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Diagnosis and Management of Hyponatremia
A Review

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IMPORTANCE Hyponatremia is the most common electrolyte disorder and it affects approximately 5% of adults and 35% of hospitalized patients. Hyponatremia is defined by a serum sodium level of less than 135 mEq/L and most commonly results from water retention. Even mild hyponatremia is associated with increased hospital stay and mortality.

OBSERVATIONS Symptoms and signs of hyponatremia range from mild and nonspecific (such as weakness or nausea) to severe and life-threatening (such as seizures or coma). Symptom severity depends on the rapidity of development, duration, and severity of hyponatremia. Mild chronic hyponatremia is associated with cognitive impairment, gait disturbances, and increased rates of falls and fractures. In a prospective study, patients with hyponatremia more frequently reported a history of falling compared with people with normal serum sodium levels (23.8% vs 16.4%, respectively; $P < .01$) and had a higher rate of new fractures over a mean follow-up of 7.4 years (23.3% vs 17.3%; $P < .004$). Hyponatremia is a secondary cause of osteoporosis. When evaluating patients, clinicians should categorize them according to their fluid volume status (hypovolemic hyponatremia, euvolemic hyponatremia, or hypervolemic hyponatremia). For most patients, the approach to managing hyponatremia should consist of treating the underlying cause. Urea and vaptans can be effective treatments for the syndrome of inappropriate antidiuresis and hyponatremia in patients with heart failure, but have adverse effects (eg, poor palatability and gastric intolerance with urea; and overly rapid correction of hyponatremia and increased thirst with vaptans). Severely symptomatic hyponatremia (with signs of somnolence, obtundation, coma, seizures, or cardiorespiratory distress) is a medical emergency. US and European guidelines recommend treating severely symptomatic hyponatremia with bolus hypertonic saline to reverse hyponatremic encephalopathy by increasing the serum sodium level by 4 mEq/L to 6 mEq/L within 1 to 2 hours but by no more than 10 mEq/L (correction limit) within the first 24 hours. This treatment approach exceeds the correction limit in about 4.5% to 28% of people. Overly rapid correction of chronic hyponatremia may cause osmotic demyelination, a rare but severe neurological condition, which can result in parkinsonism, quadriparesis, or even death.

CONCLUSIONS AND RELEVANCE Hyponatremia affects approximately 5% of adults and 35% of patients who are hospitalized. Most patients should be managed by treating their underlying disease and according to whether they have hypovolemic, euvolemic, or hypervolemic hyponatremia. Urea and vaptans can be effective in managing the syndrome of inappropriate antidiuresis and hyponatremia in patients with heart failure; hypertonic saline is reserved for patients with severely symptomatic hyponatremia.

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Hyponatremia, which is defined as a serum sodium level of less than 135 mEq/L, affects approximately 5% of adults. Approximately 20% of people who are older than 65 years of age have hyponatremia as well as 35% of patients who are hospitalized, 30% of patients with heart failure, and 50% of patients with cancer or cirrhosis.[1-4] The pathogenesis of hyponatremia is complex and heterogenous and symptoms vary widely. Hyponatremia is associated with adverse outcomes. Even mild hyponatremia is associated with increased length of hospitalization, greater resource use, and higher mortality.[4] This review summarizes current evidence regarding the pathogenesis, clinical presentation, diagnosis, and management of hyponatremia.

Methods

We searched PubMed and Google Scholar for English-language studies of pathogenesis, clinical presentation, diagnosis, and

management of adult hyponatremia published between January 2010 and December 2021. The reference lists of selected articles also were searched for relevant publications. Randomized clinical trials, systematic reviews, meta-analyses, clinical practice guidelines, and articles pertinent to general medical readership were prioritized. Of 224 publications identified during the search, 77 were included and consisted of 33 clinical trials, 14 systematic reviews, 26 reviews, 1 meta-analysis, and 3 clinical practice guidelines.

Pathogenesis

Sodium and its anions (largely chloride and bicarbonate; however, there are many others in small concentrations) comprise most of the particles dissolved in serum (osmoles), the remainder consist of glucose and urea. Typically, hyponatremia is due to water retention that dilutes the serum sodium level and osmolality (<275 mOsm/kg).[5] Effective osmolality (tonicity) refers to the contribution to osmolality by solutes with low–cell-membrane permeability (sodium, its anions, and glucose), causing transcellular water shifts. Tonicity is calculated from sodium and glucose. For patients without hyperglycemia, tonicity is approximated by doubling the serum sodium level. Normal tonicity is 270 mOsm/kg to 285 mOsm/kg. Most commonly, hyponatremia is associated with low osmolality and tonicity (<270 mOsm/kg) because levels of glucose and urea are normal. Hypotonic hyponatremia can result in cerebral edema.[5,6]

In contrast to sodium and glucose, urea raises osmolality but not tonicity because it has high–cell-membrane permeability.[5,6] This phenomenon also occurs with alcohols. A patient with hyponatremia in conjunction with uremia or severe ethanol intoxication may have high osmolality but low tonicity and therefore has an increased risk of cerebral edema.

Hyponatremia may be associated with normal or high tonicity.[5,6] Hyperglycemia translocates water from cells into extracellular fluid and causes hyponatremia simultaneously with hypertonicity; each 100-mg/dL increase in the glucose level decreases the serum sodium level by approximately 2 mEq/L. Retention of mannitol or irrigant solutions without sodium can cause isotonic or hypertonic hyponatremia. Pseudohyponatremia reflects a laboratory artifact that occurs in patients with severe hyperproteinemia or extreme hyperlipidemia, in which hyponatremia is associated with normal tonicity. Point-of-care devices are not subject to this laboratory artifact.

Water homeostasis depends on receptors residing along the anterior wall of the brain's third ventricle that respond to serum tonicity and angiotensin II by regulating water intake (thirst) and water excretion (release of vasopressin).[7] Vasopressin (antidiuretic hormone) is secreted by hypothalamic neurons in response to hypertonicity (osmotic stimulus) and decreased effective arterial blood volume (nonosmotic stimulus). Vasopressin promotes water retention by activating the vasopressin receptor 2 in the nephron's collecting duct, thereby inserting water channels in the apical membrane and increasing water permeability. Additional nonosmotic stimuli of vasopressin release include nausea, pain, acute stress (psychosis, exercise), postoperative state, and drugs such as narcotics and tricyclic antidepressants.[6,8]

According to the Edelman equation, serum sodium level $[Na^+]_s$ is approximated by the body's exchangeable sodium and potassium levels (Na_e^+ and K_e^+, respectively) divided by total body water: $[Na^+]_s \approx Na_e^+ + K_e^+$/total body water. Exchangeable sodium and potassium levels refer to the portion of their content (approximately 70% and 85%, respectively) that is osmotically active; most nonexchangeable sodium resides in bone. The Edelman equation demonstrates that hyponatremia represents excess water relative to the exchangeable sodium and potassium levels. Hyponatremia may develop with normal, decreased, or increased sodium content.[5,6,8,9]

