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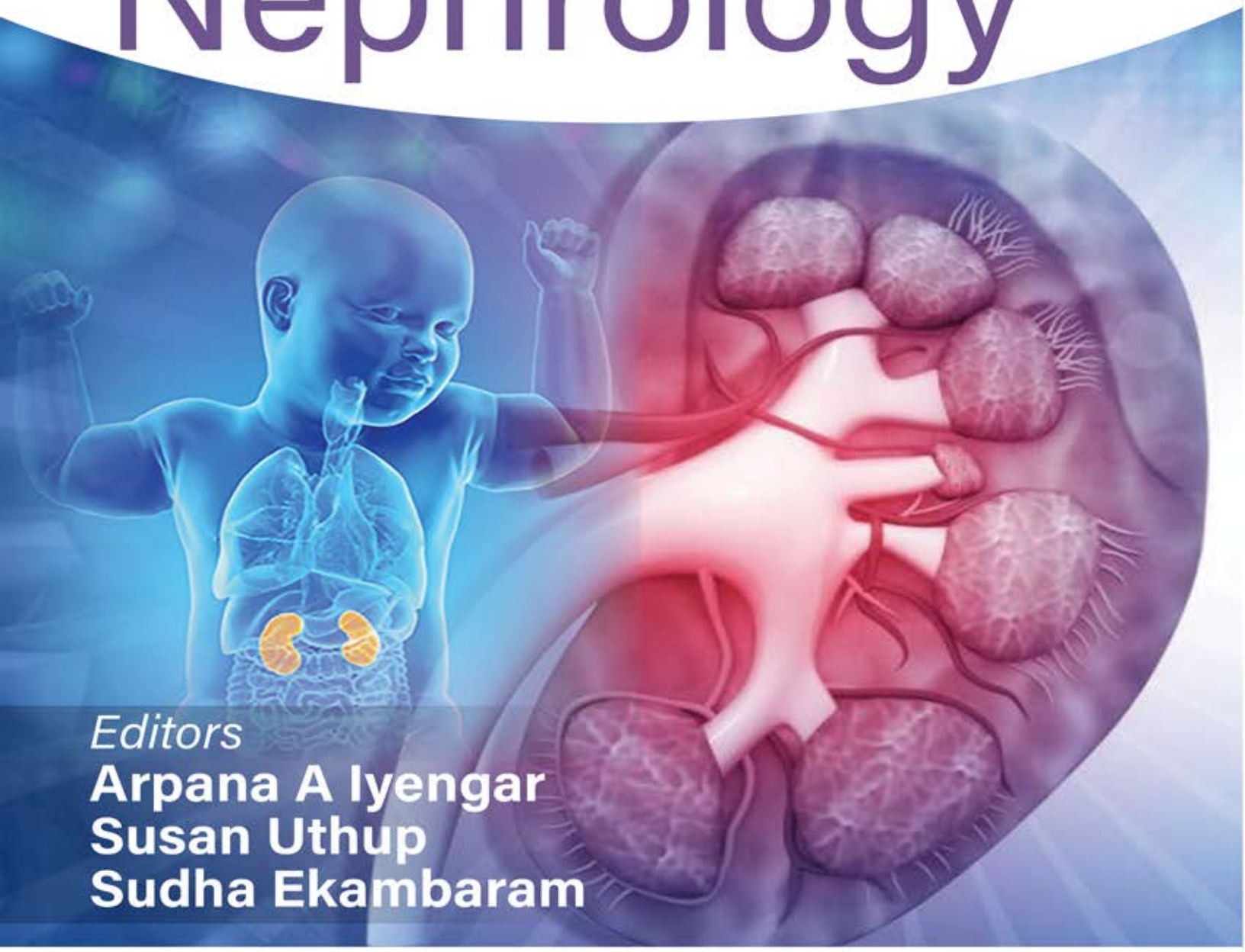
# Nammalwar's Principles and Practice of Pediatric Nephrology



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3rd Edition

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CHAPTER

# 4.2

# Disorders of Sodium: Hyponatremia and Hypernatremia

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## INTRODUCTION

Sodium is the major cation in extracellular fluid (ECF). Shift in water is mostly a result of changes in plasma sodium concentration; hence, dysnatremias mostly are a reflection of disorders of water balance. A significant portion of our body is constituted by water. The term "total body water" (TBW) denotes the total quantity of fluid in the human body and it varies with age. It is highest (75–80%) in premature infants and decreases with age. Term newborns have TBW of 70% and at the age of 1 year, it is 60%. The correction factors to assess body water according to age is given in **Table 1**.[1]

Total body water is distributed in two major compartments, around two-thirds of TBW is inside the cells, i.e., intracellular fluid (ICF); the rest one-third is outside cells, i.e., ECF. ECF is further distributed in three compartments—interstitial fluid, plasma, and transcellular fluid. In children above 1 year of age, ICF and ECF water are 40% and 20%, respectively, of body weight. Out of the ECF volume, 75% of the volume is present in the interstitial space (i.e., 15% of body weight), and 25% of that water is in the plasma (5% of body weight). The distribution of TBW is depicted in **Figure 1**.[2]

## SODIUM AND WATER BALANCE

Normally, the human body maintains plasma osmolality within a relatively narrow range (280–295 mOsm/kg) and serum sodium concentration is between 135 and 145 mEq/L. Complex neurohumoral regulations control sodium homeostasis and water balance. The autonomic nervous system is a key regulator of renin secretion, renal hemodynamics, and tubular fluid reabsorption. Sympathetic stimulation causes renin release and proximal tubular fluid reabsorption. Direct actions of the autonomic nervous system regulate short-term fluid regulation in response to changes in sodium and water balance while aldosterone and antidiuretic hormone (ADH) are responsible for long-term regulation of sodium and water reabsorption.[3]

