with a dilute urine (Uosm < 100 mosm/kg).

The first group includes mainly patients with SIADH. These patients need to be treated according to the severity and duration of their symptoms. In severely symptomatic patients, particularly those with Na+ < 120 meq/l, hypertonic saline should be used. The second group includes psychogenic polydipsia and reset osmostat where simple water restriction is enough. In beer potomania, patients should be treated with isotonic saline to replenish low sodium stores.

Hypovolaemic patients with hyponatraemia initially require isotonic saline for concurrent salt and water repletion.

Hyponatraemic patients with hyponatraemia initially require isotonic saline for concurrent salt and water repletion. Once the patient has reached a clinically euvolaemic state, there is no longer a stimulus for vasopressin release allowing self-correction of hyponatraemia. Therefore, once euvolaemia is achieved, hypotonic saline should be used instead of isotonic saline. This will prevent a rapid correction of the sodium levels.

**Fluid resuscitation rate**

There is no consensus about the optimal treatment of symptomatic hyponatraemia. Nevertheless, correction should be made of a sufficient pace and magnitude to reverse the manifestations of hyponoticity, but not be so rapid and large as to pose a risk of ODS. Most reported cases of ODS have occurred when the rate of correction exceeded 12 mmol/l/day, but isolated cases have been reported with corrections of 9 - 10 mmol/l/day. So the current consensus is that the rate of correction should not be more than 8 mmol on any day. Initially, the rate of correction may be rapid, but this also should not be more than 1 - 2 mmol/per hour for 3 - 4 hours, or even briefly if the symptoms improve. Recommended indications for stopping the rapid correction of symptomatic hyponatraemia is the cessation of life-threatening manifestations, moderation of other symptoms, or the achievement of a serum sodium concentration of 125 to 130 mmol/l.

In asymptomatic patients, the rate of correction should not exceed 1.5 mmol/l/day and less than 8 - 10 mmol/l in 24 hours. It is important to note that these asymptomatic patients are more likely to develop ODS with higher infusion rates as the brain in such patients has undergone adaptation.

The rate of infusion of the selected solution can be determined by the following formula:

\[
\text{Serum Na}^+ \text{ change with } 1 \text{ l of IVF} = \frac{\text{Na}^+ \text{ content in IVF} - \text{Measured Serum Na}^+}{[\text{Correction factor} \times \text{weight (kg)} + 1]}
\]

The correction factor is actually the total body water as a fraction of the total body weight. The correction factor varies according to age and sex as shown in Table IV. The amount of fluid to be infused in l/hr can be calculated as follows:

\[
\text{Amount of fluid (l/hr)} = \frac{(\text{total body water} + 1) \times \text{rate of correction (meq/l/hr)}}{\text{Infusate Na}^+ - \text{measured Na}^+}
\]

**Table IV: Correction factor for calculation of amount of sodium to be infused.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Correction factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric</td>
<td>0.6</td>
</tr>
<tr>
<td>Male, non-elderly</td>
<td>0.6</td>
</tr>
<tr>
<td>Female, non-elderly</td>
<td>0.5</td>
</tr>
<tr>
<td>Male, elderly</td>
<td>0.5</td>
</tr>
<tr>
<td>Female, elderly</td>
<td>0.45</td>
</tr>
</tbody>
</table>

For example, in a 60 kg elderly woman who presents with a significant altered mental status and a sodium concentration of 110 meq/l, hypertonic saline should be instituted immediately. The rate of correction in this case should initially be 2 meq/l/hr for the first two to three hours. The amount of fluid required is [(0.45*60 = 27) +1]2/513 - 110 = 0.139 l or 139 ml in the first hour.

The sodium concentration of various commonly used solutions is shown in Table V.
Table V: Various IV fluids used in the treatment of hyponatraemia and hypernatraemia and the amount of sodium in the fluid.