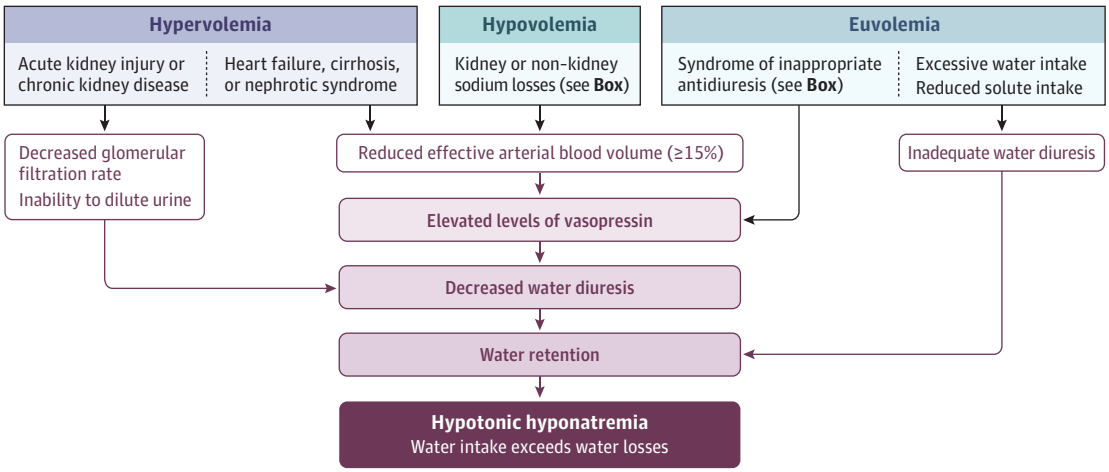
Primary polydipsia is characterized by increased total body water. Hypovolemic hyponatremia (diarrhea) is characterized by reduced exchangeable sodium and potassium levels, with a smaller decline in total body water. Hypervolemic hyponatremia (heart failure) is characterized by an increased exchangeable sodium level with a larger increase in total body water. The syndrome of inappropriate antidiuresis (SIAD) is characterized by mildly reduced exchangeable sodium and potassium levels combined with increased total body water.

Water retention in patients with hypotonic hyponatremia reflects decreased water excretion or excessive water intake (**Figure 1**). Decreased water excretion is typically associated with increased vasopressin, decreased glomerular filtration rate, or reduced solute intake. Increased release of vasopressin is the most common abnormality that occurs in patients with SIAD and in the setting of decreased effective arterial blood volume. In patients with SIAD, vasopressin release is considered inappropriate because it occurs independently of hypertonicity or decreased effective arterial blood volume. A reduction in effective arterial blood volume by approximately 15% triggers nonosmotic vasopressin release and promotes water retention in patients with hypovolemic or hypervolemic hyponatremia.[6]

In patients with hypervolemic hyponatremia, reduced effective arterial blood volume results from pump failure (heart failure), decreased vascular resistance (cirrhosis), or arterial underfilling (nephrotic syndrome).[8] Cortisol deficiency (due to adrenocorticotropic hormone deficiency or panhypopituitarism) increases vasopressin release by stimulating the pituitary and by causing vasoplegia, which is characterized by hypotension and reduced systemic vascular resistance, thereby reducing effective arterial blood volume. Gain-of-function variants of the vasopressin receptor 2 gene account for nephrogenic SIAD.[6,8] In patients with acute kidney injury or chronic kidney disease (stage 3, 4, or 5), a decreased glomerular filtration rate and an inability to achieve a urine osmolality of less than 200 mOsm/kg to 250 mOsm/kg limit water excretion.[6,8] Reduced solute intake, eg, 200 mOsm/d (beer potomania; normal diet, 600-900 mOsm/d), decreases water excretion to 4 L/d (at maximal urine dilution, 50 mOsm/kg). Hyponatremia typically does not develop unless water intake exceeds water losses from the kidneys and other routes.[5]

Of the total cases of hospital-associated hyponatremia, 40% to 75% develop after hospitalization and are due to decreased water excretion from medications (opiates, vasopressin, oxytocin), pain, nausea, organ failure, or postoperative state combined with excessive administration of hypotonic fluids.[10] Thiazide-induced hyponatremia affects approximately 7% of hospitalized patients with hyponatremia and it presents with either hypovolemic hyponatremia or euvolemic hyponatremia that resembles SIAD.[9] Patients exhibiting the SIAD-like pattern of thiazide-induced hyponatremia may have a genetic predisposition to hyponatremia that is linked to

Figure 1. Pathogenesis of Hypotonic Hyponatremia



Hypotonic hyponatremia is a disorder of water homeostasis and results from water retention. In most cases, water retention reflects decreased water diuresis. In patients with hypovolemic disorders and certain hypervolemic entities (heart failure, cirrhosis, or nephrotic syndrome), decreased water diuresis occurs due to reduced effective arterial blood volume that provides a nonosmotic stimulus to the release of vasopressin. In patients with the hypervolemic disorders of acute kidney injury and chronic kidney disease, the decreased glomerular filtration rate combined with an inability to achieve urine osmolality of less than 200 mOsm/kg to 250 mOsm/kg limit water diuresis. In patients with the syndrome of inappropriate antidiuresis (a euvolemic disorder), decreased water diuresis results from inappropriately elevated levels of vasopressin (absence of an osmotic or hemodynamic stimulus). Less frequently, excessive water intake in patients with euvolemic hyponatremia overwhelms normal water diuresis, resulting in water retention. The development of all forms of hypotonic hyponatremia requires that water intake exceeds water losses from the kidneys and other routes.

a reduction in a prostaglandin transporter in the distal nephron, which increases water reabsorption.[11] Potassium depletion contributes to the development of hyponatremia in all patients with thiazide-induced hyponatremia due to a reduction in exchangeable potassium level in the Edelman equation.[5,9]

In approximately 4% of people presenting with hyponatremia, water retention results from excessive water intake. Normal kidneys can excrete up to 1 L/h of water.[5,12] However, in patients with primary polydipsia, vasopressin may not be maximally suppressed (in those with a psychiatric disease or taking certain medications), contributing to water retention; median water intake was only 8 L/d, which is a fraction of the normal maximal level of water excretion.[12] Excessive intake of hypotonic fluids coupled with nonosmotic vasopressin secretion is the dominant pathogenesis of exercise-associated hyponatremia. Sodium loss due to sweat is a minor contributor.[13]