Antidiuretic hormone is otherwise known as arginine vasopressin (AVP) and is a product of a subset of magnocellular neurons in the paraventricular nuclei (PVN) and supraoptic nuclei (SON) of the hypothalamus. The axons from magnocellular neurons project to posterior pituitary via the pituitary stalk and their terminals contain neurosecretory granules, which store AVP till it is released. AVP has a carrier protein neurophysin II (NPII) and both are coded by a single gene on chromosome 20p13. Both ADH and NPII are produced as a single polypeptide. Then, it is cleaved within the neurosecretory granules and before release, reassembled into AVP-NPII complexes. Posterior pituitary has significant storage capacity of AVP that can last up to 30–50 days under basal circumstances and up to 5–10 days during maximal stimulation. Hence, it takes weeks after a causal insult defect in AVP synthesis to become clinically manifest and partial

**TABLE 1:** Correction factor to assess total body water (TBW).[1]

| *Age* | *Correction factor* |
|---|---|
| Newborn | 0.8 |
| Infant | 0.7 |
| Child | 0.6 |
| Adult male | 0.6 |
| Adult female | 0.5 |
| Elderly male | 0.5 |
| Elderly female | 0.45 |

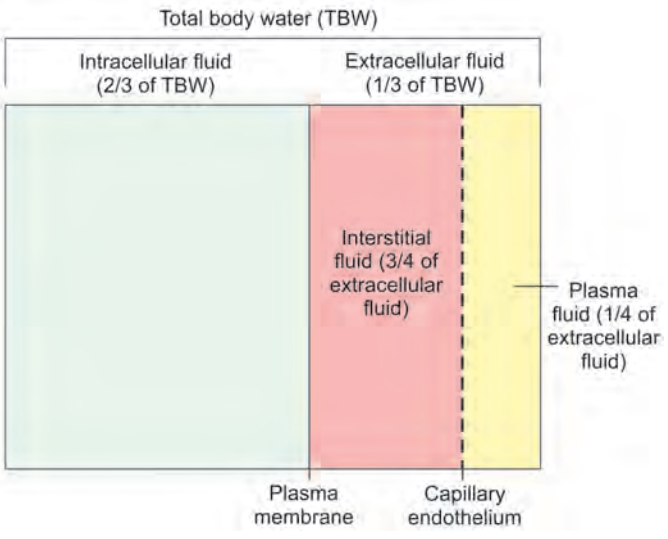


**Fig. 1:** Distribution of total body water.[2]

defects may be apparent only after prolonged deprivation of water.

Antidiuretic hormone secretion and thirst are both stimulated effectively by a small (1%) increase of osmolality and a high (5–10%) decrease in blood volume.[3] Even 1% increase in plasma osmolality is sensed by osmoreceptors in the hypothalamus (organum vasculosum of the lamina terminalis and anterior hypothalamus) which cause secretion of AVP. Normally, baseline AVP levels are low, 0.5–2 pg/mL, and rises only when plasma osmolality increases to >280 mOsm/kg. Maximal urine concentration (urine osmolality 900–1,200 mOsm/kg) is achieved at plasma AVP levels of 5–6 pg/mL. Even though plasma AVP can increase to >6 pg/mL when plasma hyperosmolality is ongoing, urine osmolality cannot be further increased since renal medullary gradient is limited. AVP secretion is inversely affected by alterations in blood volume that is, it is stimulated by 8–10% reduction in circulating blood volume and inhibited by rises in intravascular volume.

Antidiuretic hormone release is less sensitive to hypovolemia but, whenever there is a significant reduction in intravascular volume, volume takes priority over osmolality. Thus, the body enhances ADH secretion which counteracts the effect of hypo-osmolality. This is mediated via high-pressure baroreceptors located in the carotid sinus and aortic arch and low-pressure baroreceptors located in the atria and pulmonary venous circulation. These receptors are stimulated by stretch due to increase in intravascular volume and send blood volume and pressure signals through glossopharyngeal and vagus nerves, respectively, to the brainstem. From the brainstem, nerve fibers project to hypothalamic PVN and SON causing inhibition of AVP secretion. In addition to osmo- and baroregulation, there are several other factors which affect secretion of AVP. AVP release is stimulated by stress, nausea, pain, and many drugs and is inhibited by various factors.

The antidiuretic effect of AVP is mediated by V2 vasopressin receptor (V2R). This receptor is located on the basolateral side of renal collecting duct epithelial cells and is a G protein-coupled receptor, coded by X chromosome. Activation of V2R causes increase in cyclic adenosine monophosphate (cAMP) inside the cells, causing transport of aquaporin 2 (AQP-2) water channels to the apical membrane of collecting duct epithelial cells, leading to augmented permeability of these cells to water and thus, antidiuresis.

An intact thirst mechanism governs adequate water intake, which in turn is controlled by changes in intravascular volume, plasma osmolality, and blood pressure. An increase in plasma osmolality by 2–3% and decrease in effective blood volume by 4–10% stimulates thirst. Although thresholds that stimulate thirst are more than that for secretion of AVP, adequate thirst is crucial when there is AVP deficiency or insensitivity.

Our body does not have the ability to sense sodium. However, the kidneys have specialized receptors in juxtaglomerular apparatus that can detect flow of tubular fluid and its sodium concentration. This is accomplished by the macula densa cells, which send information to juxtaglomerular cells, situated at the arteriolar walls to reduce glomerular filtration rate (GFR) by a tubuloglomerular feedback mechanism. Similarly, reduced tubular flow leads to a rise in GFR. This mechanism ensures that body fluids are not lost in states with glomerular hyperfusion. In addition, renin–angiotensin–aldosterone system (RAAS) is a critical regulator of blood pressure, intravascular volume, and electrolyte balance.

Atrial natriuretic peptide (ANP) and brain natriuretic peptides result in vasodilation, natriuresis, diuresis, and decrease systemic vascular resistance and arterial blood pressure. They also reduce release of ADH and aldosterone. Sodium excretion is increased both by enhancing GFR and suppressing salt reabsorption. Wall stretch of heart cavities by increased blood volume causes secretion of natriuretic peptides (NPs). Angiotensin II and sympathetic stimulation also boost secretion of NPs, which reach the target organs via blood circulation. NP target receptors have been recognized in several sites including kidneys, adrenal glands, and blood vessels.

