Treatment

- In patients with severe symptoms or severe hyponatremia, 3%NaCl (possibly combined with a loop diuretic) should initially be used to more rapidly correct the hyponatremia. A loop diuretic can be administered concurrently with 3%NaCl to enhance the serum sodium correction by increasing free water excretion.
- Long-term management will be required for patients in whom the underlying cause of hyponatremia cannot be corrected. Depending on the cause, water restriction, increasing sodium intake, and/or a VRA may be used.

Outcomes

- The initial treatment goal is to increase serum tonicity just enough to control severe symptoms which typically requires only a small increase (5%) in serum sodium concentration.
- In all cases the goal is to avoid an increase in the serum sodium concentration of more than 6-12 mEq/L in 24 hours (0.5 mEq/L per hour) or 18 mEq/L in 48 hours period.
- A patient who has or is at high risk of experiencing severe symptoms caused by hyponatremia ([Na] < 110-115 mEq/L) should receive a small amount of 3%NaCl (513 mEq/L) until severe symptoms resolve.

Outcomes

- In SIADH, the urinary concentration of osmotically effective cations often exceeds 154 mEq/L, these patients should be preferentially treated with 3%NaCl.
- When the urine osmolality exceeds 300 mOsm/kg, it is advisable to administer an IV loop diuretic (furosemide 20-40 mg given Q6H) to increase solute-free water excretion and to prevent volume overload which can result from 3%NaCl administration.

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Outcomes

- Acute hypervolemic hypotonic hyponatremia is particularly problematic to manage because the sodium and volume needed to minimize the risk of cerebral edema or seizures can worsen already compromised liver, heart, or kidney function. These patients generally should be treated initially with 3%NaCl and water restriction.
- Loop diuretic or arginine VRA therapy is often required to facilitate urinary free water excretion.

Outcomes

- Patients with hypovolemia should be reexamined frequently. The serum [Na] should be measured Q2-4H to allow timely adjustment of the rate and composition of IV fluids to avoid too rapidly increasing the serum [Na].
- Treatment of SIADH always involves restricting water and correcting the underlying cause. The primary treatment goal is to induce a negative water balance by restricting water intake to < 1,000-1,200 mL/day.
- An additional goal is to maintain the serum [Na] close to 130 mEq/L to reduce CNS symptoms and avoid iatrogenic hypovolemia.

Outcomes

- Patients with chromic SIADH who are unable to restrict water intake sufficiently can be treated by increasing solute intake with NaCl supplementation and/or loop diuretic administration.
- The goal is to increase the daily solute intake and excretion to approximately 900 mOsm per day. 9 gm of NaCl would be required to increase the osmolar excretion to 900 mOsm/day.
- Each 1 gm NaCl tablet contains 17 mmol of Na and 17 mmol of Cl.

Demeclocycline

- Demeclocycline, a semisynthetic tetracycline antibiotic, is a treatment option for some patients with SIADH whose serum [Na] is not adequately controlled by water restriction alone.
- The usual dosage is 300 mg given orally 2-4 times daily with the delayed onset of action (3-6 days).
- Demeclocycline should not be used in patients with liver disease or compromised fluid intake, who are at high risk for demeclocycline-induced renal tubular toxicity and AKI, pregnant or younger than 8 years.

Vasopressin Receptor Antagonists

- VRAs have effects on water excretion and were the first significant breakthrough in hyponatremia treatment since loop diuretics.
- It may also may be used to treat euvolemic and hypervolemic hypotonic hyponatremia.
- Conivaptan (Vaprisol®) is FDA-labeled for use in the treatment of acute euvolemic and hypervolemic hyponatremia in hospitalized patients (only available as an IV formulation), is for up to 4 days of use.

Vasopressin Receptor Antagonists: Tolvaptan

- Tolvaptan (Samsca®) is FDA-labeled for the treatment of clinically significant ([Na] < 125 mEq/L) euvolemic or hypervolemic hyponatremia or less marked symptomatic hyponatremia that is unresponsive to other therapeutic interventions in patients with HF, cirrhosis and SIADH.
- The usual starting tolvaptan dosage is 15 mg given orally once daily, but 7.5 mg should be considered for patients older than 90 years of age.
- Tolvaptan therapy is contraindicated in patients needing rapid serum [Na] correction (2-4 hour delayed onset)

Vasopressin Receptor Antagonists: Tolvaptan

- Tolvaptan effectively produces aquaresis and increases serum [Na] in patients with chronic kidney disease (CKD3-5) who are not receiving RRT.
- VRA use should be avoided with hypertonic saline (e.g. 3%NaCl) due to the risk of too rapid and/or overcorrection of the serum [Na].
- Most common adverse effects are thirst, dry mouth, weakness, constipation, hyperglycemia and urinary frequency.
- The FDA has issued a warning that tolvaptan should not be used for more than 30 days and should not be used in patients with liver disease including cirrhosis.