Symptoms of Hyponatremia

Manifestations of hyponatremia depend on the rapidity of development, duration, and severity of hyponatremia. Symptoms are more common in patients with acute hyponatremia (developing in <48 hours) than in those with chronic hyponatremia (developing over >48 hours) because of brain volume adaptation, which is a process that corrects hypotonicity-induced brain swelling. In a prospective, single-center study of 3784 patients in an emergency department, 166 (4.4%) presented with hyponatremia; each of the 3 forms of severity of hyponatremia, mild (serum sodium level of 130-134 mEq/L), moderate (125-129 mEq/L), and severe (<125 mEq/L), occurred in approximately one-third of the patients with hyponatremia.[1]

Symptoms of hyponatremia range from mild and nonspecific (weakness, nausea, headache) to severe and life-threatening (vomiting, somnolence, seizures, cardiorespiratory distress).[14] Acute severe hyponatremia can be associated with brain herniation, respiratory arrest, permanent brain damage, and death. Menstruating women are at a higher risk of having severe symptoms when they develop acute hyponatremia. Noncardiogenic pulmonary edema can occur in patients with hyponatremia due to acute water intoxication during endurance sports or intoxication with 3,4-methylenedioxymethamphetamine ([ecstasy], which is an amphetamine used for recreational purposes), with hypoxemia worsening brain edema. Symptoms can progress suddenly and rapidly.[5,6,10,14]

Because of the skull's rigidity, brain swelling from hypotonicity-induced water entry into brain cells causes intracranial hypertension, which may reduce cerebral blood flow.[15] Prompt electrolyte and water loss from brain cells occurs (known as rapid adaptation to hypotonic water entry) and can ameliorate swelling. Brain volume normalization is completed within approximately 2 days through the loss of organic osmolytes (eg, myoinositol, glutamate) and water from brain cells (slow adaptation). Correction of brain swelling accounts for less severe manifestations of chronic hyponatremia; these manifestations are caused by persistent hypotonicity and electrolyte or organic osmolyte depletion of brain cells.[6,10,14,16] In a prospective study of 298 patients with a serum sodium level of less than 125 mEq/L, including 96% with chronic hyponatremia, the symptoms were nausea (44%), vomiting (30%), confusion (30%), headache (27%), and seizures (5%)[17]; seizures most commonly occur in patients with extreme chronic hyponatremia (serum sodium level <110 mEq/L) and a history of seizures.[18]

Mild chronic hyponatremia in older people is associated with cognitive deficits, gait disturbances, and increased rates of falls and fractures.[19] An analysis of the prospective Rotterdam Study,[20] which

included 5208 people aged 55 years or older (mean age, 70.3 years) with serum sodium levels at baseline, detected 399 patients with mild hyponatremia (mean serum sodium level, 133.4 mEq/L). The analysis reported a higher rate of prior falls at baseline in patients with hyponatremia compared with people with a normal serum sodium level (23.8% vs 16.4%, respectively; $P < .01$) and a higher rate of incident nonvertebral fractures over 7.4 years of mean follow-up in patients with hyponatremia than in people without hyponatremia (23.3% vs 17.3%, respectively; $P < .004$).[20] Hyponatremia has been identified as a secondary cause of osteoporosis and bone fractures with risk increasing with severity of hyponatremia.[21,22] Basic research studies show that a low sodium level enhances bone resorption and inhibits osteogenesis.[22]

Brain volume adaptation to hyponatremia increases the risk of osmotic demyelination, a rare but serious neurological condition.[5,23] A national study from Sweden[24] identified only 111 patients with osmotic demyelination over 14 years. Osmotic demyelination results from overly rapid correction of chronic hyponatremia, primarily after daily correction of the serum sodium level by greater than 12 mEq/L, but rarely after correction by 10 mEq/L or less.[23] Osmotic demyelination involves the central pons but often extends into extrapontine structures, which are areas of the brain with both gray and white matter. Depletion of organic osmolytes predisposes individuals to astrocyte injury, disruption of the blood-brain barrier, and myelinolysis after the osmotic stress of overly rapid correction of chronic hyponatremia.[5,23]

Similar to animal studies, clinical observations suggest that azotemia protects from osmotic demyelination.[25-27] Characteristically, a biphasic pattern evolves in which the treatment of patients with hyponatremia initially improves neurological manifestations, but is followed by symptoms of myelinolysis. Symptoms of myelinolysis occur approximately 1 day to 7 days after overly rapid correction of chronic hyponatremia; can be temporary, permanent, or progressive; and consist of hyperreflexia, pseudobulbar palsy, parkinsonism, locked-in syndrome, quadriparesis, and death.[23] Two weeks to 4 weeks after overly rapid correction of chronic hyponatremia may elapse before manifestations are apparent on brain magnetic resonance imaging consisting of hyperintense T2-weighted images.[23] Risk factors for osmotic demyelination include extreme chronic hyponatremia (serum sodium level <110 mEq/L), alcohol use disorder, liver disease or transplant, potassium depletion, and malnutrition.[5,16,23]

Of 83 patients with osmotic demyelination from the Swedish National Patient Register,[24] all had chronic hyponatremia (median serum sodium level, 104 mEq/L) and 69.9% had alcohol use disorder. Causes of hyponatremia included drugs such as thiazides, antidepressants, anticonvulsants, or opioids (56.9%); vomiting or diarrhea (41.7%); and polydipsia (31.9%).[24] Hyponatremia was mainly treated with isotonic saline (93.1%); only 1.4% received hypertonic saline. In all but 6 patients, the serum sodium level increased with therapy by 8 mEq/L or greater (median correction, 17.2 mEq/L) over 24 hours.[24] At 3 months, 7.2% had died, 9.6% had extrapyramidal rigidity, 39.8% were dependent on others for activities of daily living, and 60.2% were functionally independent (patients may have been included in >1 category).[24]

Most patients presenting with hyponatremia have chronic hyponatremia. When duration cannot be established, concern about risk of therapy makes it prudent to diagnose chronic hyponatremia. Usually acute hyponatremia cannot be definitively ascertained unless it occurs postoperatively. Most important, patients with acute hyponatremia may have undergone substantial brain volume adaptation or may have had preexisting chronic hyponatremia.[5]

