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Exam Preparatory Manual for Undergraduates

Medicine

As per the Revised Competency-based Medical Education Curriculum (NMC)



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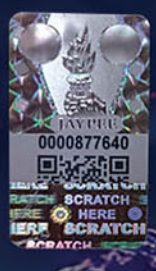
Poster of NEET PG 2025 MCQs Included

5th Edition

Foreword
H Sudarshan Ballal





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CHAPTER

11

Fluid, Electrolytes and Acid-Base Disorders

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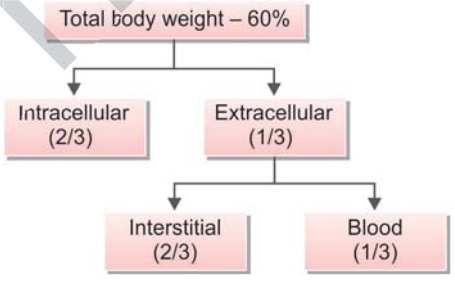
DISORDERS OF WATER BALANCE

Q. **Write short note on the normal distribution of water in the body of an average adult male.**

COMPOSITION OF BODY FLUIDS

- Water is the most abundant constituent of the body, accounting for about 50% of body weight in women and 60% of the body weight in men.
- Total body water is distributed in two major compartments:
  1. Intracellular fluid compartment (IFC) = 2/3rd of body water
  2. Extracellular fluid compartment (ECF) = 1/3rd of body water ECF consists of:
     - ♦ **Intravascular (plasma water)** compartment: 3/4th of ECF or 15% of total body weight.
     - ♦ **Extravascular (interstitial)** compartment: 1/4th of ECF or 5% of total body weight.

FLOWCHART 11.1: Distribution of body fluid compartments.



For example, the distribution of body fluid in a man of 70 kg is as mentioned in **Flowchart 11.1**.

Normal Water Balance

- In a normal person, daily fluid requirement = sum of urine output + net insensible fluid losses
  - Insensible fluid loss = 500 mL through skin + 400 mL through lung + 100 mL through stool = 1,000 mL
  - Insensible fluid input = 300 mL water through oxidation
  - Net normal daily insensible fluid loss = 1,000 mL – 300 mL = 700 mL
- *Hence, daily fluid requirement = urine output + 700 mL*
- Abnormal fluid loss:
  - 500 mL through moderate sweating
  - 1–1.5 L through severe sweating/high fever
  - 0.5–3 L through exposed wound surface (burns) and body cavity (laparotomy)
  - These parameters help to determine the daily fluid requirement in patients, especially those on intravenous fluids.

Electrolytes (Table 11.1)

- Electrolytes are ions that are either positively charged (cations) or negatively charged (anions).
- Sodium (Na^+) is the main cation, while chloride (Cl^-) and bicarbonate (HCO^-) are the major anions in the extracellular (ECF) compartment.
- Potassium (K^+) and magnesium (Mg^{2+}) are the major cations, while phosphate, sulfate, and protein are the major anions in the intracellular (ICF) compartment.
- The normal range of different electrolytes in the blood is as shown in **Table 11.1**.

TABLE 11.1: Normal range of various electrolytes, pH, and osmolality of blood.

Component	*Normal range*	*Component*	*Normal range*
Sodium (serum)	136–145 mmol/L	Calcium (plasma)	9–10.5 mg/dL
Potassium (serum)	3.5–5.0 mmol/L	pH of blood	7.35–7.45
Chloride (serum)	98–106 mmol/L	Bicarbonate (blood)	21–28 mmol/L
Magnesium (serum)	2–3 mg/L	Osmolality (serum)	285–290 mOsm/kg water
Phosphorus (serum)	3–4.5 mg/dL		

OSMOLALITY, OSMOLARITY, AND TONICITY

- **Osmolality:** Osmolality of a solution is determined by the amount of solute dissolved in a solvent (i.e., water) measured in weight (kg). When osmolality is high, solution is more concentrated, and when the osmolality is low, solution is diluted.
- **Osmolarity:** Osmolarity is the concentration of osmotically active particles, expressed as milliosmoles per liter (mOsm/L).
- Plasma osmolarity = 2 × Na^+ (mEq/L) + glucose (mg/dL)/18 + BUN (mg/dL)/2.8
- In practice, *osmola'r'ity* is the same as *osmola'l'ity* (mOsm/kg H_2O) because 1 L of water is equivalent to 1 kg of water.
- **Tonicity vs osmolality:**
  - Osmolality refers to all particles in solution
  - Tonicity describes whether the particles are effective or ineffective osmoles.
  - Tonicity = concentration of solutes that do not cross the cell membrane = effective serum osmolality.
  - A small note on effective vs ineffective osmoles—urea, ethanol, methanol, ethylene glycol are ineffective osmoles. Glucose, mannitol, glycine and maltose are effective osmoles.

VOLUME REGULATION AND OSMOREGULATION

Q. What are the factors that determine the control of ECF volume?

Q. Write a note on sodium balance.

Total body sodium is the main determinant of ECF volume: Regulation of the sodium balance, i.e., the difference between sodium intake and output, is crucial to maintaining normal ECF and plasma volume, with the kidney matching the urinary output of sodium with that of sodium intake.

A positive Na^+ balance would lead to ECF volume expansion, while conversely, a negative Na^+ balance would lead to ECF volume contraction.

Sodium intake: Daily sodium consumption varies widely between low-Na^+ diets containing 20 mmol/day (approximately 1.2 g salt/day) and high-Na^+ diets containing 200 mmol/day (approximately 12 g salt/day).

Sodium excretion: Figure 11.1 shows the renal handling of sodium by the nephron.

Na^+ is freely filtered across glomerular capillaries and is subsequently reabsorbed throughout the nephron.

- *Proximal convoluted tubule (PCT)*: Approximately 2/3rd (67%) of Na^+ is reabsorbed.
- *The loop of Henle*: About 25–30% is reabsorbed via apical Na^+ K^+ $2Cl^-$ transporter.
- *Distal convoluted tubule (DCT)*: About 5% by thiazide sensitive Na^+ Cl^- cotransporter.
- *Collecting ducts*: About 3% of Na^+ reabsorption takes place in the cortical and medullary collecting ducts.

The excretion of Na^+ is less than 1% of the filtered load, with more than 99% of the filtered load being reabsorbed.

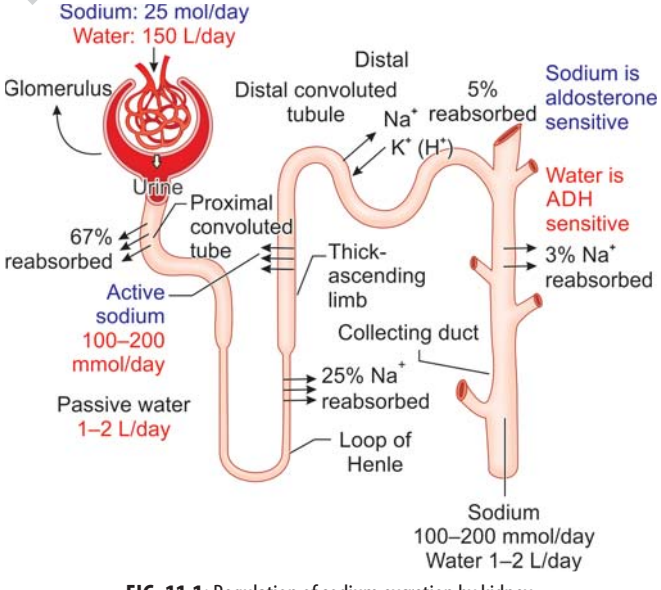


FIG. 11.1: Regulation of sodium excretion by kidney.

Renal excretion of sodium is regulated by four major steps:

1. *Renin–angiotensin–aldosterone system*:
   - The renin–angiotensin–aldosterone system is activated in response to decreased renal perfusion pressure.

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- Angiotensin II stimulates Na^+ reabsorption in the proximal tubule (Na^+–H^+ exchange).
- Aldosterone stimulates Na^+ reabsorption in the late distal tubule and the collecting duct.

2. *Sympathetic nervous system (SNS) activity*: Baroreceptors sense a decrease in arterial pressure and stimulate the SNS and cause vasoconstriction of afferent arterioles and increased proximal tubular sodium reabsorption.
3. *Atrial natriuretic peptide (ANP)*:
   - ANP—secreted by the atria in response to an increase in ECF volume, causes vasodilation of afferent arterioles, vasoconstriction of efferent arterioles, increased GFR, and decreased Na^+ reabsorption in the late distal tubule and collecting ducts.
   - Other peptides in the ANP family, including urodilatin (secreted by the kidney) and brain natriuretic peptide (BNP) (secreted by cardiac ventricular cells and the brain), have similar effects to increase GFR and decrease renal sodium reabsorption.
4. *Starling forces in peritubular capillaries*:
   - Increase in ECF volume reduces the peritubular capillary oncotic pressure and inhibit proximal tubule Na^+ reabsorption.
   - Decrease in ECF volume increases the peritubular capillary oncotic pressure and stimulate proximal tubule Na^+ reabsorption.

