

## CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

# The Syndrome of Inappropriate Antidiuresis

Horacio J. Adrogué, M.D., and Nicolaos E. Madias, M.D.

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

**An 85-year-old man is found to have a serum sodium level of 128 mmol per liter during his annual evaluation. He has noted some “mental slowing” and gait instability. The patient’s history is notable for primary hypertension and prostatic hypertrophy. His medications include amlodipine, finasteride, and tamsulosin. His blood pressure is 136/68 mm Hg without orthostatic changes; the remainder of the examination is unremarkable. Repeat testing reveals a serum sodium level of 127 mmol per liter, osmolality of 260 mOsm per kilogram of water, creatinine level 0.8 mg per deciliter (70.7  $\mu$ mol per liter), blood urea nitrogen level of 8 mg per deciliter (2.9 mmol per liter), and uric acid level of 4 mg per deciliter (0.24 mmol per liter). The urine osmolality is 645 mOsm per kilogram of water, and the sodium level is 95 mmol per liter. How should this patient be further evaluated and treated?**

From the Department of Medicine, Section of Nephrology, Baylor College of Medicine, and the Department of Medicine, Division of Nephrology, Houston Methodist Hospital — both in Houston (H.J.A.); and the Department of Medicine, Tufts University School of Medicine, and the Department of Medicine, Division of Nephrology, St. Elizabeth’s Medical Center — both in Boston (N.E.M.). Dr. Madias can be contacted at [nicolaos.madias@steward.org](mailto:nicolaos.madias@steward.org) or at St. Elizabeth’s Medical Center, 736 Cambridge St., Boston, MA 02135.

N Engl J Med 2023;389:1499-509.

DOI: 10.1056/NEJMc2210411

Copyright © 2023 Massachusetts Medical Society.

## THE CLINICAL PROBLEM

**H**YPONATREMIA (SERUM SODIUM LEVEL, <135 MMOL PER LITER) IS THE most common electrolyte abnormality and affects approximately 5% of adults overall and 35% of hospitalized patients.<sup>1,2</sup> It is categorized as mild (130 to 134 mmol per liter), moderate (125 to 129 mmol per liter), or severe (<125 mmol per liter); about 70% of hyponatremia cases are mild, whether in outpatients or inpatients. Even mild hyponatremia is associated with adverse outcomes, including increased length of hospitalization, readmission, resource use, and death.<sup>2-4</sup>

The serum sodium level approximates the ratio of osmotically active sodium and potassium content to total body water. Hyponatremia typically reflects water excess relative to these body cations, most commonly resulting from disorders impairing electrolyte-free water excretion by the kidneys (aquaresis).<sup>5</sup> Impaired aquaresis largely depends on increased secretion of arginine vasopressin (AVP), the antidiuretic hormone, which activates the vasopressin 2 receptor in the collecting duct of the nephron, thus promoting water retention. AVP is triggered by osmotic and hemodynamic stimuli (hypertonicity and reduced effective arterial blood volume, respectively).<sup>5,6</sup> In hyponatremia that is associated with hypovolemia and certain hypervolemic disorders (e.g., heart failure), water retention is driven by AVP release caused by reduced effective arterial blood volume. In contrast, in the syndrome of inappropriate antidiuresis (SIAD), a euvolemic disorder, AVP secretion occurs in the absence of osmotic and hemodynamic stimuli (and the antidiuresis is therefore deemed “inappropriate”).<sup>5-7</sup>

Hyponatremia can also reflect impaired aquaresis independent of AVP release, including low-solute intake, acute kidney injury, and chronic kidney disease

**CME**  
at [NEJM.org](http://NEJM.org)

## KEY CLINICAL POINTS

**SYNDROME OF INAPPROPRIATE ANTIDIURESIS (SIAD)**

- Hyponatremia is the most common electrolyte abnormality. The condition is usually caused by a water excess relative to sodium and potassium content.
- In SIAD, a frequent cause of hyponatremia, increased secretion of antidiuretic hormone in the absence of osmotic and hemodynamic stimuli leads to water retention by the kidneys and water excess.
- Manifestations of SIAD depend on the rapidity of development and the severity and duration of the condition. Symptoms range from mild and nonspecific (e.g., weakness and headache) to severe and life-threatening (e.g., seizures and coma).
- Causes of SIAD include cancer, medications, pulmonary conditions, disorders of the central nervous system, postoperative state, severe nausea, and stress; frequently the cause is undetermined.
- Severely symptomatic SIAD leads to emergency treatment with 3% sodium chloride to reverse cerebral edema. Consultation with a specialist is warranted.
- Management strategies for SIAD include reversal or amelioration of the underlying disorder when possible; fluid restriction; supplementation with sodium chloride, often with furosemide; and treatment with urea or tolvaptan.

(stages G3 through G5).<sup>2</sup> Infrequently, hyponatremia results from excessive water intake that overwhelms aquaresis. Regardless of pathogenesis, hyponatremia does not arise unless water intake outstrips water losses from the kidneys and through other routes.<sup>5,6</sup> This article focuses on hyponatremia caused by SIAD.