Diagnosing Hyponatremia

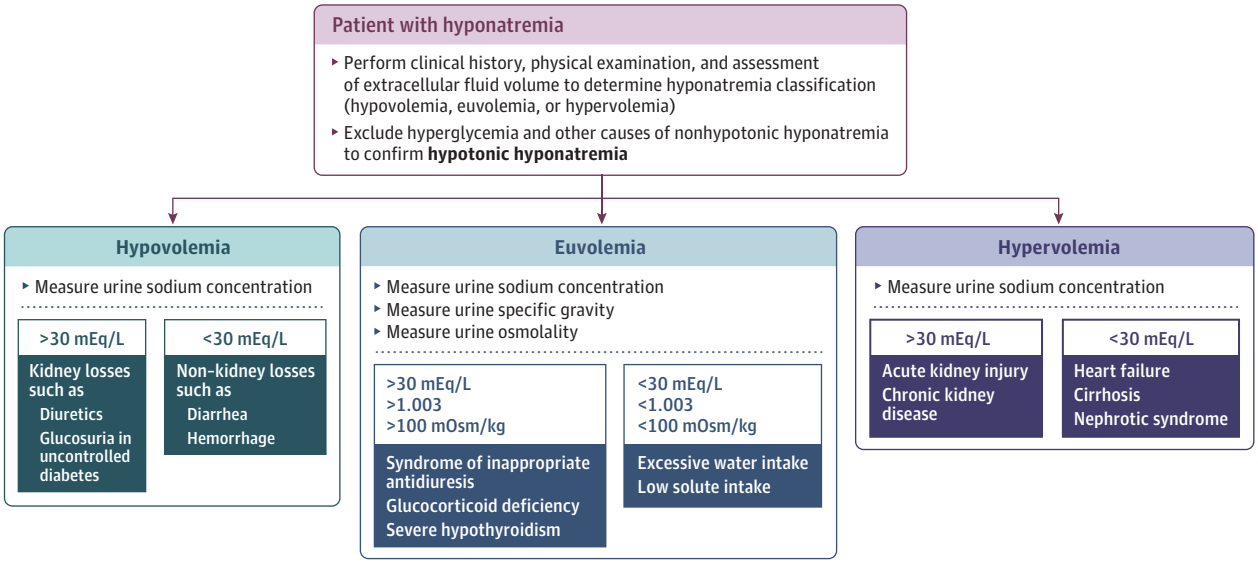
The clinical approach to hypotonic hyponatremia (**Figure 2**) is based on the pathogenesis.[10] According to the US guideline,[10] hypotonic hyponatremia can be diagnosed after excluding hyperglycemia and other causes of nonhypotonic hyponatremia. The history should assess whether the patient has had an acute or chronic illness, medication use, alcohol and illicit drug misuse, and recent surgery. Patients should be asked about fluid intake and loss, changes in body weight, and past episodes of hyponatremia. The physical examination facilitates the classification of hypovolemic, euvolemic, or hypervolemic hyponatremia. Measurement of the patient's sodium level in urine and the urine osmolality or urine specific gravity further differentiate each extracellular fluid volume category. As an example, a sodium level in urine of greater than 30 mEq/L in a patient with hypovolemic hyponatremia suggests kidney loss of sodium, whereas a sodium level in urine of less than 30 mEq/L indicates loss of sodium other than from the kidney. Diuretics increase sodium excretion in urine and impair the interpretation of sodium levels in urine; urine sampling must be obtained after the diuretic effect is gone. A urine osmolality of 100 mOsm/kg approximates urine specific gravity of 1.003; 300 mOsm/kg approximates urine specific gravity of 1.010; and 500 mOsm/kg approximates urine specific gravity of 1.020. These urine indices are used in the differential diagnosis of euvolemic hyponatremia (Figure 2).

It is important to recognize that the physical examination has low sensitivity (50%-70%) and specificity (30%-50%) in diagnosing hypovolemic hyponatremia (using response to saline infusion as the reference standard).[14,28] Therefore, the European guideline recommends that urine osmolality and the sodium level in urine be measured before assessing extracellular fluid volume.[14] However, a urine sample and urine osmolality may not be available.[29] In addition, urine indices can be affected by sodium intake, associated disease (kidney disease, heart failure), and use of diuretics. No studies have compared the 2 approaches (beginning with evaluation of volume status vs measurement of urine osmolality and the sodium level in urine), but many experts favor initial assessment of extracellular fluid volume.[4,5,10,29,30]

Serum osmolality can be measured when the diagnosis of hypotonic hyponatremia is uncertain. Increased levels of serum urea nitrogen and uric acid are consistent with hypovolemic hyponatremia, whereas low to normal values or low values are associated with euvolemic hyponatremia.[31] Additional testing should be performed based on the suspected underlying disease rather than based on the severity of hyponatremia.

Syndrome of inappropriate antidiuresis is defined by clinical euvolemic hyponatremia; inappropriately concentrated urine (osmolality >100 mOsm/kg and urine specific gravity >1.003); high urine sodium level (>30 mEq/L); and absence of thyroid, adrenal, or kidney dysfunction.[4] Glucocorticoid deficiency or severe hypothyroidism causes euvolemic hyponatremia mimicking SIAD and should be ruled out. Because SIAD is a diagnosis of exclusion, it requires testing

Figure 2. Clinical Approach to Hypotonic Hyponatremia



Clinical history and physical examination provide essential information for the diagnosis of hyponatremia and allow classification of patients with hypovolemic hyponatremia, euvolemic hyponatremia, or hypervolemic hyponatremia. Hyperglycemia and other causes of nonhypotonic hyponatremia must be excluded to confirm hypotonic hyponatremia. Measurement of urine sodium level and use of urine osmolality or urine specific gravity further differentiate each extracellular fluid volume category. Initial laboratory tests and imaging studies combined with a history and physical examination are usually sufficient to arrive at the cause of hyponatremia.

of thyroid, adrenal, and pituitary function. Addison disease (combined mineralocorticoid and glucocorticoid deficiency) causes hypovolemic hyponatremia often associated with hyperkalemia.

Measurement of vasopressin levels is not useful in evaluating the etiology of hyponatremia.[16] Radiological imaging may include chest radiograph or computed tomography and magnetic resonance imaging or computed tomography of the head for evaluation of conditions such as heart failure, mass lesion, and brain edema. However, no high-quality evidence supports routine imaging in the evaluation of SIAD. Information from the history, physical examination, and initial laboratory tests is usually sufficient to diagnose the cause of hyponatremia (**Box**).[32] More than 1 cause may be present (ie, diarrhea in a patient with SIAD due to breast cancer).

The Hyponatremia Registry,[31] consisting of 3087 patients with hyponatremia without hypovolemia from 225 sites in the US and the European Union, reported that the etiology was approximately equally divided between patients with hypervolemic hyponatremia (51% for heart failure and 42% for cirrhosis) and patients with euvolemic hyponatremia (95% for SIAD). Antidepressants are the most commonly implicated drugs in patients with SIAD. Selective serotonin reuptake inhibitors induce SIAD in up to 32% of patients, especially in older (aged >65 years), underweight women.[9] Thiazides induce hyponatremia in up to 30% of patients. Risk factors include advanced age, female sex, low body mass index, low sodium intake, and concurrent use of antidepressants or antipsychotics. Hyponatremia usually occurs soon after initiation of treatment with thiazides, but it can also develop after prolonged use of thiazides or during intercurrent illness.[33]

Chronic administration of desmopressin (a vasopressin analogue) for conditions such as central diabetes insipidus, enuresis, or von Willebrand disease can cause hyponatremia and occasionally severe cases of hyponatremia. Discontinuing desmopressin during treatment of hyponatremia can cause brisk water diuresis, overly rapid correction of serum sodium level, and osmotic demyelination.[34] Mild, transient, and largely asymptomatic exercise-associated hyponatremia is common in up to 67% of long-distance runners, but symptomatic hyponatremia is rare and occurs in less than 1%.[13] In a study including 590 patients with primary polydipsia and hyponatremia, 52% had a psychiatric condition, 15% had a medical disorder promoting excessive water intake, and 31% did not have a comorbid condition.[12]

