Clinical Nephrology Insights

Syndrome of Inappropriate Antidiuresis

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Abstract

Syndrome of inappropriate antidiuresis (SIAD)—the most frequent cause of hypotonic hyponatremia—is mediated by nonosmotic release of arginine vasopressin, which promotes water retention by activating renal vasopressin type 2 (V2) receptors. There are numerous causes of SIAD, including malignancy, pulmonary and central nervous system diseases, and medications. Rare activating mutations of the V2 receptor can also cause SIAD. Determination of the etiology of SIAD is important because removal of the stimulus for inappropriate arginine vasopressin secretion offers the most effective therapy. Treatment of SIAD is guided by symptoms and their severity, as well as the level of plasma sodium. In the absence of severe symptoms, which require urgent intervention, many clinicians focus on fluid restriction as a first-line treatment. Second-line therapeutic options include loop diuretics and salt tablets, urea, and V2 receptor antagonists.

JASN 36: 713–722, 2025. doi: https://doi.org/10.1681/ASN.0000000588

Hyponatremia is a common electrolyte disorder, affecting up to 15%–30% of acute hospital admissions (dependent on the definition and cutoff values for plasma sodium [PNa]).[1–6] Hyponatremia is classified in various manners. Severity is often defined biochemically on the basis of PNa levels.[7] Severity may also be defined by the presence of symptoms or signs of cerebral edema.[8] While clinical signs and symptoms of hyponatremia generally correlate with the degree of biochemical hyponatremia, the rate of development of hyponatremia also plays a significant role with more rapid lowering of the PNa associated with more severe symptoms.[9] Hyponatremia is also classified temporally as acute or chronic to recognize the brain cellular adaptations to hypotonicity as well as the risks of complications associated with rapid correction of the PNa.[10] Thus, when defining hyponatremia, clinicians should not focus simply on the absolute PNa value but include characterization of clinical severity as well as acuity or chronicity and, if possible, etiology.

The approach to diagnosis of hyponatremia is shown in Figure 1. This approach centers on understanding the urine osmolality and urine sodium values. The most common etiology of hyponatremia is syndrome of inappropriate antidiuresis (SIAD) driven by nonphysiological secretion of arginine vasopressin (AVP) by the posterior pituitary or by a paraneoplastic process. We prefer the term "SIAD" rather than "syndrome of inappropriate diuresis" to highlight that inappropriate antidiuresis is the pathogenetic hallmark of the condition and that this does not necessarily require presence of elevated AVP levels. The exact incidence and prevalence of SIAD is unclear as retrospective, population-based studies are often limited by incomplete diagnostic workups, but several studies have highlighted that SIAD may account for 35%–40% of patients with hyponatremia.[11–13]

The Definition of SIAD

The hallmark of most forms of SIAD is the sustained and inappropriate secretion of AVP independent of the usual osmotic changes sensed by osmoreceptors in the hypothalamus or through sensing of effective arterial blood volume (EABV) by baroreceptors.[14,15] Diagnostic criteria (Table 1) for SIAD were published in 1967[16]; those for SIAD are similar, except that some authors classify secondary adrenal insufficiency as one of its causes and exclusion of hypothyroidism is not required. These criteria highlight the importance of identifying secretion of AVP associated with nonphysiological stimuli, which accounts for most of the cases of SIAD. Numerous etiologies have been identified as leading to SIAD (Figure 2). A large registry study attempted to determine the etiology of SIAD and found that the cause was unknown (idiopathic) in 35.6%, due to malignancy in 23.6%, drug induced in 17.8%, and associated with pulmonary disease in 10.7% and with central nervous system disease in 8.5%.[13] Within the drug-induced group, the most common classes were antidepressants (35.1%), antiepileptics (22.4%), and antipsychotics (10.3%). In addition, multiple etiologies may be present at various times in a patient that lead to worsening hyponatremia. For example, patients with mild, stable hyponatremia due to a medication effect may get hospitalized with the addition of new factors that affect kidney water handling, such as nausea, new medications (diuretics, antidepressants), exacerbation of heart failure or cirrhosis, or administration of hypotonic fluids.