Body fluid osmolarity is maintained at a value of about 285–290 mOsm/L by processes called osmoregulation.

Even minor changes in body fluid osmolarity produce a series of hormonal responses that influence the reabsorption of water by the kidneys, attempting to restore osmolarity back to normal value.

These renal mechanisms for the reabsorption of water are responsible for maintaining constant body fluid osmolarity.

Vasopressin, also known as **arginine vasopressin (AVP)** or **antidiuretic hormone (ADH)**, by its effect on the renal collecting system, is the major determinant which regulates the excretion of free water.

Increased serum osmolality stimulates osmoreceptors in the anterior hypothalamus, which in turn stimulates thirst and the secretion of ADH from the posterior pituitary gland. ADH circulates via the blood to the kidneys, where it leads to the increase in the water permeability of the principal cells of the late distal tubule and the collecting duct, resulting in increased water reabsorption. Because more water is reabsorbed by these segments, the osmolarity of urine increases and the amount of urine decreases. This, along with increased water intake, restores serum osmolarity to normal levels.

Conversely, reduced serum osmolarity, via inhibition of the osmoreceptors in the anterior hypothalamus, suppresses thirst as well as the secretion of ADH, which results in excretion of large amount dilute urine, restoring serum osmolarity to normal levels.

Table 11.2 summarizes the factors which determine volume and osmoregulation.

TABLE 11.2: Determinants of volume regulation and osmoregulation.

Factor	*Volume regulation*	*Osmoregulation*
Factor sensed	Effective arterial blood volume	Plasma osmolality
Sensed by	Baroreceptors	Hypothalamic osmoreceptors
Effectors	Aldosterone, angiotensin II, sympathetic nervous system	Antidiuretic hormone, thirst
What is affected	Urine sodium excretion	Urine osmolality, thirst

ASSESSING VOLUME STATUS

Q. How do you asses volume status?

Hemodynamic assessment methods include:

- Interpretation of history and physical examination findings
- Assessment and interpretation of laboratory results
- Ultrasound and echocardiography
- Use of noninvasive monitoring
- Use of minimally invasive procedures

No single assessment is sufficient in isolation and must be considered in the context of other available assessments and clinical information.

Some of the methods used in clinical practice are described in **Table 11.3**.

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TABLE 11.3: Assessment of volume status.

Method	*Features*	*Invasive/ noninvasive*	*Static or dynamic*	*Assesses fluid responsiveness*	*Comment*
History	Thirst/vomiting/diarrhea/hemorrhage: Indicate fluid deficit Dyspnea and pedal edema favor fluid overload	Noninvasive	Static	No	–
Charting	Fluid balance charts (input/output charting) 24-hour weighing—best measure of change in water balance	Noninvasive	Dynamic	Yes	Fluid balance charts do not measure insensible loss and may have irregularities in measurement and recording Weighing may be difficult in critically ill patient
Physical examination	Tachycardia, postural hypotension, low JVP, cold extremities, poor capillary return, dry mouth, sunken facies, altered mentation, and reduced urine output suggest hypovolemia Pulmonary edema, peripheral edema, raised JVP, and S3 gallop suggests volume overload	Noninvasive	Static and dynamic	Yes	Serial examinations may detect changes in organ perfusion
Passive leg raising (PLR)	The head and the upper torso are lowered to a supine position, while simultaneously raising the legs to a 45° angle for 4 minutes This increases the venous return to the heart and is similar to the administration of 250 mL of fluid bolus. Hemodynamics are assessed before and after the PLR; if cardiac output improves, the patient is "fluid responsive" and administration of IV fluids should improve hemodynamics	Noninvasive	Dynamic	Yes	Unreliable with intra-abdominal hypertension, DVT in the leg, lower limb amputation
Biochemistry	Higher BUN creatinine ratio (>20:1), reduced urine sodium levels (<25 mEq/L), increased lactates suggest hypovolemia	Invasive	Static	No	Affected by drugs and other clinical conditions
Bedside ultrasound and echocardiography	Heart: Measurement of cardiac chamber function, pericardial tamponade Inferior vena cava: Collapse >50% indicates fluid tolerance Lung ultrasonography: More B lines correspond with increasing fluid overload. Also helps to identify pneumothorax, which causes obstructive shock	Noninvasive	Static and dynamic	Yes	Helps to identify various causes of shock such as cardiogenic, hypovolemic or obstructive
Central venous pressure	Central venous catheters through IJV or subclavian vein can be used to measure CVP Normal: 4–8 mm Hg Low CVP—hypovolemia High CVP—volume overload, cardiac causes such as CHF, cardiac tamponade, tricuspid regurgitation, pulmonary causes such as pulmonary embolism, tension pneumothorax, intermittent positive pressure ventilation	Invasive	Static	No	Poor correlation with fluid responsiveness
Pulmonary capillary wedge pressure (Swan-Ganz catheter)	A Swan-Ganz catheter is inserted through the IJV or the subclavian vein, and into the right atrium and ventricle to end in the pulmonary artery Commonly used in the management of postoperative cardiac patients and those with severe pulmonary hypertension	Invasive	Static	No	Poor correlation with fluid responsiveness
Stroke volume or pulse pressure variation	Pulse pressure analysis using data obtained form an arterial line helps to determine fluid responsiveness Steep variation—fluid responsiveness	Invasive	Dynamic	Yes	Requires sedated, mechanically ventilated patient

Contd...

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Contd...

Method	*Features*	*Invasive/ noninvasive*	*Static or dynamic*	*Assesses fluid responsiveness*	*Comment*
Transesophageal Doppler	A transducer is inserted into the esophagus to obtain accurate measures of stroke volume and cardiac output	Invasive	Dynamic	Yes	Not useful for continuous measurements
Thoracic electrical bioimpedance	Bioimpedance measures the resistance of electrical current through different body tissue and fluids, and can quantify the amount of tissue and fluid in the body	Noninvasive	Static	No	Not able to assess intravascular volume

DISTURBANCES OF BODY FLUIDS

The disturbances of body fluids can be grouped according to whether they involve volume contraction or volume expansion and whether they involve an increase or a decrease in body fluid osmolarity are described in **Table 11.4** and **Figure 11.2**.

TABLE 11.4: Disturbances in body fluids.

Type	*Example*	*ECF volume*	*ICF volume*	*Osmolarity*	*Hematocrit*	*Plasma (protein)*
Isosmotic volume contraction	Diarrhea; burn	↓	No change	No change	↑	↑
Hyperosmotic volume contraction	Sweating, fever, diabetes insipidus	↓	↓	↑	No change	↑
Hyposmotic volume contraction	Adrenal insufficiency	↓	↑	↓	↑	↑
Isosmotic volume expansion	Infusion of isotonic NaCl	↑	No change	No change	↓	↓
Hyperosmotic volume expansion	High-NaCl intake	↑	↓	↑	↓	↓
Hyposmotic volume expansion	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	↑	↑	↓	No change	↓

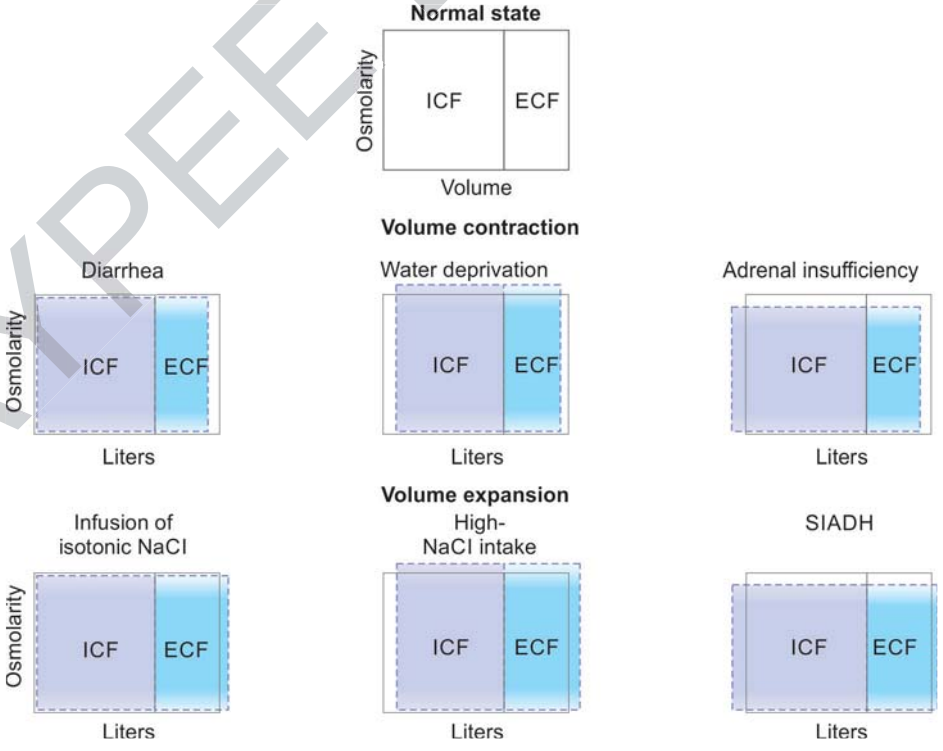

FIG. 11.2: Shifts of water between body fluid compartments.