Treatment

Treating hyponatremia requires balancing risks of hypotonicity against risks of therapy. The presence of symptoms determines the intensity of treatment.[5,10,14,16,35]

Emergency Treatment

Regardless of the duration of hyponatremia, patients with severe manifestations (somnolence, seizures, cardiorespiratory distress) and those with moderately severe symptoms (vomiting, confusion) who are at high risk of life-threatening complications require emergency treatment. Common etiologies associated with the need for emergency treatment include postoperative state, self-induced water intoxication, and preexisting intracranial (neurological or neurosurgical) pathology. Characteristically, these patients present with acute euvolemic hyponatremia.[5,10,14,16,35] Some patients with severe symptoms have an element of acute hyponatremia superimposed on chronic hyponatremia or extreme chronic hyponatremia.

Immediate treatment may include airway intubation, supplemental oxygen, ventilatory support, or anticonvulsant therapy. Admission to an intensive care unit may be necessary for optimal

Box. Causes of Hypotonic Hyponatremia

Decreased Water Diuresis

Hypovolemic Hyponatremia
- Kidney sodium losses
  - Diuretics
  - Osmotic diuresis (glucose, urea, mannitol)
  - Salt-wasting nephropathy
  - Adrenal insufficiency
  - Bicarbonaturia (renal tubular acidosis, disequilibrium stage of vomiting)
  - Ketonuria
  - Cerebral salt wasting syndrome
- Non–kidney sodium losses
  - Vomiting
  - Diarrhea
  - Blood loss
  - Excessive sweating
  - Fluid sequestration in the third space
    - Pancreatitis
    - Bowel obstruction
    - Peritonitis
    - Burns
    - Massive trauma

Hypervolemic Hyponatremia
- Heart failure
- Cirrhosis
- Nephrotic syndrome
- Kidney failure (acute or chronic)
- Pregnancy

Euvolemic Hyponatremia
- Thiazide diuretics (certain cases)
- Severe hypothyroidism
- Glucocorticoid deficiency
- Low solute intake
  - Tea and toast diet
  - Beer potomania
  - Dilute infant formula
- Syndrome of inappropriate antidiuresis
  - Malignancies
    - Pulmonary and mediastinal
    - Nasopharyngeal
    - Gastrointestinal tract
    - Genitourinary tract
  - Drugs
    - Stimulants of synthesis or release of arginine vasopressin: nicotine, tricyclic antidepressants, phenothiazines, antineoplastic agents (methotrexate, ifosfamide, cisplatin, carboplatin, vincristine, vinblastine, interferon), narcotics
    - Arginine vasopressin–like compounds and enhancers of its action: desmopressin, oxytocin, prostaglandin synthetase inhibitors
    - Mixed or unknown effects: cyclophosphamide, chlorpropamide, angiotensin-converting enzyme inhibitors, clofibrate, clozapine, selective serotonin reuptake inhibitors, 3,4-methylenedioxymethamphetamine (ecstasy), nonsteroidal anti-inflammatory drugs
  - Central nervous system disorders
    - Mass lesions: tumor, abscess, hematoma
    - Inflammatory conditions: encephalitis, meningitis, lupus
    - Demyelinating disease: Guillain-Barré
    - Cerebrovascular accident
    - Head trauma
    - Acute psychosis
    - Delirium tremens
  - Pulmonary conditions
    - Infections: bacterial or viral pneumonia, lung abscess, tuberculosis, aspergillosis
    - Asthma
    - Cystic fibrosis
    - Acute respiratory failure
    - Chronic obstructive pulmonary disease
    - Positive-pressure ventilation
  - Other
    - Exercise-associated
    - Pain
    - Severe nausea
    - General anesthesia
    - Postoperative state
    - HIV/AIDS
    - Gain-of-function variants in the arginine vasopressin receptor 2 gene

Excessive Water Intake
- Primary polydipsia
- Multiple tap water enemas
- Fresh water drowning (eg, drowning in a lake or river)
- Dilute infant formula
- Exercise-associated
- Sodium-free irrigant solutions (hysteroscopy, laparoscopy, transurethral resection of the prostate)

Adapted from Adrogué and Madias.[32]

monitoring of vital signs, central nervous system status, urine output, and fluid administration. Hypotonic fluids and hyponatremia-inducing drugs must be withheld. Current guidelines recommend correction of the serum sodium level by 4 mEq/L to 6 mEq/L within 1 to 2 hours, which can reverse hyponatremic encephalopathy (**Table 1**).[10,14,36] This may be accomplished with an intravenous bolus (central line or peripheral vein[37-39]) containing a 100-mL or 150-mL dose of 3% sodium chloride, administered over 10 minutes or 20 minutes and repeated 2 to 3 times until the desired serum sodium level is achieved. However, the serum sodium level should not be increased by more than 10 mEq/L within the first 24 hours and by 18 mEq/L within the first 48 hours (ie, correction limits). In patients at high risk of osmotic demyelination, the serum sodium level should not be increased by more than 8 mEq/L within any 24-hour period. Other experts recommend rates of correction of 8 mEq/L within any 24-hour period for patients at low risk of osmotic demyelination and 6 mEq/L for patients at high risk of osmotic demyelination.[5,23,35,40,41] Intensive monitoring of the serum sodium level is required early during treatment (after each bolus) and less frequently thereafter (every 4-6 hours over the first 24 hours).

Three studies[42-44] compared the guideline recommendations of bolus infusion of 3% sodium chloride vs conventional treatments consisting of continuous infusion of 3% sodium chloride, isotonic saline, and cause-specific measures, such as discontinuing hyponatremia-inducing drugs (**Table 2**). The Efficacy and Safety of Rapid Intermittent Correction Compared With Slow Continuous

Table 1. Guideline-Recommended Treatment of Severely Symptomatic Hyponatremia With Hypertonic Saline

	US guideline	European guideline
Patients requiring treatment with hypertonic saline	Regardless of duration: • Hyponatremia with severe manifestations (somnolence, seizures, cardiorespiratory distress) • Hyponatremia with moderately severe symptoms (vomiting, confusion) in patients at high risk of progressing to life-threatening complications	Regardless of duration: • Hyponatremia with severe manifestations (somnolence, seizures, cardiorespiratory distress) • Hyponatremia with moderately severe symptoms (vomiting, confusion) in patients at high risk of progressing to life-threatening complications
Rate of increase in serum sodium level desired (goal for change in serum sodium level)	4-6 mEq/L within 1-2 h	5 mEq/L within 1-2 h
Recommended treatment with hypertonic saline (3% sodium chloride)	100-mL bolus via central or peripheral vein over 10 min up to 3 times as needed to attain desired serum sodium level	150-mL bolus via central or peripheral vein over 20 min, repeating this step twice until the desired serum sodium level is achieved
Recommended frequency of measuring serum sodium level	After each bolus and every 4-6 h over the first 24 h	After each bolus and every 6 h over the first 24 h
Recommended increase in serum sodium level that should not be exceeded (correction limit)	At low risk for osmotic demyelination: • 10 mEq/L within first 24 h[a] • 18 mEq/L within first 48 h[a] At high risk for osmotic demyelination: • 8 mEq/L during any 24-h period[b]	At low risk for osmotic demyelination: • 10 mEq/L within first 24 h[a] • 18 mEq/L within first 48 h[a] At high risk for osmotic demyelination: • 8 mEq/L during any 24-h period[b]

[a] Other experts recommend a more strict correction limit of 8 mEq/L during any 24-hour period.