Outcomes

- When the serum Na has increased by 6-8 mEq/L, oral water or IV dextrose 5% inwater (D5W) should be given to replace urine output to minimize the risk of overcorrecting the serum [Na] and ODS.
- The initial treatment goals for patients with asymptomatic or minimally symptomatic hypervolemic (expanded ECF volume) hypotonic hyponatremia include achieving a negative water balance and minimizing rapid changes in brain cell volume until the serum [Na] is at or above 125 mEq/L.
- Management involves correction of the underlying cause as well as water restriction to < 1,000-1,200 mL/day.

Outcomes

- Additionally, dietary sodium intake should be restricted to 1,000–2,000 mg/day, depending on the degree of ECF volume expansion.
- VRAs have also been used for the treatment of hypervolemic hypotonic hyponatremia in patients with HF or cirrhosis.

Hypernatremia

- Hypernatremia, defined as a serum sodium concentration > 1145 mEq/L, is always associated with hypertonicity and intracellular dehydration, resulting from a water deficient relative to ECF sodium content.

Characteristics	Hypovolemic Hypernatremia	Euvolemic (Isovolemic) Hypernatremia	Hypervolemic Hypernatremia
Water and sodium	Water loss >> sodium loss	Water loss only	Sodium gain > water gain
Causes	Renal: osmotic diuresis, diuretic use, postoperative diuresis, high-output acute tubular necrosis	Congenital or acquired DI Nephrogenic DI Primary polydipsia	Sodium overload (eg, 3% NaCl, sodium bicarbonate, NaCl tablets, concentrated tube feedings, hypertonic dialysate, sodium-containing medications)
Effect on TBW	↓↓	↓	↑
Effect on TBNa	↓	↔	↑↑
Additional laboratory findings	Renal: UOsm high, UNa high Nonrenal: UOsm high, UNa low	Renal: UOsm low, UNa variable Nonrenal: UOsm high, UNa variable	Renal: UOsm high, UNa high
Clinical presentation	Orthostasis, hypotension, tachycardia, dry mucous membranes	Depends on severity of hypernatremia; seizures, lethargy	Peripheral and pulmonary edema, variable blood pressure
Treatment	0.9% NaCl until vital signs stable, then free water replacement	Free water replacement, AVP, or AVP analogue	Free water replacement with loop diuretic, may require hemodialysis to remove volume

AVP, arginine vasopressin; DI, diabetes insipidus; NaCl, sodium chloride; TBNa, total body sodium; TBW, total body water; UNa, urine sodium concentration; UOsm, urine osmolality.

Hypernatremia

- A water diuresis can be caused by diabetes insipidus (DI), which can be classified as either central DI (decreased AVP secretion) or nephrogenic DI (decreased kidney response to AVP).
- Patients with untreated DI excrete large volume (3–20 L/day) of dilute urine, resulting in hypernatremia.

Hypernatremia

General

- Increase in serum sodium concentration and osmolality causes acute water movement from the ICF to the ECF
- Decreased brain cell volume can cause cerebral vein rupture, leading to focal intracerebral and subarachnoid hemorrhages and irreversible CNS damage

Symptoms

- Mild: lethargy, weakness, confusion, restlessness, irritability
- Moderate: twitching
- Severe: seizures, coma, death; usually requires acute increase in serum sodium to ≥160 mEq/L (mmol/L)
- Serum sodium ≥180 mEq/L (mmol/L) is associated with high mortality
- Other symptoms (depend on etiology of hypernatremia): postural hypotension, tachycardia, dry mucous membranes, diminished skin turgor, reduced or increased urine output.
- Signs and symptoms difficult to detect in patients with underlying neurologic dysfunction

Treatment

- Patients with central DI should generally receive AVP replacement therapy with desmopressin.
- The intranasal formulation, 1-desamino-8-D-arginine vasopressin (DDAVP), is preferred; however, oral tables are available and may be useful in some patients.
- Each intranasal DDAVP (100 mcg/mL) delivers 10 mcg of desmopressin acetate. The initial dosage is 10 mcg once daily, titrated to 20 mcg twice daily based on the serum [Na].
- The oral formulation as the bioavailability is only about 5%. Thus, a 0.1 mg tablet is equivalent to 2.5 to 5 mcg of nasal spray.