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VOLUME DEPLETION (HYPOVOLEMIA)

Q. What is hypovolemia?

Hypovolemia, synonymous with ECF volume contraction, refers to a loss of salt and water.

Q. Describe the causes, clinical features, laboratory features, and treatment of volume depletion.

Causes of Hypovolemia

See **Table 11.5**.

TABLE 11.5: Causes of volume depletion (hypovolemia).

Extrarenal losses	Renal losses
➢ *Gastrointestinal losses*: – Diarrhea – Vomiting – Gastrointestinal bleeding – Enteric fistulas (high-output fistulas) – Short bowel syndrome – Post-gastrectomy dumping syndrome – External drain (tube drainage or ostomies) ➢ *Sequestration into third space*: – Pancreatitis – Crush injuries – Intestinal obstruction – Postoperative states (especially abdominal surgeries) – Severe peritonitis – Capillary leak syndrome (sepsis, anaphylaxis) – Necrotizing pancreatitis – Acute limb compartment syndrome – Skeletal fractures ➢ *Loss from skin*: – Excessive sweating – Heat stroke – Stevens-Johnson syndrome/toxic epidermal necrolysis – Severe eczema or exfoliative dermatitis – Burns	➢ *Excessive use of diuretics*: – Osmotic diuresis – Glycosuria in uncontrolled diabetes – Excessive use of mannitol – Post-obstructive diuresis – Salt-wasting nephropathies (e.g., Bartter syndrome, Gitelman syndrome) – Cerebral salt-wasting syndrome ➢ *Diabetes insipidus*: Impaired ADH secretion/response to ADH ➢ *Renal disease:* – Tubular disorders – Recovery phase of oliguric kidney injury – Release of urinary tract obstruction – Chronic interstitial renal diseases ➢ *Deficiency of mineralocorticoids*: – Addison's disease

Clinical Features

Mild to Moderate Volume Loss

- Thirst
- Postural dizziness, weakness
- Dry mucous membranes and axillae
- Cold, clammy extremities
- Collapsed peripheral veins
- Delayed capillary refill time
- Tachycardia (pulse rate >100 beats/min)
- Postural increase in pulse of 30 beats/min or more
- Postural hypotension (systolic blood pressure decrease >20 mm Hg on standing)
- Low jugular venous pulse
- Fatigue and lethargy
- Nausea
- Decreased urine output

Severe Volume Loss and Hypovolemic Shock

- Altered mental status (or loss of consciousness)
- Peripheral cyanosis
- Reduced skin turgor (in young patients)
- Marked tachycardia, low pulse volume
- Cold, mottled skin
- Oliguria/anuria
- Metabolic acidosis
- Pulmonary edema (severe cases)
- Kussmaul's breathing (severe metabolic acidosis)
- Supine hypotension (systolic blood pressure <100 mm Hg)

Laboratory Features

- **Hematocrit:** Increased due to hemoconcentration. May be reduced if hypovolemia is secondary to hemorrhage.
- **Blood urea nitrogen (BUN) and creatinine:** BUN/creatinine ratio >20:1 is usually seen. This is due to a differential increase in urea reabsorption in the collecting duct. Confounding factors include upper gastrointestinal tract hemorrhage and administration of corticosteroids, which increase urea production, as well as malnutrition and liver disease, which diminish urea production.
- **Serum sodium:** Normal, reduced, or elevated depending on the proportion of loss between water and sodium.
- **Urine osmolality and specific gravity:** These are often elevated in hypovolemic states. However, these may be altered by an underlying renal disease that leads to renal sodium wasting, concomitant intake of diuretics or a solute diuresis.

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- **Urinary sodium:** Hypovolemia normally promotes renal sodium reabsorption. Hence, urine sodium is low, typically less than 25 mmol/L in most cases of hypovolemia and states of low effective arterial volume. However, urine sodium concentration may be misleading in cases of:
  - Metabolic alkalosis (e.g., nasogastric suction or vomiting), as bicarbonaturia obligates excretion of a cation. Hence, the urine sodium concentration might not be low. In this circumstance, the urine chloride concentration should be measured, which will typically be <15 mEq/L.
  - Presence of acute tubular necrosis—kidney tubular function is impaired, thus the urine sodium concentration may not be low.
  - Use of diuretics
- **Urine chloride levels (low):** It follows a similar pattern of urine sodium concentration because sodium and chloride are generally reabsorbed together. Urine chloride is a better measure than urine sodium in cases of volume depletion with metabolic alkalosis, as described above.
- **Fractional excretion of sodium (FE Na):**
  - $[U_{Na} \times P_{creat} / U_{creat} \times P_{Na}] \times 100$.
  - In an oliguric patient with AKI, FE Na less than 1% is consistent with volume depletion; FE Na greater than 1% is more consistent with acute tubular necrosis.

Treatment:

- General principles: Monitor vitals, urine output, and lactate; correct electrolytes; avoid rapid overcorrection to prevent pulmonary edema.
- The goal of treatment is to replace the fluid deficit and ongoing losses with a fluid that resembles the lost fluid.
- The cause of hypovolemia should be treated, where possible.
- Mild-to-moderate volume depletion (often due to gastroenteritis) should be corrected by increasing oral intake of sodium and water by an oral rehydration solution.
- In severe volume depletion, prefer balanced crystalloids (Ringer's lactate, plasma-lyte) over normal saline; target MAP >65 mm Hg and urine output >0.5 mL/kg/hr; use vasopressors if fluids alone are inadequate.
- Transfusion of blood products is crucial for hemorrhage.
- Specific conditions: Apply permissive hypotension in hemorrhagic shock, Parkland formula for burns, and early goal-directed therapy in sepsis.

Q. What is dehydration? Describe the clinical features of dehydration.

- Dehydration refers to a loss of water.
- This should be differentiated from hypovolemia, which implies a loss of salt and water.
- Dehydration may cause manifestations of hypernatremia.
- **Table 11.6** describes the signs of dehydration depending on the degree of dehydration.

TABLE 11.6: Signs of dehydration depending on the degree of dehydration.

Features	*Mild*	*Moderate*	*Severe*
Peripheral pulses	Normal	Slightly decreased	Difficult to palpate
Heart rate	Normal	Slightly increased	Significantly increased (tachycardia)
Capillary refill	Normal	About 2 seconds	>3 seconds
Mucous membranes and skin	Normal	Dry	Extremely dry
Eyes	Normal	Normal	Sunken
Production of tears	Normal	Decreased	Absent
Amount of urine excreted	Normal	Decreased	Little or none
Fontanelle (in infants)	Flat	Soft	Sunken
Blood pressure	Normal	Slightly decreased	Markedly decreased (hypotension)
Respiratory rate	Normal	Slightly increased	Rapid, deep breathing (Kussmaul's in acidosis)
Skin turgor	Normal	Delayed recoil	Very delayed recoil (skin tenting)
Mental status	Alert	Irritable, restless	Lethargic, drowsy, unconscious
Extremities temperature	Warm	Cool	Cold, mottled
Jugular venous pressure	Normal	Decreased	Markedly decreased or absent

VOLUME EXPANSION (HYPERVOLEMIA)

- Hypervolemia is an expansion of the ECF compartment, due to an excess of total body sodium and water.
- Hypervolemia is typically due to renal retention of sodium and water.
- This renal retention may be primary or secondary.
- Secondary causes are secondary to reduced effective arterial blood volume depletion (arterial underfilling).
- Major causes of hypervolemia are listed in **Table 11.7**.

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TABLE 11.7: Major causes of extracellular fluid volume expansion.

Primary renal sodium retention	*Secondary renal sodium retention*
➢ Acute kidney injury ➢ Advanced chronic kidney disease ➢ Glomerular diseases ➢ Renovascular hypertension ➢ Primary hyperaldosteronism (Conn's syndrome) ➢ Cushing's syndrome ➢ Liddle's syndrome	➢ Cardiac failure ➢ Cirrhosis ➢ Nephrotic syndrome ➢ Idiopathic edema ➢ Drug-induced edema ➢ Pregnancy ➢ Sepsis ➢ Severe hypoalbuminemia (non-nephrotic causes) ➢ Hypothyroidism (myxedema edema) ➢ Severe anemia

EDEMA

Q. Define edema. What is anasarca?

Q. What are the common causes of generalized edema?

Q. List medications that can cause edema.

Q. Discuss the mechanism of edema formation. How will you differentiate between cardiac, renal and hepatic edema?

Definition

Edema: Edema is an accumulation of fluid in the interstitial space that occurs when local or systemic conditions cause capillary filtration to exceed the limits of lymphatic drainage.

Anasarca: It refers to generalized and massive edema, often accompanied by large effusions into the peritoneal, pleural, and pericardial spaces.

Table 11.8 shows the medications that cause edema.

Differences between the principal causes of edema are described in **Table 11.9**.