The prevalence of hyponatremia overall, and of SIAD specifically, increases with age; 40% of older (>65 years of age) inpatients have hyponatremia, with 25 to 40% of cases attributed to SIAD.<sup>2,4,8</sup> This increased prevalence is attributable to the frequent presence among older persons of coexisting conditions (e.g., cancer, pulmonary diseases, and disorders of the central nervous system [CNS]) and medications that predispose to SIAD.<sup>2,4,9</sup> In addition, aging impairs aquaresis by means of diminished glomerular filtration rate, decreased renal prostaglandins, and increased AVP response to osmotic and non-osmotic stimuli<sup>10</sup>; low salt and protein intake, common in older persons, also contributes to impaired aquaresis.<sup>11</sup> Even a modest increase in water intake compounds the risk of hyponatremia.<sup>5,12</sup>

Manifestations of SIAD depend on the rapidity of development and the severity and duration of hyponatremia.<sup>2</sup> Symptoms of acute SIAD (<48 hours from onset of hyponatremia) result from cerebral edema and range from mild and nonspecific (e.g., weakness and headache) to severe and life-threatening (e.g., seizures and coma). Because brain-volume regulation reverses cerebral edema, symptoms of chronic SIAD (≥48 hours from onset of hyponatremia) are commonly sub-

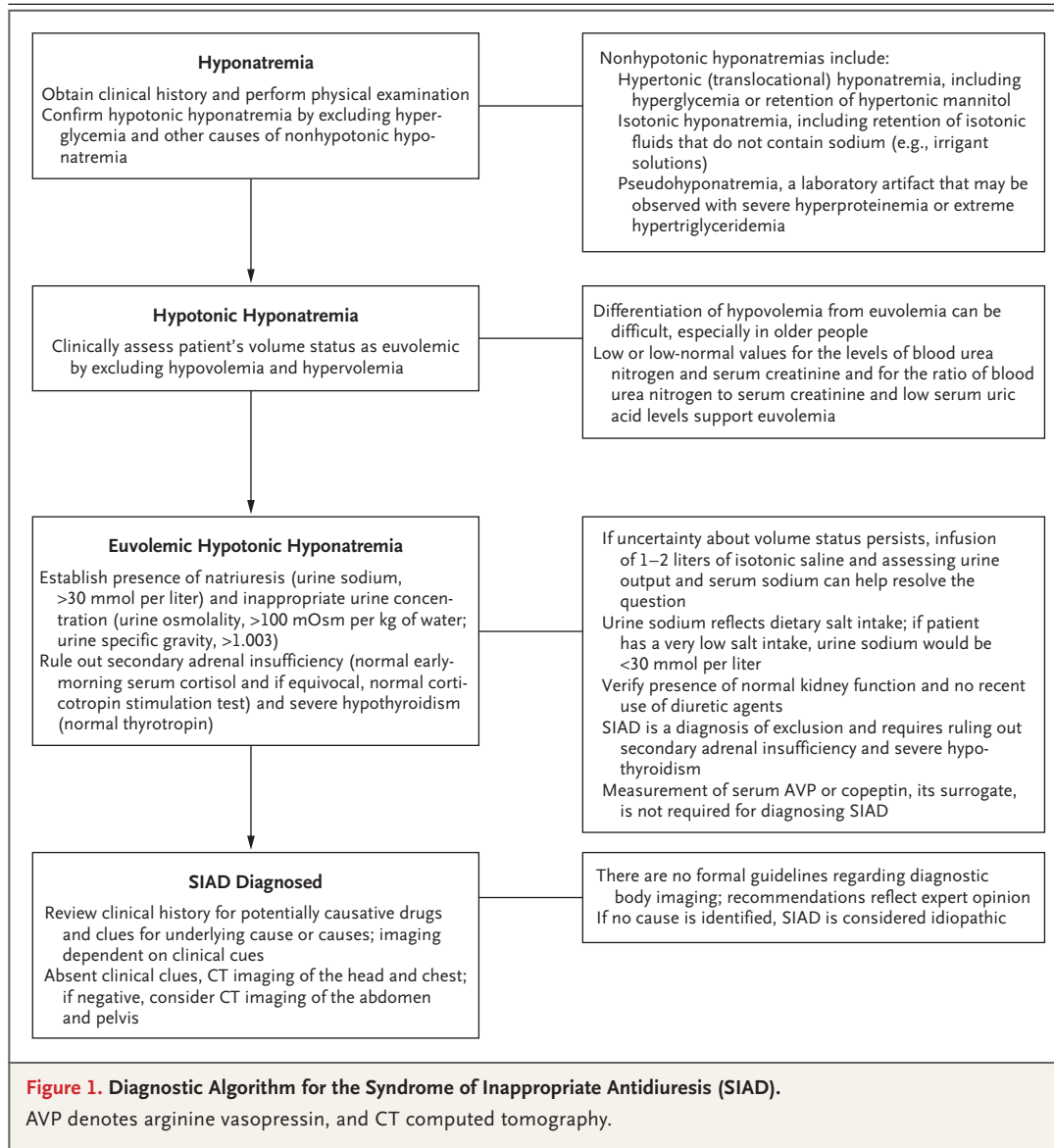
tle, although severe chronic SIAD can be associated with nausea, vomiting, headache, confusion, delirium, and, rarely, seizures.<sup>2,12</sup> Other manifestations associated with chronic SIAD, such as cognitive deficits, gait abnormalities, falls, osteoporosis, and fragility fractures, may be misattributed to normal aging.<sup>13-15</sup>

## STRATEGIES AND EVIDENCE

**DIAGNOSIS**

The diagnosis of SIAD requires clinical confirmation of euvolemic hypotonic hyponatremia (Fig. 1).<sup>16</sup> Given the low sensitivity and specificity of a physical examination in assessing volume status, European guidelines prioritize measurement of urine osmolality and sodium.<sup>17</sup> Urine studies showing natriuresis (sodium, >30 mmol per liter) and inappropriate concentration (osmolality, >100 mOsm per kilogram of water) are consistent with SIAD. However, diagnosing SIAD requires ruling out secondary adrenal insufficiency and severe hypothyroidism.<sup>3,7,16-18</sup> In practice, requisite serum and urine tests for diagnosis are often omitted; the Hyponatremia Registry showed that those tests were completed in only 21% of patients in whom SIAD was diagnosed.<sup>19</sup>