<table>
<thead>
<tr>
<th>Infusate</th>
<th>Infusate Na⁺ (mmol per litre)</th>
<th>Extracellular fluid distribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% Sodium chloride in water</td>
<td>855</td>
<td>100</td>
</tr>
<tr>
<td>3% Sodium chloride in water</td>
<td>513</td>
<td>100</td>
</tr>
<tr>
<td>0.9% Sodium chloride in water</td>
<td>154</td>
<td>100</td>
</tr>
<tr>
<td>Ringer's lactate solution</td>
<td>130</td>
<td>97</td>
</tr>
<tr>
<td>0.45% Sodium chloride in water</td>
<td>77</td>
<td>73</td>
</tr>
<tr>
<td>0.2% Sodium chloride in water</td>
<td>34</td>
<td>55</td>
</tr>
<tr>
<td>5% Dextrose in water</td>
<td>0</td>
<td>40</td>
</tr>
</tbody>
</table>

Other therapeutic options include:

1. Urea: it induces water loss by providing an osmotic load. Moreover, urea diffuses into the brain and its accumulation prevents excessive brain dehydration. It could also trigger the accumulation of organic osmolytes in brain51.

2. Demeclocycline and lithium: these act on the collecting tubule, reducing its responsiveness to ADH. They can be considered for patients with persistent hyponatraemia unresponsive to water restriction, high salt intake, and a loop diuretic52.

3. Vasopressin receptor antagonists selective for the V2 receptor may be beneficial in patients with SIADH and in hyponatraemic patients with CHF and cirrhosis53.

**Classification of Hypernatraemia**

Hypernatraemia is always associated with hypertonicity of the plasma. It can therefore be classified according to the volume status of the patient into the following categories:

1. Hypovolaemic hypernatraemia: Here the fluid lost is hypotonic, so free water loss exceeds sodium loss, resulting in hypernatraemia. Water loss can be extra-renal or renal, and these patients display signs of hypovolaemia such as tachycardia, poor skin turgor, orthostatic hypotension, and dry mucous membranes.

   a. Extra-renal loss can occur through the skin, as with profuse sweating. Sweat is hypotonic and patients who have fever, or who are exposed to very high temperatures and have limited access to water or decreased thirst, can become hypernatraemic. Similarly, patients with burns or skin diseases such as pemphigus vulgaris can also have hypernatraemia. Alternatively, extra-renal loss can occur through the GIT as in diarrhoea (especially if hypertonic fluid is used for volume replacement, or there is inadequate volume replacement), nasogastric suctioning, vomiting, and third space collection (pancreatitis or bowel obstruction). In all these cases, the urinary sodium concentration is low (< 10 meq/l) and the urine osmolality is high (> 700 mosm/kg)3 22.

   b. Renal loss can occur with diuretic use and severe osmotic diuresis resulting from hypertonic mannitol administration, severe glycosuria in diabetics, or elevated urea in the setting of post-
obstructive diuresis. In these cases, urinary Na⁺ is elevated (> 20 meq/l) and urine is isotonic or hypotonic (< 700 mosm/kg)³.

2. Euvolaemic hypernatraemia: In this case, there is pure water loss without the signs of hypovolaemia. Patients appear euvolaemic despite free water loss because most of the water is lost from intracellular space. The water loss can result from extra-renal or renal causes.

a. Extra-renal causes: Extra-renal loss of water can occur through skin or respiratory tract. Healthy adults average 500 ml/day insensible loss of water through the skin – even in the absence of discernible sweating²². The normal insensible respiratory loss is also 500 ml/day²². This can increase greatly in the presence of fever, respiratory infection, high altitude, or hyperventilation during mechanical ventilation. Skin and respiratory losses may reach up to several litres/day, but this is easily replaced by most people. Hypernatraemia results when people do not have access to water or fail to drink. Relative hypodipsia is common in elderly patients with normal mental functions and neurological status. Primary hypodipsia is another cause of extra-renal loss of free water, which results from destruction of thirst centres in the hypothalamus, caused by multiple disorders such as hypothalamic tumours, granulomatous diseases, vascular abnormalities, and trauma⁵⁶. Essential hypernatraemia is a variant of primary hypodipsia in which there is an upward resetting of the osmotic thresholds for thirst and vasopressin release, but their response to haemodynamic stimuli remains normal⁵⁷.

b. Renal causes: Renal loss of free water is due to diabetes insipidus (DI). DI is a disorder characterised by either an absence of ADH secretion (central or neurogenic DI) or a failure of the kidney to respond to ADH (nephrogenic DI)⁵⁸. In diabetes insipidus, lack of ADH or its effect results in loss of large volumes of dilute urine and a consequent rise in plasma osmolality and serum Na⁺ concentration. Thirst is stimulated and alert patients are able to maintain their plasma osmolality within the normal range. Hypernatraemia does not occur unless there is a concomitant defect in the thirst mechanism or restricted access to water. These patients are euvolaemic because water is lost both from the extracellular as well as intracellular space. Causes of DI are enlisted in Table VI³, ⁵⁸, ⁵⁹.