Causes of Pitting Dependent Edema (Table 11.10)

Pathogenesis of systemic edema from congestive heart failure, renal failure, or reduced plasma osmotic pressure is shown in **Figure 11.3**.

Pitting edema may be divided into two categories:

1. **Rapid pitting** recovery within <40 seconds and is seen with hypoproteinemia.
2. **Slow pitting edema** (>40 seconds) is usually seen in patients with normal albumin levels **(Fig. 11.4)**.

TABLE 11.8: Medications that cause edema.

Types of medication	*Class of medication*
Antihypertensive medications	➢ Calcium-channel blockers (nifedipine, felodipine, amlodipine, and verapamil) ➢ Direct vasodilators (hydralazine, minoxidil, diazoxide) ➢ Antiadrenergics (clonidine, reserpine, and methyldopa) ➢ ACE inhibitors (enalapril, ramipril) ➢ Beta-blockers (metoprolol, propranolol)
Chemotherapy	Cisplatin, docetaxel, imatinib, paclitaxel, bevacizumab
Diabetic medications	Thiazolidinediones (rosiglitazone), insulin, DPP-4 inhibitors (sitagliptin), GLP-1 receptor agonists (liraglutide)
Hormones	Estrogen, progesterone, testosterone, glucocorticoids, and fludrocortisone
Pain relief medications	NSAIDs
Psychiatric medications	➢ Monoamine oxidase inhibitors ➢ Antipsychotics (olanzapine) ➢ Selective serotonin reuptake inhibitors (SSRIs—paroxetine, fluoxetine) ➢ Lithium
Immunological/ Immunosuppressant	Cyclophosphamide, cyclosporine, interleukin 2, OKT3 monoclonal antibody, tacrolimus, rituximab
Anticonvulsant	Pregabalin, gabapentin, valproate, carbamazepine

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TABLE 11.9: Differentiating the principal causes of generalized edema.

Organ system	*History*	*Physical examination*	*Laboratory findings*
Cardiac	➢ Exertional dyspnea ➢ Paroxysmal nocturnal dyspnea ➢ Orthopnea ➢ Bendopnea ➢ Initial site of edema: pedal edema/sacral edema	Pulsus alternans, elevated jugular venous pressure, displaced or dyskinetic apical pulse, S3 gallop	Elevated BNP/NT-proBNP
Hepatic	➢ Ascites ➢ Dyspnea, when associated with significant degree of ascites ➢ Jaundice	➢ Ascites ➢ Signs of chronic liver disease (jaundice, palmar erythema, spider angiomata, male gynecomastia or female breast atrophy, testicular atrophy; signs of hepatic encephalopathy) may be present ➢ Jugular venous pressure normal or low	➢ Reduced serum albumin, other hepatic proteins (transferrin, fibrinogen) ➢ Elevated PT/INR ➢ Liver enzymes may be elevated, depending on the cause and acuity of liver injury ➢ Thrombocytopenia may be present
Renal (CKD)	➢ Symptoms of uremia, such as decreased appetite, nausea and vomiting, altered (metallic or fishy) taste, altered sleep pattern, difficulty concentrating ➢ Decreased urine output ➢ Dyspnea	➢ Pallor ➢ Hypertension ➢ Uremic fetor ➢ Pericardial friction rub	➢ Elevation of serum creatinine and cystatin C ➢ Proteinuria ➢ Hematuria ➢ Hyperkalemia ➢ Metabolic acidosis ➢ Hypocalcemia ➢ Hyperphosphatemia ➢ Anemia
Renal (nephrotic syndrome)	➢ Periorbital edema ➢ Frothy urine	➢ Periorbital edema ➢ Hypertension	➢ Proteinuria (≥3.5 g/dL) ➢ Hypoalbuminemia ➢ Hypercholesterolemia ➢ Microscopic hematuria

TABLE 11.10: Causes of pitting dependent edema.

Mechanism	*Causes*
Increased hydrostatic/ systemic venous pressure	**Systemic venous hypertension:** ➢ Congestive heart failure ➢ Pulmonary hypertension ➢ Chronic pulmonary disease (cor pulmonale) ➢ Superior vena cava syndrome. ➢ Pericardial diseases, constrictive ➢ Pericarditis and tricuspid valve disease
	Regional venous hypertension: ➢ Inferior vena cava syndrome ➢ Obstruction (e.g., venous thrombosis*) or compression of veins (e.g., external mass) ➢ Lower extremity venous insufficiency ➢ May-Thurner syndrome ➢ Lymphedema (secondary to malignancy, radiation, filariasis).
Decreased plasma oncotic pressure (hypoproteinemia)	**Impaired protein synthesis:** ➢ *Decreased protein intake*: Starvation, kwashiorkor, and malnutrition ➢ *Decreased absorption of proteins*: Malabsorption ➢ Impaired hepatic synthesis due to liver disease **Increased loss of protein:** ➢ *Skin loss*: Burns, weeping skin diseases ➢ *Urinary loss*: Nephrotic syndrome ➢ *Fecal loss*: Bowel disease, malabsorption, protein-losing gastroenteropathy
Inflammation	Acute* and chronic inflammation*
Increased capillary permeability	Vasculitis*, idiopathic cyclic edema of women (varies with menstrual cycle), postanoxic encephalopathy, Sepsis, Anaphylaxis.
Sodium retention	➢ Excessive salt intake with renal insufficiency ➢ Increased tubular reabsorption of sodium, e.g., increased renin-angiotensin-aldosterone secretion

*Causes painful edema

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Treatment of Extracellular Volume Expansion

Q. Discuss the principles of management of extracellular volume expansion/generalized edema.

General Management

- Recognize and treat the underlying cause.
- Medications that promote sodium retention (e.g., NSAIDs) should be discontinued.
- Monitor and adjust fluid status using daily weight measurements, urine output monitoring, and serial physical examinations.
- Optimize intravascular volume while preventing overcorrection, particularly in conditions like cirrhosis and nephrotic syndrome where intravascular depletion may coexist with edema.
- Use albumin infusions judiciously in hypoalbuminemic states such as nephrotic syndrome, cirrhosis, and protein-losing enteropathy.

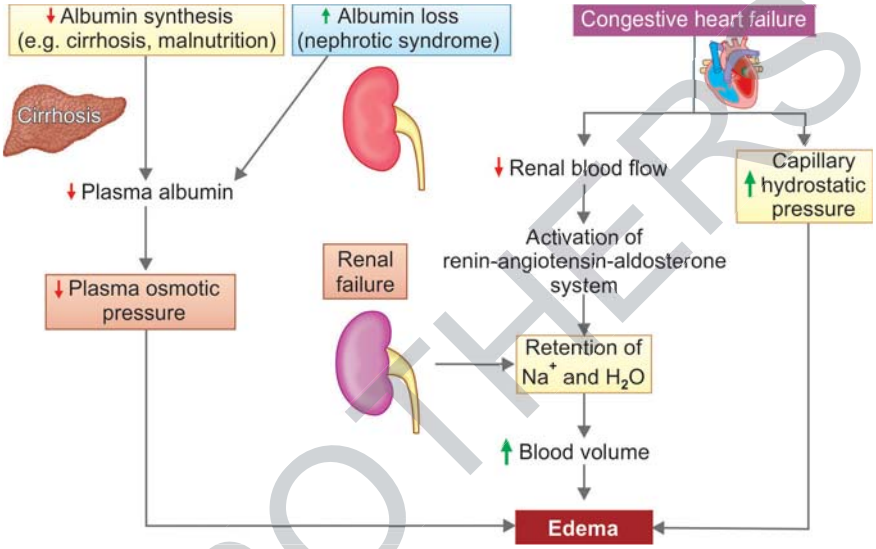

FIG. 11.3: Pathogenesis of systemic edema from congestive heart failure, renal failure or reduced plasma osmotic pressure.

- Correct underlying metabolic abnormalities such as hypernatremia, hyponatremia, and hypoalbuminemia.
- Use compression therapy (stockings, pneumatic compression devices) in cases of chronic venous insufficiency and lymphedema.
- Encourage physical activity to enhance venous return and lymphatic drainage, especially in immobile or bedridden patients.
- Achieving negative sodium balance, by dietary sodium restriction and administration of diuretics.
  - Moderate dietary sodium restriction (2 g Na^+/day) should be encouraged.
  - Restriction of total fluid intake in patients with hypervolemic hyponatremia.
  - *Diuretic therapy:* Cornerstone of management of extracellular volume overload (described later).



FIG. 11.4: Pitting edema in congestive heart failure.

Additional specific therapy based on the etiology:

- *Liver cirrhosis:* Large volume paracentesis with albumin infusion, TIPS (transjugular intrahepatic portosystemic shunt).
- *Heart failure:* Use of ACE inhibitors and angiotensin receptor blockers (ARBs) to inhibit renin-angiotensin-aldosterone system (RAAS), ultrafiltration, and left ventricular assist devices.
- *Chronic kidney disease:* ACE inhibitors and ARBs, renal replacement therapy (dialysis and kidney transplant).
- *Nephrotic syndrome:* Use of glucocorticoids, ACE inhibitors, and ARBs.
- *Edema of nutritional origin:* Thiamine for beriberi, high protein diet.