The causes of SIAD are numerous (Table 1).<sup>2,4,7</sup> Major categories of causes (and relative frequencies) of SIAD included in the Hyponatremia Registry are cancer (24%), certain drugs (18%), pulmonary conditions (11%), and CNS disorders (9%).<sup>20</sup> Additional causes are exercise, pain, stress, severe nausea, postoperative state, and, rarely,



gain-of-function variants of gene encoding vasopressin 2 receptor (in nephrogenic SIAD).<sup>2-4</sup> More than one cause is frequently present.<sup>12,21</sup> Antidepressants are the most commonly implicated drugs, especially in underweight older women<sup>22</sup>; the risk relative to the use of antidepressants has been reported to be highest with the use of selective serotonin-reuptake inhibitors and lowest with mirtazapine. No cause is identified in 17 to 60% of patients with SIAD, depending on the extent of the evaluation and patient age (occurrence is highest among older persons).<sup>21,23</sup>

Reversal of hyponatremia upon discontinua-

tion of a drug establishes the causal relationship. In the absence of clinical diagnostic clues, experts generally recommend computed tomography (CT) of the head and chest; if imaging results are negative, CT of the abdomen and pelvis may be considered.<sup>4</sup>

**MANAGEMENT**

*Emergency Treatment*

Urgent treatment is required for patients with SIAD who have severe symptoms of hyponatremia (e.g., somnolence, seizures, cardiorespiratory distress, or coma); moderately severe symp-

**Table 1. Causes of the Syndrome of Inappropriate Antidiuresis (SIAD).\***

Categories	Causes	Comments
Cancer	Pulmonary and mediastinal, nasopharyngeal, gastrointestinal, genitourinary	Most commonly observed in small-cell lung cancer (approximately 25% of the cases of SIAD that are caused by cancer), followed by head and neck cancer and olfactory neuroblastoma; ectopic production of AVP by some cancers has been documented (e.g., small-cell lung cancer and its metastases and olfactory neuroblastoma); tumor regression can reverse SIAD
Pulmonary conditions	Infections, asthma, acute respiratory failure	Most commonly seen in pneumonia of all causes; observed with positive-pressure ventilation
Central nervous system disorders	Mass lesions, infections, cerebrovascular accident, head trauma, pituitary surgery, acute psychosis	Develops in up to 56% of patients with subarachnoid hemorrhage and up to 35% of those with transsphenoidal pituitary surgery; a rare but treatable cause of rapidly progressive dementia, anti-LGI1 limbic encephalitis, leads to SIAD in 60 to 90% of patients
Drug-related	Stimulants of AVP release (e.g., opiates, ifosfamide, MDMA [also known as “ecstasy”], vincristine, and platinum compounds), enhancers of AVP effects (e.g., NSAIDs), AVP analogues (e.g., desmopressin and oxytocin), and stimulants of V2R (e.g., SSRIs, haloperidol, carbamazepine, cyclophosphamide, and chlorpropamide)	MDMA intoxication can result in severe hyponatremia because AVP stimulation is coupled with excessive ingestion of fluids on the users’ belief that they can avoid the characteristic hyperthermia; desmopressin, prescribed for enuresis (nocturnal polyuria), can cause severe hyponatremia and occasionally osmotic demyelination syndrome; antidepressants are among the most common causes, especially in underweight older women (risk is highest with SSRIs and lowest with mirtazapine); high-dose intravenous cyclophosphamide can result in severe hyponatremia if large amounts of fluid are prescribed for prevention of hemorrhagic cystitis
Other	Exercise-associated, pain, stress, severe nausea, general anesthesia, postoperative state, gain-of-function variants in V2R gene (nephrogenic SIAD)	Prevention of exercise-associated hyponatremia requires that athletes drink only in response to thirst and avoid weight gain during exercise; in postoperative state, hyponatremia reflects combined effects of pain, stress, nausea, anesthesia, opiates, and hypotonic fluids; most cases of hereditary SIAD feature persistent activation of V2R (gene located on the X chromosome) that is unresponsive to vaptans
Idiopathic		Widely variable prevalence (17 to 60% of cases), most commonly reported in older patients; occasionally, an apparent idiopathic case has later been found to have been caused by occult tumor

\* AVP denotes arginine vasopressin, LGI1 leucine-rich, glioma-inactivated 1 antibodies, MDMA 3,4-methylene-dioxymethamphetamine, NSAIDs nonsteroidal antiinflammatory drugs, SSRIs selective serotonin-reuptake inhibitors, and V2R vasopressin 2 receptor.

toms (e.g., vomiting or confusion) and a high risk for progression on the basis of the clinical presentation (e.g., postoperative state or exercise-associated); or any hyponatremia accompanying intracranial disease (e.g., subarachnoid hemorrhage or head trauma), in which case worsening of cerebral edema could be catastrophic. Typically, such patients have acute hyponatremia, but some have acute-on-chronic hyponatremia or extreme chronic hyponatremia.<sup>2,12,16,17,24-26</sup>

Traditional treatment has been the administration of 3% sodium chloride by means of slow, continuous infusion to raise serum sodium by 1 to 2 mmol per liter per hour for a few hours, with a correction limit of 8 to 10 mmol per liter over 24 hours and 18 to 25 mmol per liter over 48 hours.<sup>7</sup> The current rapid approach, supported by guidelines from a U.S.–Irish expert panel and by European guidelines, is the administration of 100 ml and 150 ml of 3% sodium chloride, respectively, administered as an intravenous bolus and repeated two or three times as needed.<sup>16,17</sup> The goal of this treatment approach is to increase serum sodium by 4 to 6 mmol per liter within 1 to 2 hours, an increase sufficient to reverse clinical manifestations of cerebral edema.<sup>16,17</sup> Guidelines set a correction limit of 10 mmol per liter within the first 24 hours and 18 mmol per liter within the first 48 hours. Correction limits are imposed because overly rapid correction of chronic hyponatremia increases the risk of osmotic demyelination, a rare but potentially devastating complication that involves the central pons or extrapontine structures and can cause hyperreflexia, pseudobulbar palsy, parkinsonism, locked-in syndrome, and death.<sup>16,17,25</sup>