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Published Online Ahead of Print: December 2, 2024

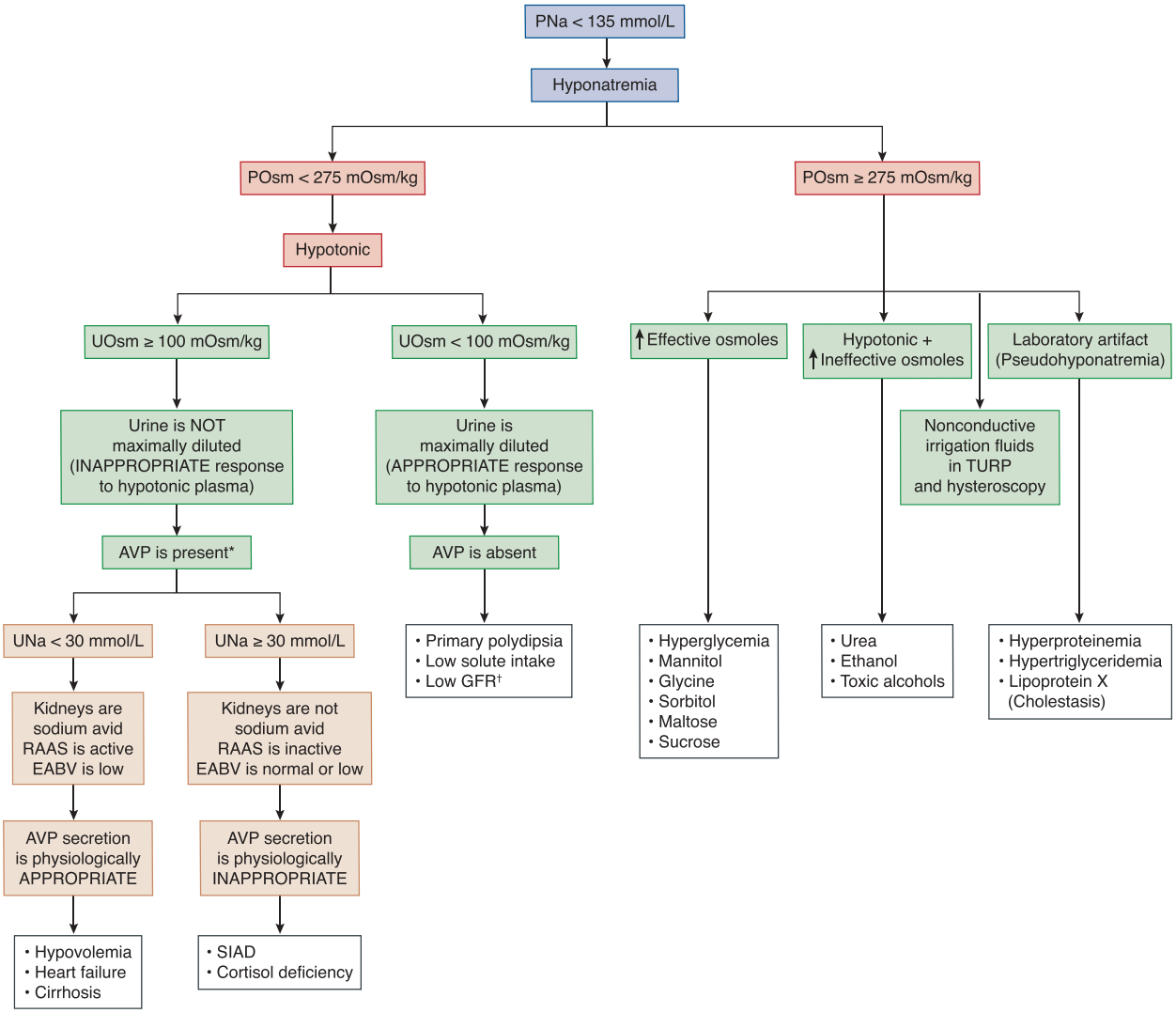

Figure 1. Diagnostic classification of hyponatremia. *The exception is patients with the nephrogenic syndrome of inappropriate antidiuresis. †Patients with hyponatremia because of a severely reduced GFR can produce diluted urine (*i.e.*, urine osmolality<plasma osmolality) but cannot maximally dilute (*i.e.*, urine osmolality <100 mOsm/kg). Note that cortisol deficiency without mineralocorticoid deficiency can result in hyponatremia without hypovolemia. Modified from ref. 123 with permission. AVP, arginine vasopressin; EABV, effective arterial blood volume; ↑, increased; PNa, plasma sodium; POsm, plasma osmolality; RAAS, renin-angiotensin-aldosterone system; SIAD, syndrome of inappropriate antidiuresis; TURP, transurethral resection of the prostate; UNa, urine sodium; UOsm, urine osmolality.

The Physiology of Water Handling

AVP is synthesized in the hypothalamus as a large precursor peptide that includes AVP, neurophysin II, and copeptin.[17–19] This precursor peptide is processed to biologically activate AVP and subsequently stored in axonal terminals in the posterior pituitary. Release into the systemic circulation occurs in response to rises in plasma tonicity (sensed by osmoreceptors in the anterior hypothalamus) and reduced EABV (sensed by peripheral baroreceptors).[15,20–22] Both of these physiological stimuli lead to eventual restoration of normal tonicity and EABV through the effects of AVP in the kidney acting through the vasopressin type 2 (V2) receptor.[23]

Kidney V2 receptors are located on the basolateral membrane of principal cells in the collecting duct. Binding to the V2 receptor increases synthesis and insertion of aquaporin 2 water channels into the cell membrane, increasing water permeability and leading to water retention from the tubular fluid resulting in more concentrated urine. AVP also promotes water resorption by increasing the medullary