### Osmolality and Tonicity

Sodium by virtue of being the dominant ECF cation, is the chief determinant of serum tonicity and osmolality. Osmolality is defined as the number of dissolved particles per kilogram of solvent. It is measured by osmometer or calculated as a sum of the solutes present in the solution. Serum osmolality is maintained at a normal range of 285–295 mOsm/kg.

Serum osmolality can be calculated by the formula:

Serum osmolality = (2 × serum Na) + (Glucose/18) + (BUN/2.8)

(Na and K are measured in mmol/L, glucose and BUN are measured in mg/dL).

Tonicity is the effective osmolality, i.e., it indicates the concentration of solutes that can exert osmotic force across the semipermeable membrane. So, only solutes, which cannot freely cross the membrane, will contribute to tonicity. In other words, solutes, which can easily move through the cell membrane like urea, do not contribute to tonicity and are considered as ineffective osmoles. Tonicity can be calculated by the following equation:

Serum tonicity = 2 × [Na] + [glucose]/18 (when glucose is measured in mg/dL)

## HYPONATREMIA

Hyponatremia is one of the most common electrolyte abnormalities in children and can lead to significant morbidity and mortality, particularly in subjects in whom change in serum sodium is acute and rapid. Hyponatremia is defined as a serum or plasma sodium <135 mEq/L and severe hyponatremia as a level <125 mEq/L.

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## Signs and Symptoms

Signs and symptoms of hyponatremia vary based on its duration and severity and can range from mild to severe to life-threatening.

### *Acute Hyponatremia*

Neurologic dysfunction is the most common manifestation of hyponatremia. Rate of change of sodium levels is more important than the absolute degree of hyponatremia. Fast alterations in sodium levels are less well tolerated than slow changes. As the serum sodium decreases, there is development of osmotic gradient between the intravascular and intracellular spaces, leading to movement of water from extracellular space to intracellular space. There acute and chronic cellular regulatory mechanisms attenuate cell volume shifts, which can minimize the volume shifts. This cerebral adaption to hyponatremia is an important factor to consider while we treat hyponatremia. When the change in serum sodium levels are more rapid and of greater degree, regulatory mechanisms do not get enough time to minimize cell volume change but also these changes will be less effective. Since skull is a closed space with limited free space, such rapid fluid shifts causes significant increase in volume of the brain and cause cerebral edema leading to neurologic manifestations.

Serum sodium levels >125 mEq/L may not create any specific clinical manifestations, and patients can have only the symptoms and signs of their underlying acute illness. As the serum sodium decreases acutely to <125 mEq/L, neurologic symptoms begin to appear, beginning with nausea and malaise. Headache, anorexia, restlessness, lethargy, muscle cramps, obtundation, and seizures can appear as serum sodium continues to falls to <120 mEq/L.

### *Chronic Hyponatremia*

Chronic hyponatremia is defined as hyponatremia persisting more than 48 hours. When low plasma sodium levels exist for more than 1 day or develop slowly over several days, cerebral adaptation mechanisms reduce the expansion in cell volume and reduce the occurrence of cerebral edema. These patients may not manifest significant symptoms till the serum sodium gets very much depressed or another acute event leads to a more severe reduction in sodium levels. However, there can be subtle neurologic manifestations such as restlessness, irritability, fatigue, or weakness.

## Evaluation and Diagnosis

The first step in evaluation of hyponatremia is to assess the volume status of the patient and measure the plasma osmolality.[1]

True hyponatremia is characterized by reduction in plasma osmolality. Other types of hyponatremia are not associated with low plasma osmolality and are due to fluid shifts as a result of osmotically active substances like urea, glucose, or mannitol, or as a result of high lipid or protein levels. Patients with true hyponatremia may be further classified according to volume status into euvolemic, hypovolemic, or hypervolemic.

The classification of hyponatremia by plasma tonicity is given in **Table 2**.[4]

**TABLE 2:** Classification of hyponatremia according to plasma tonicity.[4]

| | *Serum sodium* | *Plasma osmolality* | *Typical causes* |
|---|---|---|---|
| Hypotonic | <135 mmol/L | Low (<280 mOsm/kg $H_2O$) | SIADH; CHF; cirrhosis |
| Isotonic | <135 mmol/L | Normal (280–295 mOsm/kg $H_2O$) | Hyperglycemia; pseudohypo-natremia (hyperlipidemia, hyper-proteinemia) |
| Hypertonic | <135 mmol/L | High (>295 mOsm/kg $H_2O$) | Severe hyperglycemia with dehydration; mannitol |

(CHF: congestive heart failure; SIADH: syndrome of inappropriate antidiuretic hormone)

### *Isotonic Hyponatremia (Pseudohyponatremia)*

In pseudohyponatremia, hyponatremia is owing to the presence of hypertriglyceridemia, hypercholesterolemia, or hyperproteinemia. In the above conditions, there is reduction in the plasma water fraction and lesser measured sodium concentration. Around 93% of total plasma volume is contributed by plasma water. Assuming that the plasma sodium concentration is 140 mmol/L, the expected plasma water sodium concentration would be 150 mmol/L. The problem of pseudohyponatremia occurs with indirect ion-selective electrode (ISE) method of measuring sodium levels. ISE measures sodium concentration in total serum after diluting the sample. In hyperproteinemia or hypertriglyceridemia, since the nonaqueous fraction of plasma is increased, the serum contains a lesser volume of plasma water and lower sodium. This problem can be avoided by the use of direct ISE methods as it measures sodium activity in plasma of undiluted samples.

### *Hypertonic Hyponatremia (Translocational Hyponatremia)*

In hypertonic hyponatremic conditions, the serum osmolality is raised to more than 295 mmol/L. Increase in osmolality leads to water shifting out of the cells into ECF and ECF dilution. Hypertonic hyponatremias is most commonly caused by hyperglycemia (in the absence of insulin) and can also be associated with intravenous radiocontrast, mannitol, low-molecular weight dextrans, and sucrose. Since urea can easily cross cell membranes, it is considered an ineffective

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osmole and cannot affect serum tonicity. Hence, uremia does not lead to hypertonic hyponatremia.