[b] Other experts recommend a more strict correction limit of 6 mEq/L during any 24-hour period.

Correction With Hypertonic Saline in Patients With Moderately Severe or Severe Symptomatic Severe Hyponatremia (SALSA) trial[43] randomized 178 patients (mean serum sodium level, 118 mEq/L) to rapid intermittent bolus infusion (n = 87) or slow continuous infusion (n = 91). The primary outcome of overly rapid correction (change in serum sodium level >12 mEq/L or >18 mEq/L within 24 hours or 48 hours, respectively) was not significantly different between the 2 groups (17.2% in the rapid intermittent bolus group vs 24.2% in the slow continuous infusion group; $P = .26$). In addition, use of a lowering therapy for the serum sodium level was required frequently in both groups, but less with bolus treatment (41.4% vs 57.1% in the slow continuous infusion group; $P = .04$). The 2 groups did not differ in the efficacy of increasing the serum sodium level (target change in serum sodium level, 5-9 mEq/L) or in improving symptoms at most time points; however, at 1 hour, the bolus treatment was more effective (32.2% in the rapid intermittent bolus group vs 17.6% in the slow continuous infusion group; $P = .02$).[43] A nonrandomized study of 50 patients (mean serum sodium level, 120 mEq/L) compared a prospective bolus group (n = 22) with a retrospective continuous therapy group (n = 28).[42] The bolus group was associated with the primary outcome of observed change in the serum sodium level at 6 hours (6 mEq/L vs 3 mEq/L for the continuous therapy group; $P < .001$) and at 12 hours (8 mEq/L vs 5 mEq/L, respectively; $P < .001$), but was not associated with a difference at 24 hours (10 mEq/L vs 10 mEq/L; difference not statistically significant, P value not provided). The bolus therapy group had a higher rate of overly rapid correction (4.5% vs 0% for the continuous therapy group; $P = .48$) and use of a relowering therapy for the serum sodium level was more common in the bolus group (22.7% vs 0%, respectively; $P = .008$).[42] A nonrandomized observational study of 62 patients (mean serum sodium level, 118 mEq/L) compared a bolus of 3% sodium chloride (n = 36) with standard care (n = 26).[44] The observed change in the serum sodium level at 24 hours was not different between the groups (9 mEq/L for the bolus group vs 6 mEq/L for the standard care group; difference not statistically significant, P value not provided). Overly rapid correction at 24 hours occurred more often in the bolus group (27.8% vs 11.5% of patients in the standard care group; difference not statistically significant, P value not provided) and use of a relowering therapy for the serum sodium level was required more often (27.8% vs 0%, respectively).[44] Osmotic demyelination did not occur in any of the 3 studies.[42-44] In summary, bolus infusion attained the target change in serum sodium level faster, but was associated with higher rates of overly rapid correction and need for relowering therapy for serum sodium level. However, 2 of the 3 studies were not randomized.[42,44]

Bolus therapy with 3% sodium chloride may yield high rates of overly rapid correction because repeated fixed doses of solution are administered. A given dose may have heterogeneous effects on sodium, depending on a patient's total body water (affected by sex, weight, and body fat) and baseline serum sodium level.[5,29] A patient-specific quantitative approach was proposed using a formula (based on the Edelman equation) that incorporates baseline serum sodium level $[Na^+]_s$ and estimated total body water (TBW)[5,29]: $\Delta[Na^+]_s = [Na^+ + K^+]_{infusate} - [Na^+]_s/TBW + 1$. This formula predicts change in serum sodium level achieved after infusion of 1 L of hypertonic saline assuming no input or output other than the infusate.[5,29] According to this formula, raising the serum sodium level by 5 mEq/L in a man weighing 70 kg, in a man weighing 100 kg, or in a woman weighing 50 kg (each with a serum sodium level of 120 mEq/L) requires different amounts of hypertonic sodium, namely 503 mL, 712 mL, or 331 mL, respectively. The efficacy of the infusate formula has been validated.[45-47] Some authors discourage use of this and other formulas despite widespread use of a quantitative approach to prescribing many medications.[48-51] Randomized trials comparing the approach based on a formula with the fixed-dose approach are warranted.

During treatment, transition to water diuresis (urine flow >100 mL/h) can occur (repair of hypovolemic hyponatremia, discontinuation of hyponatremia-inducing drugs[4,5,35]) and further increases the serum sodium level. To counter risk of overly rapid correction, desmopressin can be used, anticipating water diuresis (proactive strategy) or in response to water diuresis (reactive strategy).[45,48,52,53] When desmopressin is used to avoid overly rapid correction, the recommended dose is 2 µg to 4 µg parenterally every 6 hours to 8 hours.[48,54]

Table 2. Clinical Studies Comparing Bolus Infusion of Hypertonic Saline (3% Sodium Chloride) With Conventional Therapies in Patients With Moderately Severe or Severely Symptomatic Hyponatremia