Diuretic Therapy

Q. Describe various diuretics in use.

Q. Add a note on diuretic therapy in edematous patients.

- Diuretics are the cornerstone in the management of extracellular volume overload. They are also used in the management of hypertension.

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- They act by inhibiting sodium reabsorption at various locations along the nephron.
- **Table 11.11** provides a summary of the various subclasses of diuretics.
- Caution should be exercised during therapy with diuretics as ECF volume expansion may have occurred in order to compensate for arterial underfilling, as in cirrhosis and heart failure.
- In these cases, overly rapid diuresis may lead to a significant reduction in the vascular space, which leads to decreased venous return to the heart, decreased cardiac filling pressures, decreased stroke volume, decreased cardiac output, and ultimately hypotension. Impaired renal perfusion may lead to prerenal AKI.
- This situation is more commonly seen in those patients with ascites, but without pedal edema.
- Rapid removal of excess fluid is generally necessary only in life-threatening situations, such as pulmonary edema and hypervolemia-induced hypertension.
- Most patients generally tolerate gradual correction of volume overload.

TABLE 11.11: Summary of diuretics.

Subclass, drug	*Site of action*	*Mechanism of action*	*Clinical uses*	*Toxicities*	*Comments*
Loop diuretics					
Furosemide, bumetanide, torsemide (sulfonamide loop diuretics) Ethacrynic acid: Not a sulfonamide but has typical loop activity and some uricosuric action	Ascending limb of Henle's loop	Inhibition of the Na/K/2Cl channel, leading to marked increase in NaCl excretion, K^+ wasting, metabolic alkalosis, increased urine Ca^{2+} and Mg^{2+}	Pulmonary edema, peripheral edema, heart failure, hypertension, acute hypercalcemia, type IV RTA	Ototoxicity, hypovolemia, K wasting, hyperuricemia, hypomagnesemia	Potent diuretics used in diseases associated with significant edema
Thiazides					
Hydrochlorothiazide, metolazone Chlorothiazide: *Only parenteral thiazide available (IV)* Chlorthalidone	Distal convoluted tubule (DCT)	Inhibition of Na/Cl transporter in the distal convoluted tubule leads to increase in NaCl excretion, some K wasting, metabolic alkalosis, decreased urine Ca^{2+}	Hypertension, mild heart failure, nephrolithiasis, nephrogenic diabetes insipidus, osteoporosis	Hyponatremia, hypokalemia, metabolic alkalosis, hyperuricemia, hyperglycemia	Widely used in the treatment of hypertension and less severe edema Metolazone is commonly used along with loop diuretic for "sequential blockade"
Potassium-sparing diuretics					
Spironolactone Eplerenone	Collecting tubules—alpha-intercalated cells	Aldosterone antagonists: Reduce Na retention and K wasting in kidney	Cirrhosis of liver (up to 400 mg/day of spironolactone), heart failure with reduced ejection fraction (25–50 mg/day of spironolactone), hypertension associated with hyperaldosteronism and resistant hypertension (25–50 mg/day of spironolactone)	Hyperkalemia, gynecomastia (spironolactone, not eplerenone)	Weak diuretics Interaction with other K-retaining drugs such as ACE-I, ARBs, beta-blockers and NSAIDs
Amiloride Triamterene	Collecting tubules	Blocks epithelial sodium channels (ENaC): Reduces Na retention and K wasting	Along with other diuretics to prevent hypokalemia from other diuretics Prevention of amphotericin-induced hypokalemia and hypomagnesemia Reduces lithium-induced polyuria Liddle's syndrome	Hyperkalemia, metabolic acidosis	

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Subclass, drug	*Site of action*	*Mechanism of action*	*Clinical uses*	*Toxicities*	*Comments*
Osmotic diuretics					
Mannitol	Multiple segments	Freely filtered at the glomerulus but not reabsorbed by any part of the tubular system. Retains fluid osmotically within the tubular lumen and limit the extent of sodium reabsorption in multiple segments. Marked increase in urine flow, reduced brain volume, decreased intraocular pressure, initial hyponatremia, then hypernatremia	Renal failure due to increased solute load (rhabdomyolysis, chemotherapy), raised intracranial pressure, raised intraocular pressure	Nausea, vomiting, headache	Not used for generalized edema
Carbonic anhydrase inhibitors					
Acetazolamide	Proximal convoluted tubule (PCT)	Indirectly inhibits Na^+ -H^+ exchange by reducing the elimination of secreted H^+ in the PCT	Glaucoma, mountain sickness, edema with alkalosis	Hyperchloremic metabolic acidosis, hypokalemia, renal stones may worsen hepatic encephalopathy in cirrhotics	Weak diuretic
Other drugs with diuretic action					
➢ SGLT2 inhibitors—refer to Chapter 12 (Diabetes Mellitus) ➢ Desmopressin, vasopressin (ADH) antagonists—see section on vasopressin receptor antagonists					

LYMPHEDEMA: NONPITTING EDEMA

Characteristics: Edema due to impaired ability of the lymphatic vasculature to collect and transport interstitial fluid, which in the latter stages is characterized by nonpitting edema which does not resolve on limb elevation and is often associated with trophic skin changes such as fibrosis, induration, acanthosis, and warty overgrowths **(Fig. 11.5)**.

Lymphedema may be primary or secondary. It may involve the upper limb or the lower limb.

Classification of primary lymphedema: Based on age at lymphedema onset:
- Lymphedema congenital—at or shortly after birth (<1 year old)
- Lymphedema praecox—from ages 1–35 years
- Lymphedema tarda—>35 years old

Causes of lymphedema:
- Primary causes:
  - Milroy disease
  - Lymphedema—distichiasis syndrome
  - Hypertrichosis—lymphedema–telangiectasia syndrome
  - Yellow nail syndrome—lymphedema, yellow nail beds, pleural effusion, and bronchiectasis
- Secondary causes:
  - Infections:
    - Filariasis—most common secondary cause worldwide
    - Recurrent bacterial infections
    - Tuberculosis
  - Malignancy and malignancy-related treatments—most common secondary cause in developed countries:
    - Associated malignancies:
      - Breast cancer—most common
      - Lower extremity melanoma



FIG. 11.5: Massive nonpitting edema with elephantiasis caused by filariasis of the leg.

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        - Gynecologic cancer
        - Genitourinary cancer
        - Head and neck cancer
    - Mechanism:
        - Neoplastic disruption of lymphatics
        - Radiotherapy-induced damage to lymphatics
        - Surgical removal of lymph nodes
- Inflammatory disorders:
    - Rheumatoid arthritis
    - Psoriatic arthritis
    - Sarcoidosis
- Circumferential wounds to extremities
- Burns

Clinical features and staging of lymphedema:

- Typically unilateral or asymmetric
- Features of underlying etiology
- The International Society of Lymphology (ISL) provides a staging system for staging lymphedema:
    - Stage 0 or Ia: Usually asymptomatic
    - Stage I: Edema present; edema reduced by limb elevation
    - Stage II:
        - Early stage II: Pitting edema present
        - Late stage II: Nonpitting edema
        - Limb elevation does not reduce edema
    - Stage III: Elephantiasis present with fibrotic changes. Nonpitting edema.
- **Kaposi-Stemmers sign:** The thickened skin folds at the base of the second finger/toe, making it difficult for the examiner to lift the dorsum of the fingers/toes of the affected limb. This can be seen at any stage of the lymphedema.
- Peau d'orange appearance
- Look for scrotal swelling in patients with suspected filariasis.

Complications of Lymphedema

- *Infection*: Recurrent cellulitis, lymphangitis
- Lymphangiosarcoma **(Stewart-Treves syndrome)**
- Progressive fibrosis and tissue hardening
- Elephantiasis
- Ulceration and skin breakdown
- Deep vein thrombosis (DVT)
- Decreased wound healing
- Functional impairment and disability

Psychosocial Impact Evaluation

- Blood smear to evaluate for presence of microfilaria
- Radionuclide lymphoscintigraphy (isotope lymphography) is the preferred test if diagnosis is unclear.
- Duplex Doppler ultrasound for examining the deep venous system may supplement the evaluation of extremity edema.
- MRI and CT: Both provide objective evidence of structural changes such as cutaneous thickening, presence of edema within the epifascial plane, and can also detect characteristic "honeycomb" pattern of subcutaneous tissue.

Treatment

See **Table 11.12**.

TABLE 11.12: Treatment of lymphedema.

Complex decongestive physiotherapy (CDPT): ➢ Manual lymphatic drainage: Mild manual tissue compression ➢ Compression with multilayered bandage wrapping ➢ Skin care ➢ Exercise, weight reduction, limb elevation ➢ Diuretics have not been shown to be useful *Control of infection*: ➢ Treatment of cellulitis ➢ An extended period of oral antibiotics may be considered in patients with three or more episodes of cellulitis in a year	*Surgery*: ➢ Reconstructive surgery: – For early lymphedema – Microsurgical lymphatic-venous anastomosis – Autologous vessel transplantations ➢ Debulking surgery (excisional procedures): – Suction-assisted lipectomy – Staged cutaneous/subcutaneous excision

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Localized Edema

See **Box 11.1**.