Formula for corrected Na calculation in hyperglycemic states:[5]

Corrected Na = measured serum Na + [1.6 × (glucose – 100)/100]

(Na is measured in mmol/L, glucose is measured in mg/dL).

## *Hypotonic Hyponatremia (True Hyponatremia)*

This condition is characterized by decreased serum osmolality (<275 mmol/L). It is further classified depending on the child's extracellular volume status into hypovolemic, euvolemic, and hypervolemic hyponatremia.

*Hypovolemic hyponatremia:* In hypovolemic hyponatremia, there is a loss of TBW and sodium. Often, the child presents with features of dehydration, like nausea, vomiting, tachycardia, and low blood pressure. Sodium and water loss may be of renal or extrarenal origin. Kidneys can be the source of water loss in conditions like renal failure, overzealous diuretic use, renal tubular acidosis, and mineralocorticoid deficiency.[6] Kidney functions are preserved in extrarenal water losses due to sweating, third-space losses like burns, or pancreatitis, heat exposure, diarrhea, vomiting, pulmonary losses, biliary drains, and high-output gastrointestinal fistulas.[6,7] Urinary sodium can be used to differentiate between these two causes (high in renal water loss and low in extrarenal water loss).

Cerebral salt wasting (CSW) is a cause for hyponatremia arising as a result of intracranial disease and mimics syndrome of inappropriate antidiuretic hormone (SIADH) as both are characterized by elevated urine sodium, concentrated urine, and no edema. But the patient is hypovolemic in CSW while in SIADH the patient is euvolemic. CSW can occur as a result of different conditions like intracerebral hemorrhage, stroke, brain tumors, head injury, tuberculous meningitis, and intracranial surgery. The exact mechanism by which diuresis and natriuresis occur in CSW is not known. Differentiation between CSW and SIADH is described in **Table 3**.

*Hypervolemic hyponatremia:* Hypervolemic hyponatremia is characterized by an increase in TBW and reduction in sodium levels. Such children have features of fluid overload, including peripheral edema, ascites, anasarca, or pulmonary edema. Causes include nephrotic syndrome, chronic kidney failure, cirrhosis, or congestive heart failure. In renal failure, urinary sodium levels are high, whereas it is low in patients with cirrhosis, congestive heart failure, or nephrotic syndrome.

*Euvolemic hyponatremia:* In euvolemic hyponatremia, total body sodium levels are normal and intravascular volume is slightly decreased, without clinical features of dehydration.

The various causes and criteria for SIADH diagnosis are given in **Table 4 and Box 1**. SIADH is the most common cause of euvolemic hyponatremia. Other causes are hypothyroidism,

**TABLE 3:** Difference between SIADH and CSW.

| *Features* | *CSW* | *SIADH* |
|---|---|---|
| Dehydration | Present | Absent |
| Serum sodium | Decreased | Decreased |
| Urinary sodium excretion | Increased | Variable |
| Urine osmolality | Increased | Increased |
| Serum osmolality | Low | Low |
| Vasopressin | Low | High |
| Polyuria | Present | Absent |
| BUN | Increased | Normal |
| Blood pressure | Low | Normal or increased |
| ANP | Increased | Normal |
| Treatment | Saline/3% NaCl | Fluid restriction |

(ANP: atrial natriuretic peptide; BUN: blood urea nitrogen; CSW: cerebral salt wasting; SIADH: syndrome of inappropriate antidiuretic hormone)

**TABLE 4:** Common causes of syndrome of inappropriate antidiuretic hormone (SIADH).[1]

| *Category* | *Cause* |
|---|---|
| Malignancy | • Bladder carcinoma<br>• Duodenal carcinoma<br>• Ewing sarcoma<br>• Head or neck carcinoma<br>• Leukemia<br>• Lymphoma<br>• Mesothelioma<br>• Pancreatic carcinoma<br>• Pulmonary carcinoma<br>• Prostatic carcinoma<br>• Sarcoma<br>• Thymoma<br>• Ureteral carcinoma |
| Pulmonary | • Acute respiratory failure<br>• Asthma<br>• Cystic fibrosis<br>• Empyema<br>• Pneumonia<br>• Pneumothorax<br>• Positive pressure ventilation<br>• Tuberculosis |
| Central nervous system | • Acute intermittent porphyria<br>• Acute psychosis<br>• Agenesis of corpus callosum<br>• Atrophy of cerebrum or cerebellum<br>• Brain abscess<br>• Brain tumors<br>• Cavernous sinus thrombosis<br>• Cerebrovascular accidents<br>• Delirium tremens<br>• Guillain-Barré syndrome<br>• Encephalitis<br>• Head trauma<br>• Hydrocephalus |

*Contd…*

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*Contd…*

| Category | Cause |
|---|---|
| | • Meningitis<br>• Multiple system atrophy<br>• Neonatal hypoxia<br>• Rocky Mountain spotted fever<br>• Subarachnoid hemorrhage |
| Medications/drugs | • Alcohol abuse and malnutrition<br>• Butyrophenones<br>• Carbamazepine<br>• Cisplatin<br>• Chlorpropamide<br>• Clofibrate<br>• Cyclophosphamide<br>• Cytoxan<br>• Desmopressin<br>• Ecstasy<br>• Interferon α and γ<br>• Methotrexate<br>• Monoamine oxidase inhibitors<br>• Monoclonal antibodies<br>• Morphine<br>• Nicotine<br>• Nonsteroidal anti-inflammatory drugs<br>• Opiates<br>• Oxcarbazepine<br>• Oxytocin<br>• Phenothiazines<br>• Selective serotonin reuptake inhibitors<br>• Sodium valproate<br>• Thiazide diuretics<br>• Tricyclic antidepressants<br>• Vasopressin<br>• Vinca alkaloids |
| Others | • AIDS<br>• Glucocorticoid insufficiency<br>• Idiopathic<br>• Myxedema<br>• Postoperative period |