TABLE 66-9 Drugs Used in Central and Nephrogenic DI

Drug	Indication	Dose
Desmopressin acetate	Central and nephrogenic	5-20 mcg intranasally q12-24hr
Chlorpropamide	Central	125-250 mg orally daily
Carbamazepine	Central	100-300 mg orally twice daily
Clofibrate	Central	500 mg orally four times daily
Hydrochlorothiazide	Central and nephrogenic	25 mg orally q12-24hr
Amiloride	Nephrogenic	5-10 mg orally daily
Indomethacin	Central and nephrogenic	50 mg orally q8-12hr

Edema: Diuretics

- Edema may be treated less acutely, which a comprehensive approach that includes not only diuretics but also sodium and water restriction and optimal treatment of the underlying disease.
- Diuretics are the primary pharmacologic therapy for edema when severe or then treatment of the underlying disease and sodium and water restriction are insufficient.
- Loop diuretics (furosemide, torsemide) inhibit the Na^+-K^+-$2Cl^-$) carrier in the loop of Henly.

Edema: Diuretics

- Thiazide and thiazide-like diuretics (HCTZ, chlorthalidone, indapamide, metolazone) inhibit the Na+-Cl= carrier in the distal tubule.
- Potassium-sparing diuretics (triamterene, amiloride) inhibit the sodium channel in the cortical collecting duct either directly.
- Interfering with aldosterone activity (spironolactone, eplerenone).
- Carbonic anhydrase inhibitor (acetazolamide) acts in the proximal convoluted tubules and has been used in patients eith diuretic resistance.

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Edema: Diuretics

- All diuretics act by inhibiting sodium reabsorption in the renal tubules, increasing the fractional excretion of sodium (FeNa).
- Loop diuretics are the most potent diuretics. Thiazide-and potassium-sparing diuretics are less potent.
- Although a large portion of the filtered sodium is reabsorbed in the proximal nephron, the efficacy of proximal acting diuretics (e.g. acetazolamide) is limited by excess fluid and sodium reabsorption in the loop of Henle.
- Sodium reabsorption by the distal tubule can compensate for reduced reabsorption in the loop of Henle when Na intake is high.

Edema: Diuretics

- The effectiveness of thiazide and loop diuretics is dependent on the drug concentration in the tubular lumen. These diuretics are delivered to the tubular lumen via active transport by the proximal tubular cell.
- Loop diuretic resistance can be caused by pronounced sodium reabsorption in the distal nephron when sodium absorption in the loop of Henle is blocked.
- Patients with diuretic-resistant edema can be treated with a loop diuretic and metolazone.

Edema: Diuretics

- Adverse effects associated with loop and thiazide diuretics include hypokalemia, excess ECF volume loss (hypovolemia), hypomagnesemia, metabolic alkalosis and hyperuricemia.
- Sodium imbalance is a concern with diuretic therapy: hyponatremia with thiazides, hypernatremia with loops.
- Calcium imbalance can occur with diuretic use: hypocalcemia with loops, hypercalcemia with thiazides.
- Loop diuretics cause hypercalciuria and can lead to bone disorders (osteopenia, osteoporosis) or kidney stones when used chronically.

Edema: Diuretics

- Chronic use of potassium-sparing diuretics can cause a mild metabolic acidosis and hyperkalemia.
- Spironolactone can cause reversible gynecomastia in about 10% of men and in about 50% of men receiving 150 mg/day or more.

Edema: Cirrhosis

- Secondary hyperaldosteronism from activation of the renin-angiotensin-aldosterone system plays a major role in the pathogenesis of edema in patients with cirrhosis.
- Therefore, these patients should initially be treated with an aldosterone antagonist (spironolactone) in the absence of impaired GFR and hyperkalemia.
- Thiazides can be added for patients with a creatinine clearance greater than 50 mL/min.
- For patients with diuretic-resistant edema, a loop diuretic may be used instead of thiazide.