2. Hypervolaemic hypernatraemia: It results from pure Na⁺ overload. It is rare and frequently iatrogenic. This is seen in excessive sodium bicarbonate administration during cardio-pulmonary resuscitation, over-correction of hyponatraemia, hypertonic dialysate in peritoneal and haemodialysis, and hypertonic enteral and parenteral hyperalimentation. Non-iatrogenic causes include mineralocorticoid deficiency and near drowning in salty water.

Causes of hypernatraemia are enlisted in Table VI³, ⁵⁹.

**Table VI: Causes of hypernatraemia.**

<table>
<thead>
<tr>
<th>Hypernatraemia due to net water loss</th>
<th>Pure water (euvolaemic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unreplaced insensible losses (dermal and respiratory)</td>
<td>Hypodipsia</td>
</tr>
<tr>
<td>Neurogenic (central) diabetes insipidus</td>
<td>Post-traumatic</td>
</tr>
<tr>
<td>Tumours, cysts, histiocytosis, tuberculosis, sarcoidosis</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Aneurysms, meningitis, encephalitis, Guillain–Barré syndrome</td>
<td>Ethanol ingestion (transient)</td>
</tr>
<tr>
<td>Nephrogenic diabetes insipidus</td>
<td>Congenital nephrogenic diabetes insipidus</td>
</tr>
<tr>
<td>Acquired nephrogenic diabetes insipidus</td>
<td>Renal disease (e.g., medullary cystic disease)</td>
</tr>
<tr>
<td>Hypercalcaemia or Hypokalaemia</td>
<td>Drugs (lithium, demeclocycline, foscarne, methoxyflurane, amphotericin B, vaspressin V₂–receptor antagonists)</td>
</tr>
<tr>
<td>Hypotonic fluid (hypovolaemic)</td>
<td>Renal causes</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Osmotic diuresis (glucose, urea, mannitol)</td>
</tr>
<tr>
<td>Post-obstructive diuresis</td>
<td>Polyuric phase of acute tubular necrosis</td>
</tr>
<tr>
<td>Intrinsic renal disease</td>
<td>Gastrointestinal causes</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Nasogastric drainage</td>
</tr>
</tbody>
</table>
Enterocutaneous fistula
Diarrhoea
Use of osmotic cathartic agents (e.g., lactulose)

Cutaneous causes
Burns
Excessive sweating
Pemphigus vulgaris

Hypernatraemia due to hypertonic sodium gain (hypervolaemic)
Hypertonic sodium bicarbonate infusion
Ingestion of sodium chloride
Ingestion of sea water
Sodium chloride-rich emetics
Intrauterine injection of hypertonic saline
Hypertonic sodium chloride infusion
Hypertonic dialysis
Primary hyperaldosteronism
Cushing’s syndrome

Clinical features: The principal manifestations of hypernatraemia largely reflect CNS dysfunction and are prominent when the increase in serum Na⁺ is large or occurs rapidly. Neurological symptoms occur as a consequence of cellular dehydration in the brain²,³. Loss of brain volume results in traction on the cerebral vessels, which may then tear. It is also associated with cerebral bleeding, subarachnoid haemorrhage, and venous sinus thrombosis³,⁴. So the threshold for getting a CT scan in a patient with hypernatraemia and altered mental status should be low. Convulsions are usually absent and are more commonly seen in cases of inadvertent sodium loading or aggressive rehydration. Signs and symptoms of hypernatraemia are listed in Table VII.

Table VII: Clinical features of hypernatraemia.