**BOX 1:** Diagnostic criteria for syndrome of inappropriate antidiuretic hormone (SIADH).

*Bartter and Schwartz criteria for SIADH:*
- Hypotonic hyponatremia (effective SOsm < 275 mOsm/kg $H_2O$)
- Euvolemia
- Less than maximally dilute urine (UOsm > 100 mOsm/kg $H_2O$)
- Elevated urine sodium excretion (UNa > 30 mEq/L)
- Absence of cirrhosis, chronic kidney failure, heart failure, hypothyroidism, and diuretic usage

*Additional data supporting SIADH diagnosis:*
- Serum uric acid <4 mg/dL
- Fractional excretion of uric acid >10%
- Worsening of hyponatremia with intravenous normal saline infusion relative to serum osmolality
- Plasma vasopressin level inappropriately elevated relative to serum osmolality
- Abnormal response to water load (excretion <80% of 20 mL/kg load in 4 hours with failure to dilute urine to <100 mOsm/ kg $H_2O$

nausea, excessive pain, stress, or water intoxication caused by psychogenic polydipsia. Reset osmostat is the second most common form of SIADH and is seen in a subset of patients with SIADH. Such patients are able to adjust urinary water excretion by regulating secretion of ADH, but their threshold for ADH secretion is at a lower serum osmolality set point, leading to premature release of ADH. Patients are still able to suppress ADH and dilute their urine once their set point is reached but only after suffering significant hyponatremia. This preserved ability to secrete ADH is what distinguishes patients with reset osmostat from other types of SIADH.

## Clinical Evaluation

History taking and clinical examination should be targeted toward identifying the volume status of the child, history of excessive free water intake, and evidence of ADH effect based on urinary output, and evidence of a concentrated urine.[8]

- History of fluid loss (e.g., vomiting, diarrhea, profound bleeding, diuretic therapy) and signs of extracellular volume depletion (e.g., decreased skin turgor, tachycardia, or orthostatic or persistent hypotension) indicate hypovolemia, which is associated with appropriate ADH secretion and retention of free water. In children, the most common cause of fluid loss associated with hyponatremia is gastroenteritis.
- History or clinical finding of edema and ascites is suggestive of hypervolemic conditions with effective circulatory volume depletion, such as heart failure, cirrhosis, or nephrotic syndrome.
- History suggestive of underlying SIADH like brain injury or infection, and pulmonary disease. In SIADH, there is decrease in urine output and inappropriately concentrated urine due to ADH release in spite of low serum sodium concentration and osmolality.
- History of excess water intake indicate primary or psychogenic polydipsia (e.g., older child with psychiatric disease).
- History of diseases associated with excess renal salt losses like CSW or primary tubular disorders (e.g., renal tubular acidosis, Bartter and Gitelman syndromes), or skin loss like cystic fibrosis.
- History of anuria or oliguria may indicate severe kidney impairment with an inability to excrete free water.

## Investigations

Laboratory tests to assess serum and urine osmolality and urine sodium may help in finding the etiology of hyponatremia. Urine osmolality >100 mOsmol/kg in a normovolemic child with hyponatremia should be considered as evidence of impaired water handling as in such situations, normally ADH should be depressed. Such children will most likely have highly concentrated urines with urine osmolality significantly more than plasma osmolality. In contrast, reset osmostat and psychogenic polydipsia are associated with a urine osmolality <100 mOsmol/kg.

An algorithm showing diagnostic approach to hyponatremia is depicted in **Flowchart 1**.[9]

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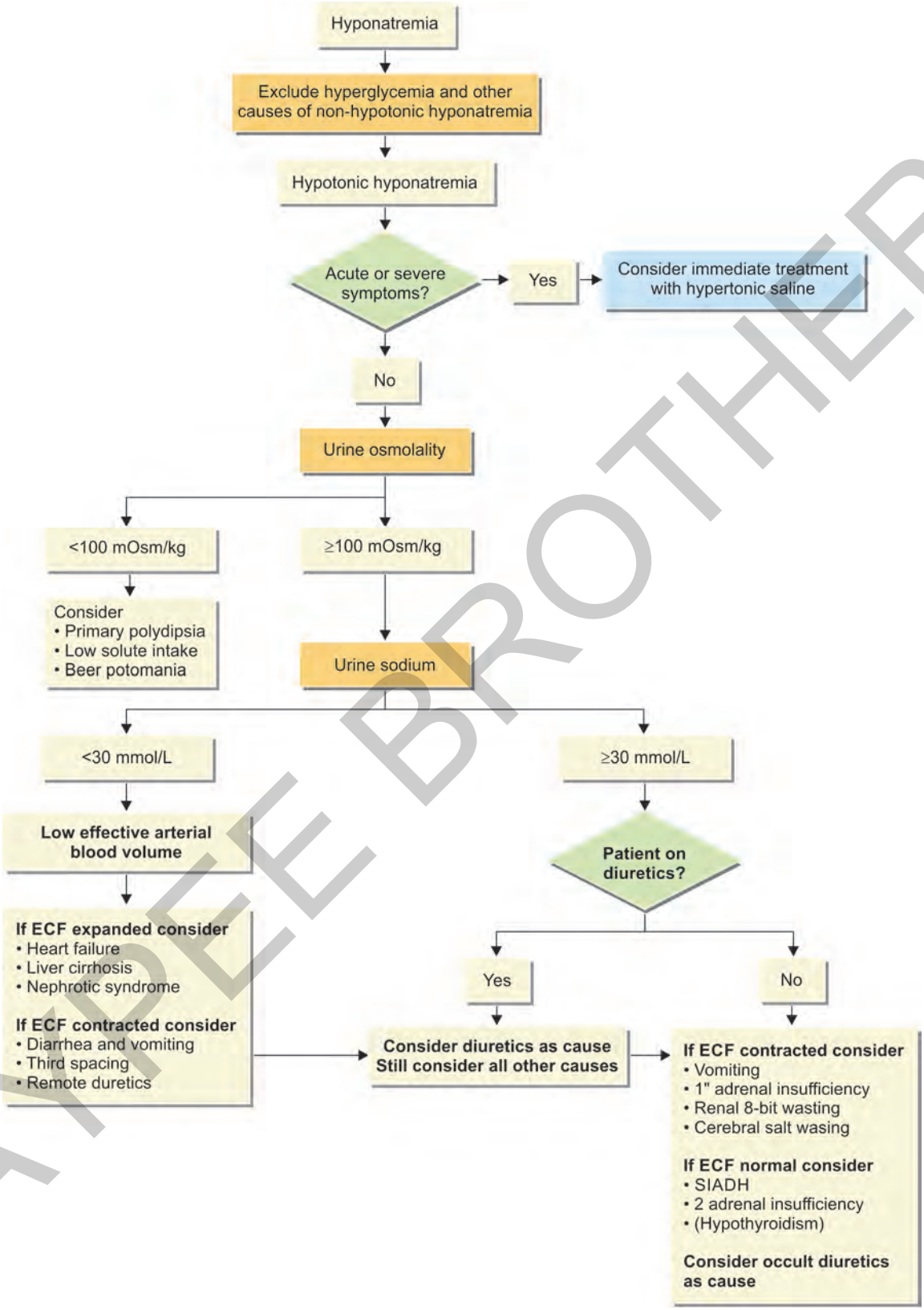
**Flowchart 1:** Diagnostic approach to hyponatremia.[4]