Source	Trial or study description	Aim of study	Study groups	Results	Adverse outcomes
Garrahy et al,[42] 2019	Included data collected prospectively and retrospectively; not a randomized clinical trial	To compare efficacy and safety of bolus vs continuous infusion of 3% sodium chloride to treat patients with syndrome of inappropriate antidiuresis and severe symptoms	N = 50 (mean serum sodium level: 120 mEq/L) Bolus group (n = 22; prospective) 100 mL administered up to 3 times (per US guideline) Continuous group (n = 28; retrospective) 20 mL/h (adjustable rate)	Observed change in serum sodium level At 6 h: 6 mEq/L in bolus group vs 3 mEq/L in continuous group ($P < .001$) At 12 h: 8 mEq/L in bolus group vs 5 mEq/L in continuous group ($P < .001$) At 24 h: 10 mEq/L in bolus group vs 10 mEq/L in continuous group (difference not statistically significant, *P* value not provided) Reached goal of change in serum sodium level by 8-12 mEq/L within 24 h 77.3% in bolus group vs 75.0% in continuous group ($P = .45$)	Overly rapid correction defined as change in serum sodium level >12 mEq/L within 24 h 4.5% in bolus group vs 0% in continuous group ($P = .48$) Underwent relowering therapy for serum sodium level 22.7% in bolus group vs 0% in continuous group ($P = .008$) Osmotic demyelination 0 cases Mortality 0% in bolus group vs 3.6% in continuous group ($P = .12$)
Baek et al,[43] 2021	Open-label randomized clinical trial	To compare risk of overly rapid correction and efficacy of bolus vs continuous infusion of 3% sodium chloride to treat patients with moderately severe or severe symptoms	N = 178 (mean serum sodium level: 118.2 mEq/L) Bolus group (n = 87) 2 mL/kg administered 1 time for moderately severe symptoms or 2 mL/kg administered twice for severe symptoms (per European guideline) Continuous group (n = 91) 0.5 mL/kg/h administered for moderately severe symptoms or 1 mL/kg/h administered for severe symptoms (adjustable rate for both doses) Moderately severe symptoms 66 patients in bolus group vs 68 patients in continuous group ($P = .86$) Severe symptoms 21 patients in bolus group vs 23 patients in continuous group ($P = .86$)	Overly rapid correction: >12 mEq/L within 24 h or >18 mEq/L within 48 h 17.2% in bolus group vs 24.2% in continuous group ($P = .26$) Reached goal of change in serum sodium level by 5-9 mEq/L At 1 h: 32.2% in bolus group vs 17.6% in continuous group ($P = .02$ in intention-to-treat analysis only) At 6 h: 57.5% in bolus group vs 59.3% in continuous group ($P = .80$) At 24 h: 89.7% in bolus group vs 86.8% in continuous group ($P = .56$) At 48 h: 69.0% in bolus group vs 73.6% in continuous group ($P = .49$)	Underwent relowering therapy for serum sodium level 41.4% in bolus group vs 57.1% in continuous group ($P = .04$) Osmotic demyelination 0 cases Mortality 4.6% in bolus group vs 1.1% in continuous group ($P = .20$)
Chifu et al,[44] 2021	Observational study; not a randomized clinical trial	To compare efficacy and safety of bolus infusion of 3% sodium chloride vs standard care to treat patients with moderate or severe symptoms	N = 62 patients (mean serum sodium level: 118 mEq/L) Bolus group (n = 36) 150 mL administered once for moderate symptoms or 150 mL administered twice for severe symptoms (per European guideline) Comparator group (n = 26) Standard care Moderate symptoms 17 patients in bolus group vs 16 patients in comparator group (*P* value not provided) Severe symptoms 19 patients in bolus group vs 10 patients in comparator group (*P* value not provided)	Observed change in serum sodium level At 24 h: 9 mEq/L in bolus group vs 6 mEq/L in comparator group (difference not statistically significant, *P* value not provided) Reached goal of change in serum sodium level by 5-10 mEq/L At 24 h: 50% in bolus group vs 26.9% in comparator group (difference not statistically significant, *P* value not provided) Reached goal of change in serum sodium level by 8 mEq/L At 48 h: 69.4% in bolus group vs 61.5% in comparator group (difference not statistically significant, *P* value not provided)	Overly rapid correction defined as change in serum sodium level >10 mEq/L within 24 h and >8 mEq/L within next 24 h or having a serum sodium level >130 mEq/L At 24 h: 27.8% in bolus group vs 11.5% in comparator group (difference not statistically significant, *P* value not provided) At 48 h: 13.9% in bolus group vs 3.8% in comparator group (difference not statistically significant, *P* value not provided) Underwent relowering therapy for serum sodium level 27.8% in bolus group vs 0% in comparator group (*P* value not provided) Osmotic demyelination 0 cases Mortality in combined cohort: 11.3%

A retrospective study compared the outcomes of 112 patients with a serum sodium level of 125 mEq/L or less receiving hypertonic saline with desmopressin (n = 32) or without desmopressin (n = 80) proactively or reactively. Both groups achieved similar rates of target change in the serum sodium level at 24 hours (65.6% in the group receiving hypertonic saline with desmopressin vs 52.5% in the group receiving hypertonic saline without desmopressin; $P = .21$). Desmopressin did not decrease the incidence of overly rapid correction but increased duration of 3% sodium chloride (39.3 hours in the group receiving hypertonic saline with desmopressin vs 12.6 hours in the group receiving hypertonic saline without desmopressin; $P = .002$) and the amount of fluid received per patient (899 mL vs 514 mL, respectively; $P = .003$).[55] Another retrospective study of 64 patients with a serum sodium level of less than 115 mEq/L treated with hypertonic saline reported that safe correction of the serum sodium level (≤8 mEq/L) within 24 hours was higher in those receiving desmopressin (n = 47) than in those who did not receive desmopressin (n = 17) (68% vs 41%, respectively; $P = .04$).[56] In a retrospective study of 1450 patients, desmopressin slowed the rate of correction for the serum sodium level and prolonged hospital stay (6 days vs 5 days without desmopressin; $P < .001$), but was associated with higher rates of overly rapid correction (29.1% vs 15.5%, respectively; $P < .001$).[57] Administration of desmopressin required more frequent monitoring of the serum sodium level. These retrospective data were inconclusive and randomized clinical trials are warranted.

Overly rapid correction represents a medical emergency and must be treated promptly except in documented cases of acute water intoxication in which the risk of osmotic demyelination is minimal.[5,10,14,16,35,58] Desmopressin (rescue therapy) and 5% dextrose in water can return the serum sodium level below the recommended limit. If signs of osmotic demyelination appear, immediate relowering of the serum sodium level should be pursued.[59-61]

Clinicians should be mindful that potassium supplementation during treatment of hyponatremia also increases the serum sodium level (Edelman equation), risking overly rapid correction and osmotic demyelination.[5,62] Extreme caution is required because retention of only 2 mEq/kg of potassium increases the serum sodium level by 4 mEq/L when total body water is 50% of body weight. Upon completing emergency treatment of hyponatremia, the underlying cause of hyponatremia should be addressed.

Nonemergency Treatment

Approximately 2% of patients with hyponatremia require emergency treatment.[1,31] For other patients, reasonable efforts should be made to correct hyponatremia, even in its mildest form, because of its effect on health outcomes. For most patients, management requires reversing or ameliorating the underlying cause. Treating vomiting and diarrhea and discontinuing drugs associated with hyponatremia (thiazides, antidepressants) corrects hyponatremia. By contrast, in patients with advanced heart failure and malignancy-related SIAD, treatment should focus on improving hyponatremia and its symptoms. Patients with mild or moderate hyponatremia and only mild symptoms can be treated as outpatients unless the underlying cause requires hospitalization. Regardless of the cause and symptoms, patients with a serum sodium level of less than 120 mEq/L require hospitalization and close monitoring of the serum sodium level during treatment, initially at least every 8 hours.