For patients at high risk for osmotic demyelination (i.e., chronic hyponatremia of <110 mmol per liter, alcohol use disorder, liver disease or transplantation, potassium depletion, or malnutrition), the correction limit is 8 mmol per liter during any 24-hour period.<sup>12,16,17</sup> Other experts recommend stricter correction limits: in any 24-hour period, a correction limit of 8 mmol per liter for patients at low risk for osmotic demyelination and 6 mmol per liter for patients at high risk.<sup>2,12,25</sup> If hyponatremia is known to be acute (e.g., occurring during a postoperative state), adherence to correction limits is unnecessary. However, the duration of hyponatremia usually cannot be ascertained<sup>12</sup>; even in exercise-associated hyponatremia, preexisting chronic hypona-

tremia cannot be ruled out. Emergency treatment requires close monitoring, preferably in the intensive care unit, and consultation with a specialist (i.e., intensivist, nephrologist, or endocrinologist).<sup>2</sup>

A nonrandomized study involving patients with severe symptomatic SIAD who were treated with 100 ml of 3% sodium chloride administered as an intravenous bolus showed an increase in serum sodium levels that was greater than that observed in a historical comparison group in which patients received 3% sodium chloride in a continuous infusion (6 mmol per liter vs. 3 mmol per liter at 6 hours) and reported greater neurologic improvement in that time interval<sup>27</sup>; overcorrection occurred in 4.5% of the patients who received sodium chloride by intravenous bolus as compared with none of the patients who received continuous infusion, and sodium-relowering therapy was used in 23% and 0%, respectively. Two other small studies also showed high rates of overcorrection (17% and 28%) and sodium-relowering therapy (41% and 28%) with the bolus approach (150 ml per dose); however, these studies included many participants with hypovolemia in whom aquaresis probably developed after volume repletion.<sup>28,29</sup>

Overcorrection can occur because of excessive administration of 3% sodium chloride owing to repeated fixed-dose boluses.<sup>2,12,30</sup> The effects that a given dose has on the serum sodium level depend on the sodium level at baseline and the total body water (the latter affected by sex, weight, and body fat). An individualized approach to the administration of 3% sodium chloride can be applied with the use of a formula that effectively predicts the change in the serum sodium level after the infusion of 1 liter of any solution if there is no other input or output. The change from baseline in sodium level is calculated according to the following formula: (sodium+potassium) infusate—sodium level at baseline÷total body water+1.<sup>2,5,12</sup> The formula has been validated with regard to patients with SIAD who remain antidiuretic, with actual serum sodium levels at 24 hours that are very similar to predicted levels.<sup>31,32</sup>

Overcorrection can also occur because of transition to aquaresis (urine output, >100 ml per hour) after the discontinuation of causative drugs or reversal of transient SIAD (e.g., postoperative state). The effect of aquaresis on serum

sodium can be quantitated by means of a simple fluid-loss formula.<sup>12</sup> To counter such risk, desmopressin can be used proactively (anticipating aquaresis) or reactively (responding to aquaresis).<sup>25,32,33</sup> However, randomized trials of desmopressin are lacking in these contexts; retrospective studies have shown no consistent benefit associated with its use and potential complications, including volume overload, longer hospitalization, more testing, and worsening hyponatremia.<sup>34-36</sup> If overcorrection develops, urgent treatment is required, including discontinuation of 3% sodium chloride, infusion of a 5% solution of dextrose in water, and administration of desmopressin as rescue therapy.<sup>2,25</sup> Because potassium retention increases serum sodium, special caution is required with potassium supplementation when treating hyponatremia to avoid overcorrection.<sup>2,12</sup>

#### *Nonemergency Treatment*

Fewer than 5% of patients with hyponatremia have sufficiently severe symptoms to need emergency treatment.<sup>2,19</sup> For the majority of patients, treatment focuses on addressing the underlying cause (or causes) and is typically administered on an outpatient basis; exceptions include treatment of patients who are hospitalized for management of an underlying cause of hyponatremia or whose serum sodium level is less than 120 mmol per liter. Among patients in the latter group, the absence of severe manifestations is evidence of substantial brain-volume adaptation, so close monitoring of serum sodium levels is indicated during treatment to minimize the risk of osmotic demyelination. If the underlying cause can be reversed (e.g., drug effects or pneumonia), hyponatremia resolves within several days.

Observational studies in patients with moderate or severe chronic SIAD have shown associations between correction of sodium levels and improvements in neurocognitive performance, motor function, and mood<sup>13,37,38</sup>; however, other aspects of patient care, including treatment of associated coexisting conditions, may confound these findings. Limited data from randomized, controlled trials bear out findings of improvement on the physical component score of the 12-item Short-Form Health Survey Questionnaire (a tool for evaluating quality of life) with increases in sodium levels.<sup>39</sup> In addition, increases in serum sodium levels in patients with chronic

SIAD and mild or moderate hyponatremia have been associated with increases in markers of osteoblast function,<sup>40,41</sup> although the effects on the incidence of fractures are not known. These observations support reasonable efforts to correct hyponatremia of any level in patients with SIAD.

Several therapies are available for patients with SIAD (Table 2). Fluid restriction, the first-line treatment, is inexpensive and safe but of limited efficacy; urine output of less than 1.5 liters per day or urine osmolality greater than 500 mOsm per kilogram of water predicts SIAD that is unresponsive to this approach.<sup>2,16</sup> A randomized, controlled trial that assessed fluid restriction (fluid intake limited to 1 liter per day) as compared with no hyponatremia treatment in 46 patients with chronic SIAD (in whom transient and reversible causes were ruled out) showed a modest rise in serum sodium levels with fluid restriction (3 mmol per liter vs. 1 mmol per liter at day 4; and 4 mmol per liter vs. 1 mmol per liter at day 30). Only 17% and 4% of patients, respectively, had a rise in serum sodium of at least 5 mmol per liter at day 4.<sup>42</sup>