(ECF: extracellular fluid; SIADH: syndrome of inappropriate antidiuretic hormone)

## Treatment

The approach to treatment depends on child's:

- Volume status
- Hemodynamic stability
- Presence or absence of symptoms of hyponatremia
- Severity of the symptoms
- Duration of hyponatremia.

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### *Severe Central Nervous System Symptoms*

Correction of hyponatremia should be immediately started if the patient has seizures or altered mental status. In such children, 3–5 mL/kg of 3% saline (maximum 100 mL) is recommended as initial treatment.[10] The bolus should be given over 10–60 minutes. After giving the initial hypertonic saline bolus, a repeat measurement of plasma sodium should be done and the bolus is repeated if seizures are ongoing. After acute central nervous system (CNS) symptoms have stopped, further sodium correction is done in a slower manner such that the total daily correction is <12 mEq/L (including the initial hypertonic saline infusion). The most important complication of symptomatic hyponatremia is evolving cerebral edema, and in such cases, the risk of morbidity from delayed therapy is more than that of complication from too fast correction and osmotic demyelination. That is why, aggressive initial correction is indicated for the first 3–4 hours (or until the symptoms resolve) at a rate not to exceed a rise in serum sodium of 2 mEq/L per hour.[11-13] Often, an initial goal is to raise the serum sodium by 5 mEq/L over the first several hours as seizures seem to resolve with this therapeutic approach.[14]

### *Chronic Hyponatremia*

In the child with no symptoms or only mild neurologic symptoms (e.g., nausea and malaise), there is no need for hypertonic saline infusion. The serum sodium deficit is calculated using the equation:

Total body Na deficit = (desired serum Na – actual serum Na) × TBW

The targeted rate of correction in this setting is 6–10 mEq/L over 24 hours.

### *Hyponatremia with Normal or Increased Effective Circulating Volume*

In a hyponatremic patient with normal or increased effective circulating volume (ECV) due to SIADH, restriction of water to 60% of usual daily maintenance fluid requirement will lead to slow correction of fluid overload and normalization of plasma sodium as excess free water is excreted. Concurrent administration of maintenance electrolytes and adequate replacement of ongoing fluid and electrolyte losses should be done to prevent further imbalances. It is important to avoid hypotonic fluids since any ongoing ADH secretion will result in free water reabsorption by the distal tubules which will counter hyponatremia correction of via fluid restriction.

In adults, vasopressin receptor antagonists like tolvaptan are used but there is limited data on their use in children and hence they are not used routinely in the treatment of pediatric hyponatremia.

### *Hyponatremia with Decreased Effective Circulating Volume*

Treatment of hyponatremia in a patient with reduced ECV will depend on the underlying condition.

In a hypervolemic child with decreased ECV due to cirrhosis, nephrotic syndrome, or heart failure, treatment is fluid restriction and treatment of the underlying etiology condition. In such children, edema and ascites are the results of retention of free water by the kidneys and its movement from the vascular into interstitial spaces. When fluids are restricted, there is slow rebalancing of preexisting water overload and total body sodium, thus preventing further worsening of symptoms.

In contrast, children with true depletion of ECV due to hypovolemia, like in gastrointestinal losses, there is usually a reduction in both TBW and salt. In such cases, the treatment is to administer isotonic fluid, which will lead to restoration of circulating volume and improvement in blood flow to the kidneys. The administered isotonic fluid will remain in the ECV, which leads to inhibition of the activated renin–angiotensin–aldosterone axis (RAAS system) and ADH release. This in turn will reduce free water reabsorption which is the mediator for hyponatremia. The patient should then continue to be administered sufficient water and sodium to replace current and ongoing losses which will restore fluid and sodium balance.

## Clinical Case Scenario

A 6-year-old girl admitted with suspected intracranial tumor has sudden worsening of sensorium. She is normotensive and normovolemic. Her weight is unchanged at 20 kg. On evaluation, her serum sodium was found to be 115 mEq/L.

*Solution:*

The total desired correction of sodium level is 10 mEq/L in 24 hours, i.e., to 125 mEq/L.

Sodium deficit = 0.6 × body weight × (desired – observed) sodium = 0.6 × 20 × (125–115) = 120 mEq

Since patient is having symptomatic hyponatremia, we want a fast initial correction of around 4–5 mEq/L over 4 hours. So, to raise his serum sodium to 120 mEq/L, he requires 60 mEq of sodium = 115 mL of 3% saline over 4 hours (1 liter of 3% saline contains 513 mEq of sodium).