Hypovolemic Hyponatremia

Isotonic saline or other crystalloid solution is used for parenteral volume repletion. Sodium-rich broth and sodium chloride tablets can be used for oral treatment. Hypotonic fluids should be withheld. Strict adherence to limits of correction for the serum sodium level is required. Uncertainty about the presence of hypovolemic hyponatremia can be addressed by infusing 1 L to 2 L of saline and assessing urine flow and the serum sodium level. Vaptans can worsen both hypovolemia and hemodynamics and should be avoided.[10,14,63] In patients with thiazide-induced hyponatremia, drug replacement with loop diuretics (rarely associated with hyponatremia) may be required.

Euvolemic Hyponatremia

The most common causes of SIAD are malignancies, central nervous system disorders, and medications (Box). Drug-induced SIAD requires discontinuation of causative agents, if feasible. Therapeutic measures for SIAD include fluid restriction, increased solute intake (sodium chloride, protein, urea), and vaptans; isotonic saline worsens the serum sodium level and is not indicated. Fluid restriction represents the mainstay of therapy but adherence can be difficult.[64,65] The sum of urine sodium and potassium levels divided by the serum sodium level can guide stringency of fluid restriction. A ratio of less than 1 calls for mild fluid restriction (<1.5 L/d), whereas higher ratios require severe fluid restriction (<1 L/d). Patients with low urine flow (<1.5 L/d) and highly concentrated urine (urine specific gravity >1.020; osmolality >500 mOsm/kg) are less likely to respond to fluid restriction.[4,5] Augmentation of sodium chloride intake (dietary or tablets) combined with furosemide (20-40 mg/d) promotes water excretion. An open-label randomized clinical trial of 92 patients showed that the addition of this regimen in patients assigned to severe fluid restriction did not benefit correction of the serum sodium level ($P = .70$). The incidence of hypokalemia was 42% in the combined group and 13% in the severe fluid restriction alone group ($P = .01$).[66]

Additional therapies are available. Oral or enteral urea therapy (15-60 g/d) increases the serum sodium level by promoting water diuresis; 30 g of urea (500 mOsm) is associated with 1 L of water excretion when urine osmolality is 500 mOsm/kg. To improve palatability of this therapy, urea can be dissolved in fruit juice or syrup. Urea therapy can be substituted for sodium chloride tablets and furosemide or vaptans.[16,67-72] Urea therapy can be used to treat nephrogenic SIAD, which is a hereditary disorder characterized by persistent activation of the vasopressin receptor 2 in the collecting duct.[73] Patients with SIAD commonly have low protein intake; increasing daily protein intake to 1 g/kg improves hyponatremia by simulating urea therapy. Limited information suggests that empagliflozin, a sodium-glucose cotransporter-2 inhibitor, which promotes osmotic diuresis via glucosuria, may help management of SIAD.[74,75]

Vaptans (vasopressin receptor antagonists) block the vasopressin receptor 2 located in the collecting duct and promote water diuresis.[16,76] Conivaptan (an intravenous preparation) also blocks the vasopressin receptor 1a and is associated with hypotension in up to 14% of patients. Conivaptan can be administered to hospitalized patients for up to 4 days.[77] Longer treatment is not recommended because of interactions with drugs also metabolized by the CYP3A4 hepatic isoenzyme, such as simvastatin, amlodipine, and ketoconazole. Tolvaptan (an oral agent) is initiated in the hospital and is

effective in the long-term management of SIAD.[78] In the SALT-1 and SALT-2 randomized clinical trials,[79] normalization of the serum sodium level at day 30 occurred in 66.6% of patients receiving tolvaptan (15 mg/d initially and allowed dose increase to 60 mg/d) and in 26.8% of patients receiving placebo ($P < .05$). Thirst increases substantially with vaptans, limiting the increase in the serum sodium level. Lifting fluid restriction and frequent monitoring of the serum sodium level after initiating treatment with vaptans decreases the risk of overly rapid correction.[63,80] Rare cases of osmotic demyelination have been reported and approximately 10% of patients develop hypernatremia. A dose of 7.5 mg/d of tolvaptan, which is lower than the recommended dose, is effective and safe.[81,82] The US Food and Drug Administration warns that tolvaptan should not be used longer than 30 days and should not be administered to patients with liver disease. Cost and safety limit long-term use of vaptans.

Hormonal therapy with hydrocortisone or levothyroxine is indicated for patients with hyponatremia because of a glucocorticoid deficiency or severe hypothyroidism. Careful monitoring is needed to prevent overly rapid correction. Individuals with exercise-associated hyponatremia and mild to moderate symptoms require restriction of hypotonic fluids and oral administration of salty broth or 100 mL of 3% sodium chloride.[13] Athletes should be advised to drink only in response to thirst and ensure no weight gain during exercise. Management of primary polydipsia requires behavioral support to reduce fluid intake. Use of ice chips and sour candies may alleviate mouth dryness.[10,14]

Hypervolemic Hyponatremia

Treating hyponatremia in patients with heart failure requires fluid restriction and adjustment of medications to attain optimal hemodynamics. Loop diuretics increase fluid and electrolyte excretion, thereby reducing fluid overload, but overuse and stringent sodium chloride restrictions can exacerbate hyponatremia.[5] Temporary discontinuation of diuretics and lifting stringent sodium chloride restrictions may be required for treating hyponatremia in patients with heart failure.[2,5] Low potassium levels should be increased. Additional therapeutic options are urea or vaptans.[2,10,16,83] Severe hyponatremia unresponsive to these measures may require limited hypertonic saline administration.[2]

Fluid restriction, loop diuretics, and potassium repletion are treatments for patients with cirrhosis and mild hyponatremia.[5,10,14,16,35] Advanced liver disease is associated with more severe hyponatremia and with hypotension and oliguria. In patients with advanced liver disease and severe hyponatremia, diuretics and antihypertensives should be withdrawn; potassium levels should be increased; and midodrine, albumin, hypertonic saline, and kidney replacement therapy considered.[84,85] Cautious correction of patients with severe hyponatremia to a serum sodium level of greater than 125 mEq/L is indicated prior to liver transplant to decrease risk of osmotic demyelination.[86,87] Urea and vaptans are contraindicated in patients with cirrhosis and hyponatremia.[10,14,63]

Limitations

This review has several limitations. First, it was restricted to English-language publications. Second, high-quality data are lacking for some of the covered topics. Third, the literature review may have missed some relevant publications. Fourth, not all aspects of hyponatremia were discussed.

Conclusions

Hyponatremia affects approximately 5% of adults and 35% of patients who are hospitalized. Most patients should be managed by treating their underlying disease and according to whether they have hypovolemic, euvolemic, or hypervolemic hyponatremia. Urea and vaptans can be effective in managing the syndrome of inappropriate antidiuresis and hyponatremia in patients with heart failure; hypertonic saline is reserved for patients with severely symptomatic hyponatremia.

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