Other therapies involve increasing salt, urea, or protein intake,<sup>16,17,24,26</sup> although data are lacking from randomized, blinded trials. In a retrospective study involving 83 patients with chronic SIAD, patients who took salt tablets (median dose, 5 g per day) had a mean increase in serum sodium levels of 5.2 mmol per liter, as compared with 3.1 mmol per liter in patients who did not receive salt tablets.<sup>43</sup> Salt tablets plus furosemide are widely used on the premise that replacement of salt lost in the urine promotes aquaresis, thus raising serum sodium levels. However, in an open-label, randomized, controlled trial involving 92 patients with SIAD, treatment with salt tablets plus furosemide and severe fluid restriction as compared with fluid restriction alone resulted in modestly higher sodium levels at day 7 but no difference at day 28; the addition of salt plus furosemide also increased the risk of acute kidney injury and hypokalemia.<sup>44</sup>

Small observational studies ranging in duration from 2 days to 1 year have shown improvements in sodium levels among outpatients and inpatients who received urea in addition to moderate fluid restriction (fluid intake limited to 1 to 1.5 liters per day).<sup>24,45</sup> A retrospective study showed that among 12 patients treated only with urea, serum sodium levels increased

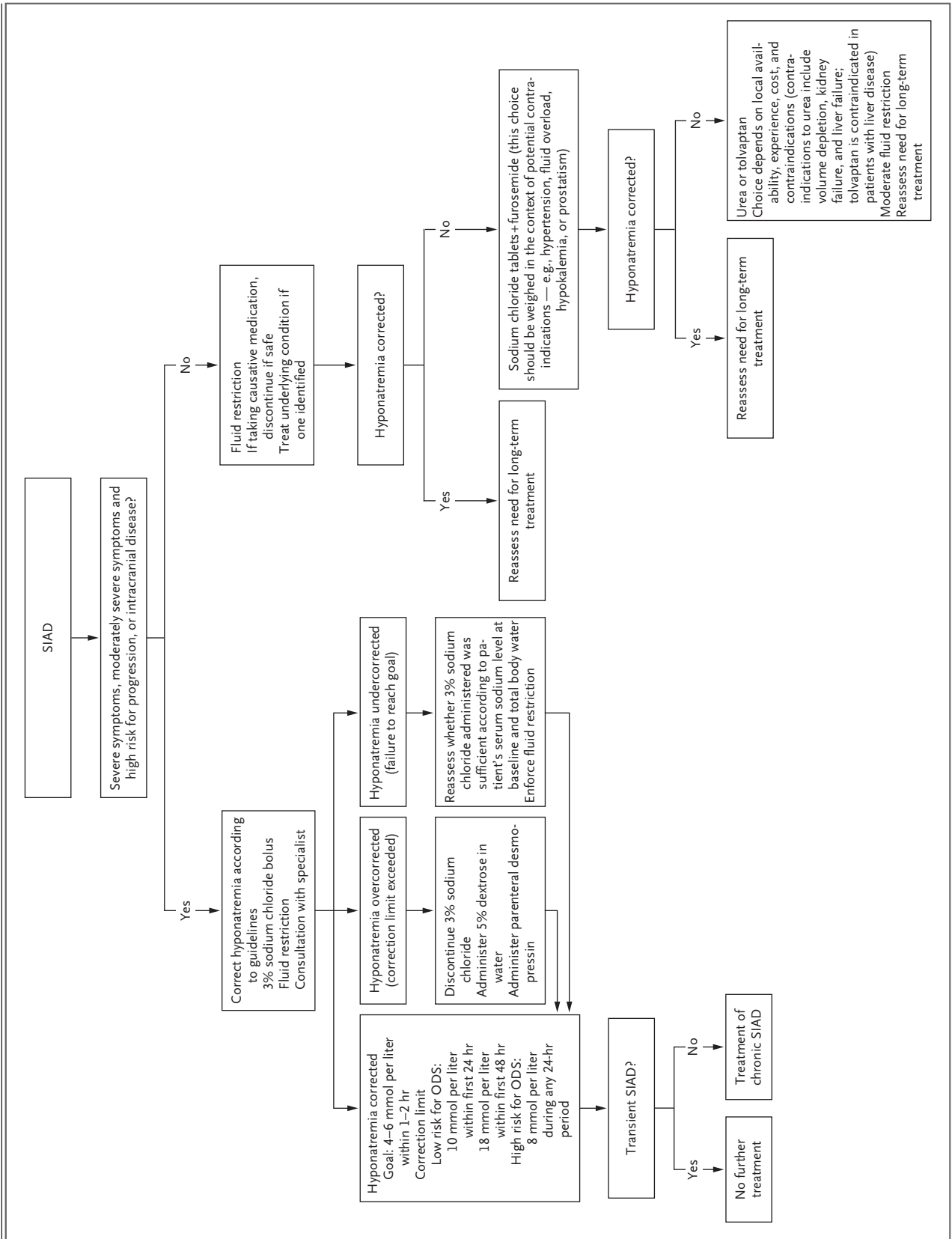
by 6 mmol per liter over 4 days without incidents of overcorrection or other serious adverse effects.<sup>46</sup> Urea has been used effectively in managing nephrogenic SIAD.<sup>45</sup> Patients with SIAD commonly have low protein intake<sup>11</sup>; increasing protein intake (to approximately 1 g per kilogram of body weight) may ameliorate hyponatremia by mimicking urea therapy, but data regarding this effect are lacking.

Tolvaptan, which competitively inhibits the vasopressin 2 receptor in the collecting duct, is a highly effective therapeutic agent.<sup>47</sup> In a subset analysis involving 110 patients with SIAD who were included in two randomized, placebo-controlled trials of tolvaptan for the treatment of hyponatremia, patients who received tolvaptan had larger increases in serum sodium levels than patients who received placebo. The average daily area under the curve for the serum sodium level among patients who received tolvaptan was 5.3 mmol per liter from baseline to day 4 and 8.1 mmol per liter from baseline to day 30; among patients who received placebo, the average daily area under the curve for the serum sodium level was 0.5 mmol per liter from baseline to day 4 and 1.9 mmol per liter from baseline to day 30. Patients who received tolvaptan had less need for fluid restriction and a shorter duration of hospitalization than those who received placebo.<sup>39</sup> However, thirst and dry mouth were common, and overcorrection of hyponatremia occurred in 5.9% of patients treated with tolvaptan.<sup>39</sup> In an open-label extension of these trials, daily therapy with tolvaptan continued to be effective over 4 years.<sup>48</sup> Tolvaptan is contraindicated with concomitant use of hypertonic saline, and caution is recommended in patients with serum sodium levels of less than 120 mmol per liter because of limited safety information.<sup>24,26,47</sup> Tolvaptan is ineffective in the management of nephrogenic SIAD.<sup>4</sup> A treatment algorithm for SIAD is shown in Figure 2.