Anorexia, nausea, and vomiting
Altered mental status, agitation, irritability
Stupor, lethargy, and coma
Signs of neuromuscular hyperactivity: hyperreflexia, spasticity, tremor, asterixis, chorea, and ataxia.
Focal neurological deficits: hemiparesis and extensor plantars.

Management of hypernatraemia
Hypernatraemia (Na⁺ > 145 meq/l)
Plasma osmolality > 290 mosm/kg

Fig. 2: Algorithm for management of Hypernatraemia.
Management

Proper management of hypernatraemia requires a two-pronged approach: addressing the underlying cause and correcting the prevailing hypertonicity. Figure 2 shows an algorithm for diagnosis and treatment of hypernatraemia.

The treatment of hypernatraemia depends on the volume status of the patient. Patients with hypovolaemic hypernatraemia should be treated with isotonic saline particularly if there is evidence of circulatory collapse. Otherwise, if the volume depletion is mild without evidence of circulatory failure, hypotonic fluids such as one-quarter saline (0.2% saline), half isotonic saline (0.45%), pure water, or 5% dextrose should be used. Even in cases of circulatory failure, once haemodynamic stability is achieved, hypotonic fluids should be used. Euvolaemic patients also require pure water replacement with hypotonic saline or free water. When administering dextrose containing solutions, blood glucose should be closely monitored, because hyperglycaemia will worsen the hypertonic state and may lead to osmotic diuresis. Patients with central DI can be given 5 - 10 units of aqueous vasopressin subcutaneously every 3 - 4 hours. Serum sodium concentration and urinary specific gravity should be monitored every 2 - 4 hours to prevent over-correction. Vasopressin is preferred over desmopressin because vasopressin has a shorter duration of action. This will however be ineffective in nephrogenic DI. Hypervolaemic patients have sodium overload, and they require natriuresis with a loop diuretic and free water replacement. Dialysis may be required in patients with severe renal failure to achieve natriuresis.

Rate of correction of hypernatraemia

The rate of correction of hypernatraemia depends on the rate of development of hypernatraemia. In cases of acute hypernatraemia (< 48 hrs), rapid correction improves the prognosis without increasing the risk of cerebral oedema, because accumulated electrolytes are rapidly extruded from the brain cells. In such patients, the serum sodium can be reduced by 1 meq/l/hour. In chronic hypernatraemia, a slower pace is required, as full dissipation of accumulated brain solutes during adaptation occurs over a few days. In these patients the appropriate rate of correction is 0.5 meq/l per hour. The target should be to decrease the serum sodium by 10 meq/l in one day, except in those in whom the disorder has developed over a matter of hours. The goal of treatment is to achieve a sodium concentration of 145 meq/l. Lowering the plasma osmolality with hypotonic fluids too rapidly can lead to iatrogenic cerebral oedema because of osmotic shift of water into the brain. Allowances must be made for ongoing hypotonic fluid loss (obligatory or incidental) while calculating the fluid requirement. The amount of fluid required can be calculated using the following formula:

\[
\text{Amount of fluid (l/hr)} = \frac{(\text{total body water} + 1) \times \text{rate of correction (meq/l/hr)}}{\text{Infusate Na}^- - \text{measured Na}^+}
\]

For example, in an elderly 80 kg male with a serum sodium concentration of 160 meq/l, the rate of decrease should be 0.5 meq/l/hr. The amount of 0.45% saline required will be \([(0.5 \times 80) + 1] \times 0.5 = 246 \text{ l or 246 ml/hr.}

Table V lists the characteristics of various solutions used in management of hypernatraemia.

Both hypernatraemia and hyponatraemia initially present with non-specific signs and symptoms and can only be diagnosed if a high index of suspicion is maintained for these conditions. The treatment of both these conditions is tricky, as over-treatment can lead to potentially dangerous complications and under-treatment is associated with significant mortality and morbidity. It is therefore essential to monitor the serum sodium concentration every 2 - 4 hours to prevent treatment related complications. Frequent neurological examination should also be performed during treatment as it can help in early detection of ODS and cerebral oedema.

References

1. Genanri FJ. Hypo-hypernatraemia: disorders of water


30. Tanneau RS, Henry A, Rouhart F et al. High incidence of neurologic complications following rapid correction of