Once CNS symptoms have improved, the rest of the correction can be given slowly to target a total of 10 mEq/L correction in 24 hours.

## Osmotic Demyelination Syndrome

Osmotic demyelination syndrome (ODS) is an iatrogenic irreversible clinical syndrome consisting of neurologic features which occurs following a very fast correction of serum sodium.[15] It was earlier known as central pontine myelinolysis (CPM), but now CPM is considered as a subset of ODS in which the clinical effects are primarily due to brainstem damage. Other children with ODS can have foci of demyelination anywhere else within the CNS.[15] ODS occurs when the generally agreed safe limits of serum sodium correction are exceeded, that is correction >12 mEq/L in 24 hours, >25

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mEq/L in 48 hours, or inadvertent hypernatremia during hyponatremia.[14,15] The neuronal damage is likely due to the result of rapid swelling of brain and nervous system cells during fluid administration, since these cells are not able to adapt quickly to the change in osmolality.[16] Children suffering from chronic hyponatremia are especially vulnerable to ODS, particularly those with underlying hypoxia, malnutrition, alcoholism, toxins, other CNS disease, or other metabolic syndromes. Clinical features of ODS include confusion, fluctuating levels of consciousness, mutism, behavioral changes, dysarthria, dysphagia, and seizures.[15] Patients can progress to a locked-in state, in which they are awake but unable to move or communicate, or quadriparesis.

## HYPERNATREMIA

Hypernatremia is defined as serum sodium concentration >145 mEq/L and it is less common in children compared to hyponatremia. Hypernatremia is always associated with intracellular dehydration caused by decrease of TBW.

### Etiology

Etiology of hypernatremia can vary depending on the volume status of the patient, i.e., hypovolemic, euvolemic, or hypervolemic.

#### *Hypovolemic Hypernatremia*

- Impaired thirst mechanisms—hypodipsia, adipsia
- Inability to acquire adequate free water—elderly, infants, or critically ill patients (e.g., patients on a ventilator, in a coma)
- Gastrointestinal losses—diarrhea, vomiting, nasogastric drainage
- Diuresis—osmotic diuretics, impaired urinary concentration—obstructive uropathy, sickle cell disease, nephronophthisis, cystinosis, and acute or chronic kidney disease.

#### *Euvolemic Hypernatremia*

- Diabetes insipidus (DI)
- Hypodipsia.

#### *Hypervolemic Hypernatremia*

- Salt poisoning
- Primary hyperaldosteronism
- Formula-fed infants
- Administration of isotonic saline to replete hypotonic losses.

#### *Diabetes Insipidus*

Diabetes insipidus is characterized by lack of response to ADH, which can be central or peripheral. Due to deficiency of ADH effect, urine is maximally dilute with low urine osmolality. Even though sodium is excreted in the urine, it is less than the excretion of water and this disproportionate excretion of water compared to sodium leads to hypernatremia.

- *Central DI:* This condition is characterized by insufficient ADH production or release. It may be congenital or acquired. Congenital causes include CNS malformations and genetic syndromes with associated CNS anomalies. Acquired etiologies include infiltrative processes of the hypothalamic-pituitary stalk, CNS tumors, and sequelae from neurological surgeries and trauma.
- *Nephrogenic DI:* This condition is characterized by inadequate renal tubular response to circulating ADH. The causes can be further divided into congenital or acquired.

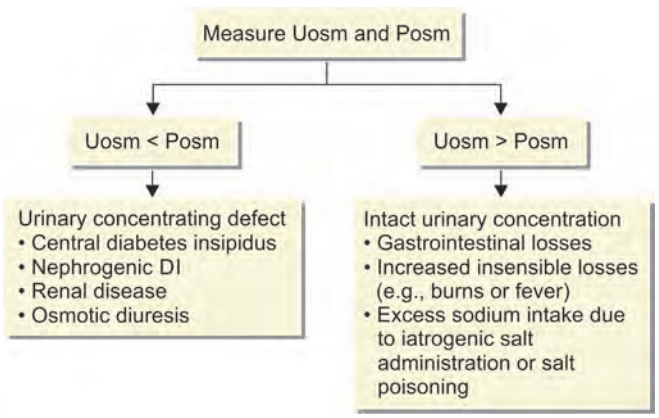
### Clinical Manifestations

Symptoms of hypernatremia are similar to those of hyponatremia, because both affect primarily the CNS. In the presence of hypernatremia, brain cells shrink significantly as water moves from inside the cells into the ECF space. This fluid shift can lead to intracerebral hemorrhage due to tearing of cerebral blood vessels by exertion of shear force. Hypernatremia can also lead to impaired glucose use, reduced left ventricular contractility, hyperventilation, muscle cramps, and rhabdomyolysis. The clinical manifestations include lethargy, weakness, or restlessness; infants can present only with irritability. Clinical findings include nuchal rigidity, hypertonia, brisk reflexes, asterixis, chorea, myoclonus, or seizures. If untreated, the child can progress to seizures, coma, or death. Clinical features are related to increase in serum sodium levels and also rapidity of increase in sodium level, as these determine the degree and rapidity of development of brain cell dehydration.

### Evaluation

The first step is to assess the volume status of the patient. Assessment of plasma and urine osmolality may help in identification of underlying etiology of hypernatremia **(Flowchart 2)**.[17] Urine osmolality less than plasma osmolality indicates a concentrating defect, which denotes the possibility of excess urinary water losses. When urine osmolality is more than plasma osmolality, it indicates that such a child has

**Flowchart 2:** Urine and plasma osmolality in hypernatremia.[17]




(DI: diabetes insipidus)

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intact urinary concentrating mechanisms and points toward extrarenal causes for hypernatremia (gastrointestinal or skin water losses, or excess salt intake).

A detailed algorithm depicting approach to hypernatremia is given in **Flowchart 3**.[18]

## Treatment

Treatment depends on the volume status, degree of hypernatremia, and rapidity of its development. Hypovolemia takes precedence over correction of sodium.