More recent data support a potential role for empagliflozin, a sodium glucose cotransporter 2 inhibitor that promotes osmotic diuresis by means of glucosuria, in the treatment of patients with SIAD. In a randomized, controlled trial involving 87 patients, fluid restriction to 1 liter per day plus treatment with empagliflozin was associated with a greater increase in serum sodium levels at day 5 than fluid restriction alone (10 mmol per liter vs. 7 mmol per liter). How-

**Table 2. Treatment Approaches.**

Treatment	Mechanism	Amount or Dose	Efficacy	Adverse Effects	Comments
Fluid restriction	Reduces electrolyte-free water intake and total body water; should include all fluids, not just water	Moderate, <1.5 liters per day; severe, <1 liter per day	First-line treatment; difficult to adhere to and thus often ineffective	Increases thirst; may result in low caloric intake	Inexpensive and safe; predictors of failure at baseline include urine output of <1.5 liters per day, urine osmolality >500 mOsm per kg of water, and the sum of urine sodium and urine potassium levels exceeding the serum sodium level; contraindicated in subarachnoid hemorrhage and other intracranial processes
Sodium chloride supplement	Increases body sodium content, reduces electrolyte-free water intake, and increases water excretion	2–5 g per day (500 mg per tablet); frequently combined with furosemide 20 mg twice daily or equivalent loop diuretic to increase aquaresis	Limited long-term efficacy	Increases body sodium content, risking sodium and fluid excess; combining with furosemide can cause potassium depletion	Inexpensive; addition of sodium chloride plus furosemide to severe fluid restriction has no persistent benefit with respect to correction of serum sodium levels; contraindicated in hypertension, heart failure, and other sodium-retentive states
Urea	Increases electrolyte-free water excretion (by means of osmotic diuresis); decreases sodium excretion	15–60 g per day orally or enterally combined with moderate fluid restriction; 30 g of urea (500 mOsm) increases water excretion by 1 liter (for urine osmolality of 500 mOsm per kg of water)	Short- and long-term efficacy reported in observational studies	Nausea, diarrhea, and bitter taste; rare overly rapid correction of serum sodium, but osmotic demyelination not reported	Palatability is improved by dissolving in fruit juice or syrup (European guideline provides a recipe); citrus-flavored U.S. formulation (ure-Na) is available; initially used in Europe but more recently prescribed worldwide; contraindicated in volume depletion, kidney failure, and liver failure
Tolvaptan	Sole therapy that addresses underlying pathophysiology; competitive vasopressin receptor 2 blocker	15–60 mg per day orally combined with moderate fluid restriction; initiated in hospital to allow close monitoring of serum sodium (every 6–8 hr or more frequently depending on risk of osmotic demyelination syndrome) and dose adjustment; fluid restriction should not be used during the initial dose-finding phase to decrease risk of overly rapid correction of serum sodium; 7.5 mg per day appears as effective as 15 mg per day as a starting dose	Highly effective both in short- and long-term use; aquaretic response and increase in serum sodium correlate directly with severity of hyponatremia	Polyuria and increased thirst; overly rapid correction of serum sodium occurs in 13 to 25% of patients in real-life experience (appears to be exclusive to baseline serum sodium of <125 mmol per liter); sporadic cases of osmotic demyelination syndrome; 7.5-mg dose not associated with overly rapid correction in chronic SIAD	Food and Drug Administration warns against use for >30 days (on the basis of duration of pivotal trials) and in patients with liver disease; not recommended by the European guideline owing to risks of overly rapid correction of serum sodium level and hepatotoxicity; hepatotoxicity not observed in tolvaptan trials for hyponatremia, but reversible hepatotoxicity was reported in trials that used high doses of tolvaptan to alter course of polycystic kidney disease; cost is a barrier to use in some countries





**Figure 2 (facing page). Treatment Algorithm for SIAD.**  
ODS denotes osmotic demyelination syndrome.

ever, although the frequency of serious adverse events did not differ materially between the empagliflozin and placebo groups in that trial, empagliflozin was associated with transient kidney dysfunction in 4 patients and overcorrection of hyponatremia in 2 patients (as compared with no patients and 1 patient, respectively, in the placebo group).<sup>49</sup> In a subsequent randomized 4-week crossover trial involving 14 patients, treatment with empagliflozin resulted in an increase of 4.1 mmol per liter in the serum sodium level, as compared with no increase with placebo.<sup>50</sup>

#### AREAS OF UNCERTAINTY

Whether the observed associations between chronic hyponatremia and adverse outcomes (such as fractures and increased risk of death) are causal remains uncertain, although some evidence supports causal relationships. For example, the experimental induction of chronic SIAD in aged rats resulted in loss of bone density, sarcopenia, cardiomyopathy, and hypogonadism.<sup>14,51</sup>

Whether reversing hyponatremia results in improved long-term outcomes is also uncertain. A meta-analysis of observational studies showed substantially lower occurrences of in-hospital and postdischarge death among patients whose hyponatremia improved during hospitalization as compared with patients whose hyponatremia did not improve.<sup>52</sup> However, the possibility of confounding by coexisting conditions and other aspects of treatment cannot be excluded.