Box 11.1: Various type of localized edema.

- *Facial edema*: Trichinosis, hypothyroidism, allergies, nephrotic syndrome, and angioedema
- *Pretibial myxedema*: Graves' thyrotoxicosis
- *Neurogenic edema*: Secondary to autonomic dysfunction
- *Lipedema*: Adiposity of the legs
- *Pseudothrombophlebitis*: It is unilateral edema with raised venous pressure caused by a popliteal cyst

DISORDERS OF SODIUM BALANCE

HYPONATREMIA

Q. GM23.4 **Enumerate the causes and describe the clinical features and the correct approach to the diagnosis and management of the patient with hyponatremia.**

Q. List the causes of drug-induced hyponatremia.

Box 11.2 shows the drugs causing hyponatremia.

Box 11.2: Drugs causing hyponatremia.

- Vasopressin analogs: Desmopressin, oxytocin
- Medications that stimulate release of vasopressin or potentiate the effects of vasopressin: SSRIs, antidepressants, morphine, and other opioids
- Medications that impair urinary dilution: Thiazide diuretics
- Medications that cause hyponatremia by unknown mechanism: Carbamazepine, antipsychotics, NSAIDs, cyclophosphamide, vincristine, nicotine, and chlorpropamide
- Illicit drugs: Ecstasy (MDMA)—associated with acute, life-threatening hyponatremia

Definition: Hyponatremia is defined as a condition in which serum sodium is <135 mEq/L.

- It is a **disorder of water regulation**, i.e., it usually results from increased water retention.
- It is the most common disorder of electrolytes in clinical practice, being reported in 10–30% of acutely or chronically hospitalized patients.

Classification of hyponatremia:

- Based on **duration and rate of development** of hyponatremia:
  - Acute hyponatremia <48 hours
  - Chronic hyponatremia ≥48 hours—**more** common
- Based on **serum sodium concentration** of hyponatremia:
  - Mild: Serum sodium 130–135 mEq/L
  - Moderate: Serum sodium 125–129 mEq/L
  - Severe: Serum sodium <125 mEq/L
- Based on serum osmolality and volume status, hyponatremia is subdivided into three main types **(Fig. 11.6)**.

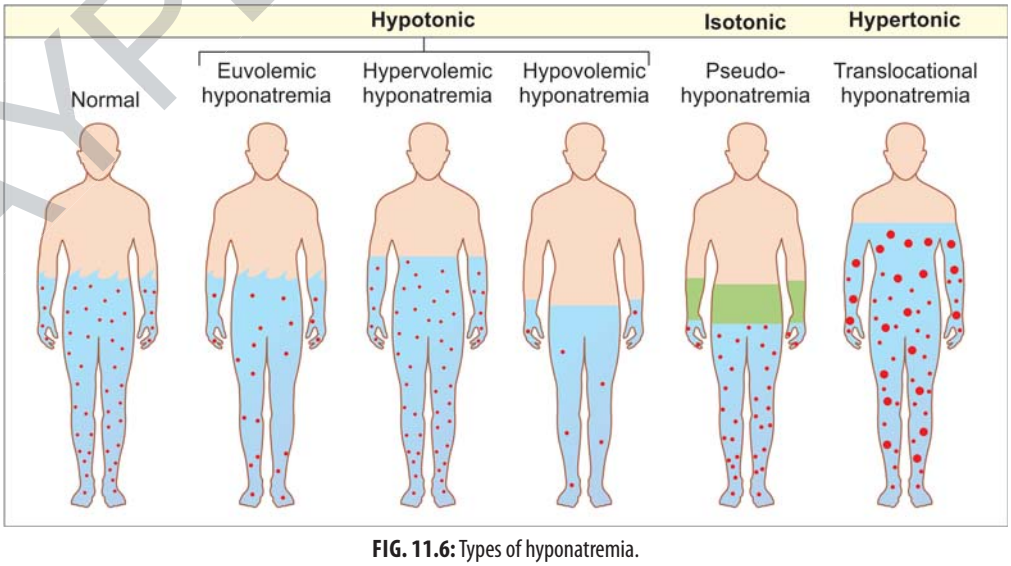

FIG. 11.6: Types of hyponatremia.

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Hypotonic Hyponatremia (Box 11.3)

- Serum osmolality <280 mOsm/kg H_2O
- Most common type of hyponatremia
- Due to:
  - Inadequate solute intake
  - Excess electrolyte-free water intake
  - Retention of electrolyte-free water due to:
    - Presence of AVP
    - Kidney disease
    - Use of diuretics: Diuretics cause volume depletion and release of AVP; and may also lead to diminished sodium transport in renal diluting sites.
- Consequences of hypotonic hyponatremia: Cell edema, predominantly cerebral edema
- Subtypes:
  - Hypovolemic hyponatremia
  - Hypervolemic hyponatremia
  - Euvolemic hyponatremia

Box 11.3: Alternate classification of hypotonic hyponatremia based on the ability to excrete dilute urine.

- Unimpaired urine dilution (ADH levels are not elevated)
  - Primary polydipsia
  - Low dietary solute intake (beer potomania, tea and toast diet)
- Impaired urine dilution but normal suppression of ADH
  - Advanced renal failure
  - Diuretic-induced hyponatremia
- Impaired urine dilution due to unsuppressed ADH secretion
  - Reduced effective arterial blood volume
    - Hypovolemic hyponatremia
    - Heart failure and cirrhosis (hypervolemic hyponatremia)
    - Addison's disease
  - Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Disorders with impaired urine dilution due to abnormal V2 receptor (nephrogenic SIADH)
- Abnormally low osmostat which leads to low threshold for release of ADH
- Exercise-induced hyponatremia
- Cerebral salt wasting

Hypovolemic Hyponatremia

- Hypovolemic hyponatremia results from loss of fluids rich in sodium and/or potassium.
- This stimulates thirst and AVP secretion, leading to water retention.
- Causes:
  - GI losses:
    - Diarrhea
    - Vomiting
  - Renal losses:
    - Diuretics (predominantly thiazide diuretics)
    - Cerebral salt wasting
    - Adrenal insufficiency
    - Salt-losing nephropathies
  - Dermal losses:
    - Burns
    - Sweating
  - Third spacing:
    - Pancreatitis
    - Sepsis
    - Bowel obstruction

Hypervolemic Hyponatremia

- Caused by renal sodium and water retention
- Causes:
  - Cirrhosis of liver
  - Heart failure
  - Chronic kidney disease
  - Nephrotic syndrome

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Euvolemic Hyponatremia
- Most common dysnatremia in hospitalized patients
- Causes:
  - SIADH
  - Nephrogenic syndrome of inappropriate antidiuresis
    - Due to mutation causing activation of vasopressin receptor 2 (V2R)
  - Low solute intake: "tea and toast" diet, beer potomania
  - Hypothyroidism
  - Glucocorticoid deficiency
  - Exercise associated hyponatremia
    - Due to excessive water intake combined with impaired water excretion due to persistent ADH secretion
  - Water intoxication.

Isotonic Hyponatremia

- Serum osmolality 280–295 mOsm/kg H_2O
- Pseudohyponatremia due to hyperlipidemia or hypoproteinemia (e.g., multiple myeloma).

Hypertonic Hyponatremia

- Serum osmolality >295 mOsm/kg H_2O
- Due to presence of additional osmoles (glucose/mannitol)
- Hyperglycemia
- *Note:* Sodium correction in hyperglycemia: For every 100 mg/dL increase in blood sugar, sodium concentration will fall by approximately 2 mEq/L
- Hypertonic fluid infusion
- Radiocontrast.

Effect of Hypotonic Hyponatremia on Brain (Fig. 11.7)

Hyponatremia induces generalized cellular swelling due to entry of water from ECF to ICF. The symptoms of hyponatremia are primarily neurological and are due to the development of cerebral edema within a rigid skull.

- **Swelling and reduced osmolality:** Within minutes of hyponatremia, the reduced osmolality causes a shift of fluid from the ECF to the ICF, leading to brain swelling. This usually occurs when the hyponatremia develops rapidly.
- **Rapid adaptation:** The brain tries to rapidly adapt to this hypotonic environment by the loss of electrolytes such as sodium, potassium, and chloride. These are osmotically active and help in partially restoring the brain volume.
- **Slow adaptation:** Further loss of osmotically active organic compounds such as glutamate, myoinositol, and taurine from the brain cells also help in restoring brain volume.
- The adaptation process takes about 48 hours, which is the basis for the classification of acute and chronic hyponatremia based on the threshold of 48 hours.
- **Slow versus rapid correction of hypotonicity:**
  - Before adaptation (<48 hours), decreased extracellular osmolality triggers water to enter brain cells, increasing the risk of cerebral edema.
  - After adaptation (>48 hours), rapid increase in serum sodium concentration can cause brain cells to release water, increasing the risk of osmotic demyelination. Hence sodium should be corrected at a slow rate in chronic hyponatremia.