### *Hypovolemia with Hypernatremia*

If the patient has significant volume depletion, the first step is to ensure cardiovascular stability. If the child has moderate to severe hypovolemia, initially isotonic fluid is given for fluid resuscitation in order to reinstate blood volume and organ perfusion. At the same time, it is important to avoid overzealous fluid resuscitation so that inadvertent volume overload and its associated cerebral edema can be prevented.

### *Free Water Correction*

When hypernatremia is the sole abnormality, the goal is to correct sodium by replacing the free water deficit, which can be calculated by the formula:

Free water deficit in milliliters = 0.6 × weight × ([current plasma Na/140] – 1)

It can also be calculated by the formula:

Free water deficit in milliliters = (4 mL/kg) × (weight in kg) × (desired change in plasma Na)

This formula is based on the estimate that administration of 4 mL/kg of free water will reduce plasma sodium by roughly 1 mEq/L.

Free water can be delivered as isotonic fluids like half normal saline, 5% dextrose, or as enteral fluids. For children with chronic hypernatremia (plasma sodium ≥ 150 mEq/L for >24 hours) or those with acute severe hypernatremia (plasma sodium >160 mEq/L), the targeted reduction in plasma sodium should not exceed 0.5 mEq/L/h (i.e., 10–12 mEq/L/day). Too rapid treatment of hypernatremia is associated with a risk of cerebral edema.

### *Ongoing Losses and Maintenance Needs*

Hypernatremia correction by the above formulae considers only free water losses that have already occurred up to the time of calculation. In addition, patients have normal maintenance needs and may also have ongoing excess free water losses not so far considered (e.g., continuing diarrhea or persistent fever). Children should receive maintenance fluids as well as replacement of these ongoing losses to prevent further derangements in plasma sodium level.

## Clinical Case Scenario

A 3-year-old boy (weight 10 kg) recently diagnosed with DI came to emergency room (ER) with history of stopping medications for the last 5 days. His blood pressure was 100/60 mm Hg and he was apparently euvolemic. His serum sodium was 170 mEq/L.

In this case, free water deficit = 0.6 × weight × ([current plasma Na/140] – 1) = 0.6 × 10 × ([170/140] – 1) = 1,200 mL.

Since the current deficit is 30 mEq/L and the maximal rate of correction should be 10 mEq/L/day, this should be given over 3 days, i.e., 400 mL/day.

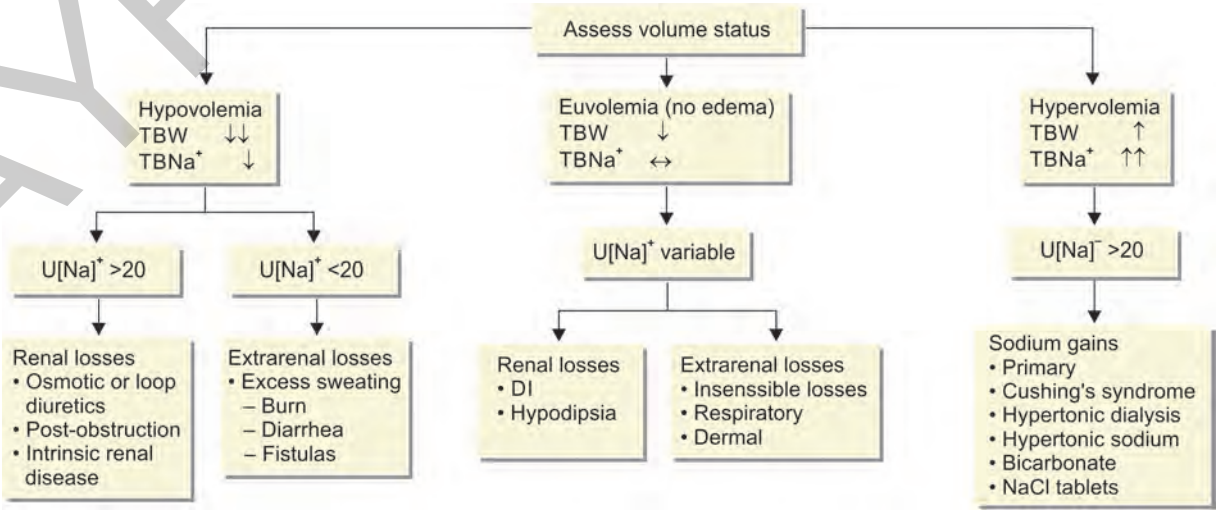
Another method of calculation is: Free water to be given over 24 hours = (4 mL/kg) × (weight in kg) × (desired change in plasma Na) = 4 × 10 × 10 = 400 mL/day.

In addition, ongoing losses and maintenance requirements needs to be replaced.

### *Hypervolemic Hypernatremia*

It is important to avoid rapid administration of fluids as it may cause volume overload and pulmonary edema. Extra salt

**Flowchart 3:** Algorithmic approach to hypernatremia.[18]




(DI: diabetes insipidus; TBW: total body water)

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and water removal can be achieved by use of loop diuretics like furosemide. If there is concomitant renal failure, dialysis will be required.

### Treatment of Specific Etiologies

Wherever a definite underlying long-term condition can be identified, such as central or nephrogenic DI, treatment of the etiologic disease should be initiated (e.g., treatment with desmopressin for central DI) in addition to providing free water replacement.

## CONCLUSION

Abnormalities in serum sodium level are the most common electrolyte abnormalities in clinical practice and are sometimes multifactorial. Assessment of volume status is the key in managing such patients. Slow and steady correction with frequent laboratory monitoring and avoiding rapid fluctuations in serum sodium levels is paramount for optimal clinical outcomes.

## KEY POINTS

- Sodium is the key determinant of serum osmolality and tonicity.
- Dysnatremias reflect disorders of water balance.
- The main manifestations of dysnatremias are related to CNS.
- Classification is based on volume status.
- Treatment depends on volume status, degree, and rapidity of development of dysnatremia.
- Too rapid correction can lead to ODS in hyponatremia and cerebral edema in hypernatremia.

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