Prospective studies are needed to assess emergency management of hyponatremia with the use of guideline-directed fixed doses of hypertonic saline (administered as an intravenous bolus) as compared with an individualized formula-based approach. Encouraging reports regarding

the efficacy and safety of smaller starting doses of tolvaptan warrant additional investigation.<sup>53</sup> Long-term randomized trials are needed to compare treatment with tolvaptan, urea, and empagliflozin (as well as other sodium glucose cotransporter 2 inhibitors) with respect to efficacy outcomes, safety, and costs.

#### GUIDELINES

Recommendations from a U.S.–Irish expert panel<sup>16</sup> and European guidelines<sup>17</sup> regarding the diagnosis and management of hyponatremia, including hyponatremia due to SIAD, have been published previously. Our recommendations align with these guidelines.

#### CONCLUSIONS AND RECOMMENDATIONS

The patient who is described in the vignette has hyponatremia consistent with SIAD. To confirm the diagnosis, testing is needed to rule out secondary adrenal insufficiency and severe hypothyroidism. Because he is taking no medications associated with SIAD and no other cause is apparent, we would pursue CT imaging of the chest and head; if imaging is negative, we would consider the case idiopathic. His high urine osmolality level predicts a poor response to fluid restriction as monotherapy. Given the patient's hypertension and prostatism, we would avoid recommending salt tablets and furosemide. We would instead recommend urea at a dose of 15 g twice daily (delivered as an oral urea formulation) along with fluid restriction to 1500 ml per day, although data from randomized trials are not available to support this approach. Alternatively, we would consider long-term use of tolvaptan at a starting dose of 7.5 mg per day; however, the cost of this therapy may be a barrier for some patients. Sodium levels should be closely monitored during treatment.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

#### REFERENCES

1. Burst V. Etiology and epidemiology of hyponatremia. *Front Horm Res* 2019;52:24-35.
2. Adrogué HJ, Tucker BM, Madias NE. Diagnosis and management of hyponatremia. *JAMA* 2022;328:280-91.
3. Cuesta M, Garrahy A, Thompson CJ. SIAD: practical recommendations for diagnosis and management. *J Endocrinol Invest* 2016;39:991-1001.
4. Warren AM, Grossmann M, Christ-Crain M, Russell N. Syndrome of inappropriate antidiuresis: from pathophysiology to management. *Endocr Rev* 2023;44:819-61.
5. Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000;342:1581-9.
6. Rondon-Berrios H, Berl T. Physiology