TABLE 11.13: Classification by severity of symptoms of hyponatremia.

Severity	*Serum sodium level*	*Neurologic symptoms*	*Typical duration of hyponatremia*
Mild	<135 mmol/L	Headache, irritability, difficulty concentrating, altered mood, and depression	Chronic
Moderate	Generally <130 mmol/L	Nausea, confusion, disorientation, altered mental status, unstable gait, and falls	Acute or chronic
Severe	Generally <125 mmol/L	Vomiting, seizures, obtundation, respiratory distress, and coma	Acute

Clinical Features

- Hyponatremia is essentially a laboratory diagnosis.
- History and physical examination should determine the volume status of the patient and try to identify the cause of the hyponatremia.
- Symptoms due to hyponatremia depend on the acuity of presentation and the serum sodium levels, as described in **Table 11.13**.

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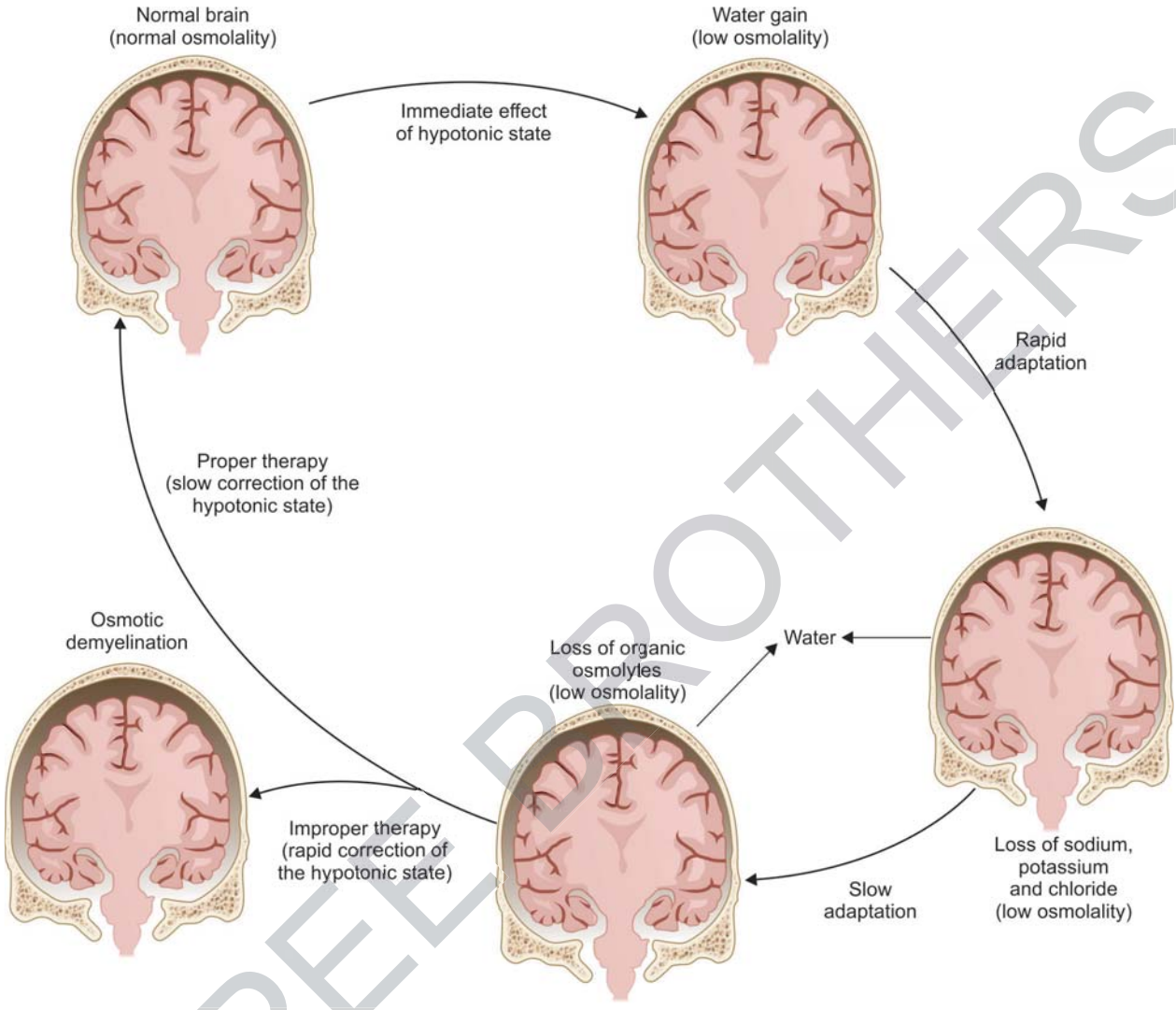

FIG. 11.7: Effects of hyponatremia on the brain.

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Investigations

- **Step 1: Serum sodium:**
  - Hyponatremia is diagnosed when serum sodium is <135 mEq/L
  - Based on severity, hyponatremia is classified as:
    - Mild: Serum sodium 130–135 mEq/L
    - Moderate: Serum sodium 125–129 mEq/L
    - Severe: Serum sodium <125 mEq/L
- **Step 2: Serum osmolality:**
  - Serum osmolality <275 mOsm/kg H_2O indicates hypotonic hyponatremia.
  - Serum osmolality between 280 and 295 mOsm/kg H_2O indicates isotonic hyponatremia (pseudohyponatremia).
  - Serum osmolality >295 mOsm/kg H_2O indicates hypertonic hyponatremia.
- **Step 3: Urine osmolality:**
  - It should be measured in patients with hypotonic hyponatremia to confirm if urine is appropriately dilute.
  - If urine osmolality is less than 100 mOsm/kg H_2O
    - It indicates that there is no diluting defect.
    - This may be seen in primary polydipsia or due to low solute intake (e.g., beer potomania)

- Low urine osmolality may also be seen in patients with hypovolemic hyponatremia who have been volume resuscitated, if osmolality is measured after administration of isotonic saline.

- If urine osmolality is more than 200 mOsm/kg H_2O, assess volume status and urine sodium.

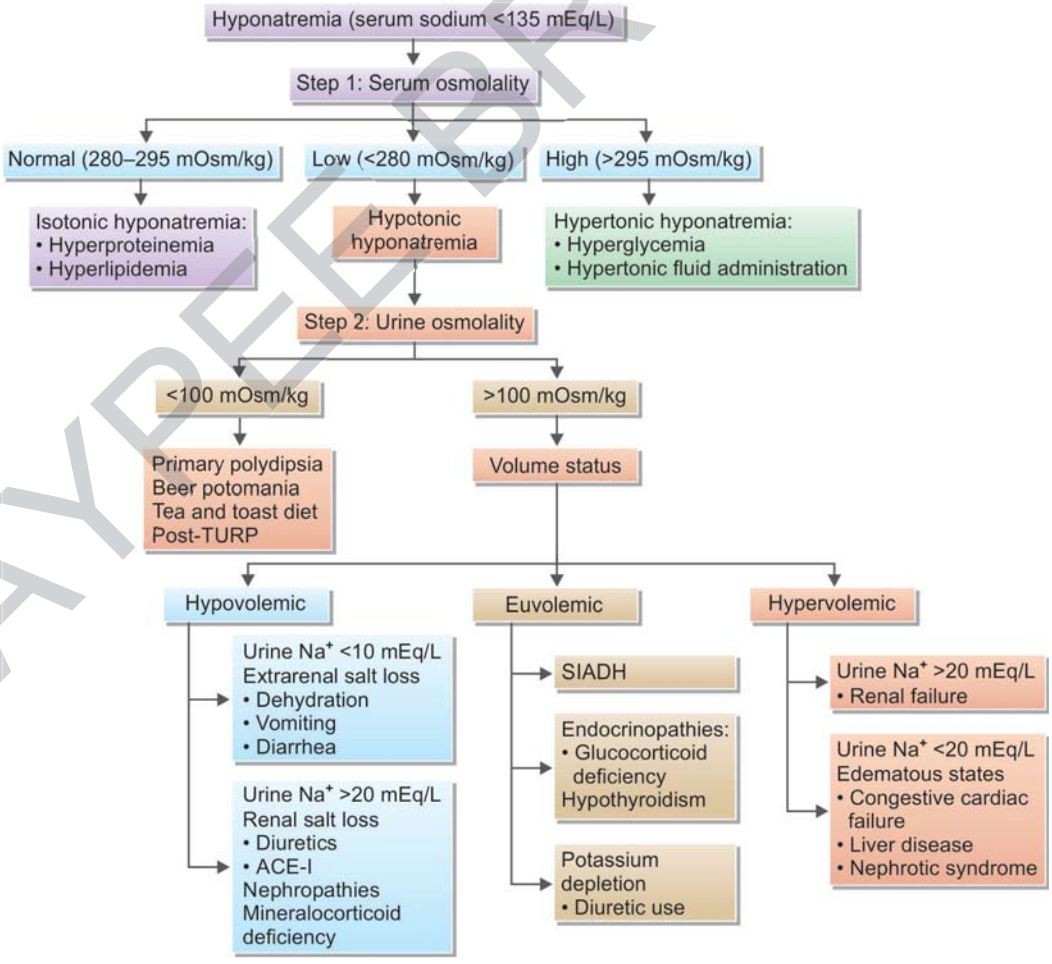
- **Step 4: Urine sodium (Table 11.14)**
- **Other investigations:**
  - Thyroid function test: To rule out hypothyroidism
  - Serum cortisol ± ACTH: To exclude adrenal insufficiency
  - Serum creatinine: To look for renal insufficiency
  - Serum uric acid: May help assess volume status
  - Other tests to diagnose the underlying cause, as guided by history and physical examination:
    - Serum lipids and serum protein electrophoresis in cases of pseudohyponatremia to look for hypercholesterolemia and multiple myeloma, respectively.
    - Echocardiogram, BNP: For heart failure
    - Ultrasound abdomen: Cirrhosis
    - Urine for proteinuria
    - CT brain/chest/abdomen: To help detect paraneoplastic SIADH.