- and pathophysiology of water homeostasis. *Front Horm Res* 2019;52:8-23.
7. Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007;356:2064-72.
  8. Cuesta M, Garrahy A, Slattery D, et al. Mortality rates are lower in SIAD, than in hypervolaemic or hypovolaemic hyponatraemia: results of a prospective observational study. *Clin Endocrinol (Oxf)* 2017; 87:400-6.
  9. Zerah L, Bihan K, Kohler S, Mariani L-L. Iatrogenesis and neurological manifestations in the elderly. *Rev Neurol (Paris)* 2020;176:710-23.
  10. Cowen LE, Hodak SP, Verbalis JG. Age-associated abnormalities of water homeostasis. *Endocrinol Metab Clin North Am* 2013;42:349-70.
  11. Decaux G, Musch W, Gankam Kengne F, Couturier B, Soupant A, Vanderghenst F. Low-solute intake in chronic asymptomatic hyponatraemia related to syndrome of inappropriate secretion of ADH (SIADH): think about food beyond water intake! *Nephrol Dial Transplant* 2020;35: 2013-4.
  12. Adrogué HJ, Madias NE. The challenge of hyponatremia. *J Am Soc Nephrol* 2012;23:1140-8.
  13. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006;119(1):71.e1-71.e8.
  14. Barsony J, Kleess L, Verbalis JG. Hyponatremia is linked to bone loss, osteoporosis, fragility and bone fractures. *Front Horm Res* 2019;52:49-60.
  15. Murthy K, Ondrey GJ, Malkani N, et al. The effects of hyponatremia on bone density and fractures: a systematic review and meta-analysis. *Endocr Pract* 2019;25:366-78.
  16. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med* 2013;126:Suppl 1: S1-S42.
  17. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant* 2014;29:Suppl 2: i1-i39.
  18. Garrahy A, Thompson CJ. Hyponatremia and glucocorticoid deficiency. *Front Horm Res* 2019;52:80-92.
  19. Greenberg A, Verbalis JG, Amin AN, et al. Current treatment practice and outcomes: report of the hyponatremia registry. *Kidney Int* 2015;88:167-77.
  20. Verbalis JG, Greenberg A, Burst V, et al. Diagnosing and treating the syndrome of inappropriate antidiuretic hormone secretion. *Am J Med* 2016;129(5):537.e9-537.e23.
  21. Shapiro DS, Sonnenblick M, Galperin I, Melkonyan L, Munter G. Severe hyponatraemia in elderly hospitalized patients: prevalence, aetiology and outcome. *Intern Med J* 2010;40:574-80.
  22. Liamis G, Megapanou E, Elisaf M, Milionis H. Hyponatremia-inducing drugs. *Front Horm Res* 2019;52:167-77.
  23. Shepshelovich D, Leibovitch C, Klein A, et al. The syndrome of inappropriate antidiuretic hormone secretion: distribution and characterization according to etiologies. *Eur J Intern Med* 2015;26:819-24.
  24. Decaux G, Gankam Kengne F. Hypertonic saline, isotonic saline, water restriction, long loops diuretics, urea or vaptans to treat hyponatremia. *Expert Rev Endocrinol Metab* 2020;15:195-214.
  25. Sterns RH. Treatment of severe hyponatremia. *Clin J Am Soc Nephrol* 2018;13: 641-9.
  26. Lawless SJ, Thompson C, Garrahy A. The management of acute and chronic hyponatraemia. *Ther Adv Endocrinol Metab* 2022;13:20420188221097343.
  27. Garrahy A, Dineen R, Hannon AM, et al. Continuous versus bolus infusion of hypertonic saline in the treatment of symptomatic hyponatremia caused by SIAD. *J Clin Endocrinol Metab* 2019;104: 3595-602.
  28. Baek SH, Jo YH, Ahn S, et al. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia: the SALSA randomized clinical trial. *JAMA Intern Med* 2021;181:81-92.
  29. Chifu I, Gerstl A, Lengenfelder B, et al. Treatment of symptomatic hyponatremia with hypertonic saline: a real-life observational study. *Eur J Endocrinol* 2021; 184:647-55.
  30. Pelouto A, Refardt JC, Christ-Crain M, Zandbergen AAM, Hoorn EJ. Overcorrection and undercorrection with fixed dosing of bolus hypertonic saline for symptomatic hyponatremia. *Eur J Endocrinol* 2023;188:322-30.
  31. Liamis G, Kalogirou M, Saugos V, Elisaf M. Therapeutic approach in patients with dysnatraemias. *Nephrol Dial Transplant* 2006;21:1564-9.
  32. Sood L, Sterns RH, Hix JK, Silver SM, Chen L. Hypertonic saline and desmopressin: a simple strategy for safe correction of severe hyponatremia. *Am J Kidney Dis* 2013;61:571-8.
  33. Rondon-Berrios H, Sterns RH. Hypertonic saline for hyponatremia: meeting goals and avoiding harm. *Am J Kidney Dis* 2022;79:890-6.
  34. Tran LK, Marino KK, DeGrado JR, Szumita PM, Dube KM. Evaluation of desmopressin in critically ill patients with hyponatremia requiring 3% hypertonic saline. *Am J Med Sci* 2021;361:711-7.
  35. Jingushi N, Tsuzuki S, Fujii K, Uenishi N, Iwata M, Terasawa T. Association of intranasal desmopressin therapy with overcorrection of severe hyponatremia: a retrospective, propensity score-based, single-center cohort study. *J Crit Care* 2021;64:53-61.
  36. MacMillan TE, Cavalcanti RB. Outcomes in severe hyponatremia treated with and without desmopressin. *Am J Med* 2018;131(3):317.e1-317.e10.
  37. Brinkkoetter PT, Grundmann F, Ghassabeh PJ, et al. Impact of resolution of hyponatremia on neurocognitive and motor performance in geriatric patients. *Sci Rep* 2019;9:12526.
  38. Suárez V, Norello D, Sen E, et al. Impairment of neurocognitive functioning, motor performance, and mood stability in hospitalized patients with euolemic moderate and profound hyponatremia. *Am J Med* 2020;133(8):986-993.e5.
  39. Verbalis JG, Adler S, Schrier RW, et al. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. *Eur J Endocrinol* 2011;164:725-32.
  40. Potasso L, Refardt J, Meier C, Christ-Crain M. Effect of hyponatremia normalization on osteoblast function in patients with SIAD. *Eur J Endocrinol* 2021;186:1-8.
  41. Monnerat S, Refardt J, Potasso L, Meier C, Christ-Crain M. An increase in plasma sodium levels is associated with an increase in osteoblast function in chronic SIAD. *J Clin Endocrinol Metab* 2023 April 25 (Epub ahead of print).
  42. Garrahy A, Galloway I, Hannon AM, et al. Fluid restriction therapy for chronic SIAD: results of a prospective randomized controlled trial. *J Clin Endocrinol Metab* 2020;105(12):dgaa619.
  43. Spanuchart I, Watanabe H, Aldan T, Chow D, Ng RCK. Are salt tablets effective in the treatment of euolemic hyponatremia? *South Med J* 2020;113:125-9.
  44. Krisanapan P, Vongsanin S, Pin-On P, Ruengorn C, Noppakun K. Efficacy of furosemide, oral sodium chloride, and fluid restriction for treatment of syndrome of inappropriate antidiuresis (SIAD): an open-label randomized controlled study (the EFFUSE-FLUID trial). *Am J Kidney Dis* 2020;76:203-12.
  45. Rondon-Berrios H. Urea for chronic hyponatremia. *Blood Purif* 2020;49:212-8.
  46. Rondon-Berrios H, Tandukar S, Mor MK, et al. Urea for the treatment of hyponatremia. *Clin J Am Soc Nephrol* 2018;13: 1627-32.
  47. Rondon-Berrios H, Berl T. Vasopressin receptor antagonists in hyponatremia: uses and misuses. *Front Med (Lausanne)* 2017;4:141.
  48. Berl T, Quittnat-Pelletier F, Verbalis JG, et al. Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol* 2010;21:705-12.
  49. Refardt J, Imber C, Sailer CO, et al. A randomized trial of empagliflozin to increase plasma sodium levels in patients with the syndrome of inappropriate antidiuresis. *J Am Soc Nephrol* 2020;31:615-24.

50. Refardt J, Imber C, Nobbenhuis R, et al. Treatment effects of the SGLT2 inhibitor empagliflozin on chronic syndrome of inappropriate antidiuresis: results of a randomized, double-blind, placebo-controlled, crossover trial. *J Am Soc Nephrol* 2023;34:322-32.
51. Barsony J, Manigrasso MB, Xu Q, Tam H, Verbalis JG. Chronic hyponatremia exacerbates multiple manifestations of senescence in male rats. *Age (Dordr)* 2013; 35:271-88.
52. Corona G, Giuliani C, Verbalis JG, Forti G, Maggi M, Peri A. Hyponatremia improvement is associated with a reduced risk of mortality: evidence from a meta-analysis. *PLoS One* 2015;10(4):e0124105.
53. Hanna RM, Velez JC, Rastogi A, et al. Equivalent efficacy and decreased rate of overcorrection in patients with syndrome of inappropriate secretion of antidiuretic hormone given very low-dose tolvaptan. *Kidney Med* 2019;2:20-8.

Copyright © 2023 Massachusetts Medical Society.

**IMAGES IN CLINICAL MEDICINE**

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal's* website at [NEJM.org](http://NEJM.org). At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.