TABLE 11.14: Differentiating hypotonic hyponatremia based on volume status and urine sodium.

Volume status	*Urine sodium (mEq/L)*	*Etiology*
Hypovolemic	≤20	Nonrenal sodium loss
	>20	Renal sodium loss
Hypervolemic	≤20	Cirrhosis, heart failure, and nephrotic syndrome
	>20	Renal failure
Euvolemic	>20	Most patients with euvolemic hyponatremia

Approach to the diagnosis of the cause of hyponatremia **(Flowchart 11.2)**.

FLOWCHART 11.2: Diagnosing the cause of hyponatremia.



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Management

The management of hypotonic hyponatremia depends on the severity, duration of symptoms, and the underlying cause.

Goals of Treatment

- To correct serum sodium levels to avoid complications of severe hyponatremia
- To avoid overly rapid correction of hyponatremia, which may lead to osmotic demyelination
- Correct underlying causes

1. **Severe symptomatic hyponatremia:**
   - Goal: Rapid increase of serum sodium by 4–6 mEq/L is recommended irrespective of whether hyponatremia is acute or chronic.
   - This is done by IV infusion of hypertonic saline.
     - Protocol 1: 100 mL bolus of 3% saline is infused over 10 minutes; repeated up to 3 times, as necessary.
     - Protocol 2: 150 mL bolus of 3% saline over 20 minutes. Check serum sodium concentration after 20 minutes. Consider repeating twice or until a target of 5 mEq/L increase in serum sodium concentration.
   - Follow-up management:
     - If symptoms improve: Stop infusion of hypertonic saline
       - Start treatment based on etiology, if identified
     - If symptoms do not improve:
       - Continue IV infusion of 3% hypertonic saline aiming for an increase in sodium concentration by 1 mmol/L/hr
     - *Note:* Stop hypertonic saline when either:
       - Symptoms improve or
       - Serum sodium concentration increases by 10 mEq/L in total or
       - Serum sodium concentration reaches 130 mEq/L
2. **Mild or asymptomatic hyponatremia:**
   - Treatment depends on whether hyponatremia is acute or chronic and based on the underlying etiology
   - Rate of correction:
     - Acute hyponatremia: Rate of correction does not need to be restricted in well-documented cases of acute hyponatremia
     - Chronic hyponatremia/duration of hyponatremia unknown:
       - Increase serum sodium with a goal of ≤6–8 mEq/L/day and not more than 18 mEq/L in 48 hours
       - Monitor serum sodium every 2–4 hourly
3. **Estimating the effect of 1 L of any IV saline infusion on serum sodium levels:**
   - Change in serum sodium = [(infusion sodium concentration + infusion potassium concentration) – serum sodium concentration/total body water + 1]
   - The sodium content of various intravenous fluids is mentioned in **Table 11.15.**
   - This formula may be used to determine the amount of saline and the rate of fluid infusion required to correct hyponatremia.
   - However, this formula is only a rough guide and is limited by the fact that it does not account for ongoing electrolyte or water losses.
   - Use of this formula does not serve as a replacement for regular serum sodium monitoring. Sodium levels should be monitored every 2–4th hourly.

TABLE 11.15: Sodium content of various intravenous fluids per liter.

Intravenous fluid	*Sodium content*
7.5% $NaHCO_3$	900 mEq/L
3% NaCl	512 mEq/L
0.9% NaCl normal saline	154 mEq/L
Ringer lactate	130 mEq/L
0.45% NaCl Half NS	77 mEq/L
Isolyte G	63 mEq/L
Isolyte M	40 mEq/L
5% dextrose	Nil

4. **Additional treatment based on the underlying etiology (in mild or asymptomatic disease)**
   a. Hypovolemic hyponatremia:
      - In patients with asymptomatic hypovolemic hyponatremia, isotonic saline can be used to restore the intravascular volume.
      - Amount of 0.9% saline to be replaced may be calculated by the above formula and overcorrection of chronic hyponatremia should be avoided.
      - Fludrocortisone can be used in cerebral salt-wasting syndrome.
   b. Hypervolemic hyponatremia:
      - Fluid restriction:
        - The amount of fluid intake should be (urine output – 500 mL)
        - Amount of fluid to be restricted can also be determined by calculating the urine: plasma electrolyte ratio [urinary (Na) + (K)/plasma (Na)]
          a. If the ratio is more than 1, then the fluid can be aggressively restricted up to less than 500 mL/day.

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b. For approximately 1 then the fluid can be restrict up to 500–700 mL
c. For ratio less than 1, fluids can be restricted up to 1 L.
- ❑ Loop diuretics
- ❑ Vasopressin antagonists may be useful when the above measures fail (see section on Vaptans below)

c. Euvolemic hyponatremia:
- ◆ Treat the underlying cause where possible
- ◆ Fluid restriction
- ◆ Loop diuretics
- ◆ Oral salt tablets in patients with SIADH
- ◆ Oral urea tablets in patients with SIADH
- ◆ Demeclocycline in patients with chronic asymptomatic hyponatremia due to SIADH if unresponsive to fluid restriction
- ◆ Vasopressin antagonists

5. **Correction of inadvertent rapid overcorrection of sodium:**
- Discontinue hypertonic saline/other measures of active sodium correction
- Infusion of electrolyte free water (e.g., 5% dextrose)
- IV desmopressin

Vasopressin Receptor Antagonists (VAPTANS)

Q. Write short note on VAPTANS.

- Nonselective (mixed V1A/V2): *Conivaptan*: Intravenous
- Selective:
  - *V1A selective (V1RA)*: Relcovaptan
  - *V1B selective (V3RA)*: Nelivaptan
  - *V2 selective (V2RA)*: Tolvaptan, lixivaptan, mozavaptan, satavaptan. V2 selective (V2RA) can cause an electrolyte-free aquaresis, reduce urine osmolality and raise serum Na. Their mechanism of action is presented in **Figure 11.8**.
- Tolvaptan and conivaptan are FDA-approved drugs.
- **Tolvaptan**, an oral V2 selective agent, is the most commonly used agent.
  - Indication: Use in euvolemic or hypervolemic hyponatremia (heart failure).
  - Dose:
    - ♦ Initially 15 mg/day
    - ♦ Maximum 60 mg/day
  - Treatment should be limited to 30 days
  - Monitor serum sodium and volume status
  - Contraindicated in:
    - ♦ Hypovolemic hyponatremia
    - ♦ Acute hyponatremia and severe symptomatic hyponatremia (urgent need to raise serum sodium levels)
    - ♦ Pregnancy
    - ♦ Severe liver dysfunction and cirrhosis
- Vaptans are not suitable for hyponatremia due to cerebral salt wasting and psychogenic polydipsia where the ADH level is appropriate.
- Caution: It should **NOT** be used along with hypertonic saline.
- Adverse effects:
  - Thirst 8–16%; dry mouth 4–13%, polyuria
  - Hypernatremia develops in 5%.
  - Rapid correction of serum sodium levels may predispose to osmotic demyelination syndrome.
  - Hyperglycemia
  - GI hemorrhage in cirrhosis

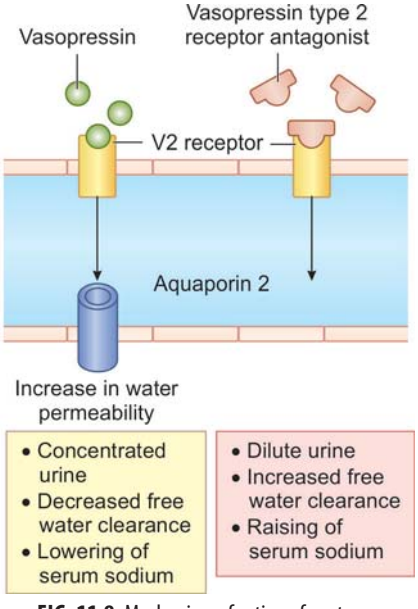

FIG. 11.8: Mechanism of action of vaptans.

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