interstitial osmotic gradient, which is critical in drawing fluid out of the tubules into the vascular space. AVP does this by both increasing expression of the sodium-potassium-2 chloride cotransporter in the loop of Henle (increasing sodium reabsorption into the interstitium) as well as the epithelial sodium channels and by increasing urea transporters (UT-A1s; increasing urea deposition into the interstitium).[24–27]

Pathogenesis of SIAD

In 1980, Zerbe and colleagues performed a series of classic human studies that classified patterns of AVP secretion before and after infusion with hypertonic saline to raise

Table 1. Diagnostic criteria for syndrome of inappropriate antidiuresis

Main criteria for diagnosis of SIAD[a]
• Plasma osmolality <275 mOsm/kg
• Urine osmolality >100 mOsmol/kg
• Clinical euvolemia (absence of signs of hypovolemia or hypervolemia)
• Urine sodium >30 mmol/L (reflecting steady-state intake of sodium and water)
• Normal kidney function
• No recent diuretic use (particularly thiazide diuretics)
Supplemental criteria
• Plasma uric acid <4 mg/dl
• BUN <10 mg/dl
• Failure to correct hyponatremia after NaCl 0.9% infusion
• Fractional excretion of urea >55%
• Fractional excretion of uric acid >12%

SIAD, syndrome of inappropriate antidiuresis.
[a]Some classifications exclude hyponatremia caused by cortisol deficiency and hypothyroidism. Some authors consider secondary adrenal insufficiency as a cause of syndrome of inappropriate antidiuresis because its presenting clinical features are indistinguishable from those of other etiologies. Except for severe, clinically obvious myxedema, hypothyroidism does not cause hyponatremia, and we believe measurements of thyroid hormones to exclude the diagnosis to be unnecessary.

plasma osmolality.[28] While these patterns have limited clinical utility, they are useful in understanding the underlying pathology and presentations of SIAD. The first pattern shows persistently elevated AVP levels independent of changes in plasma osmolality. This is the most common pattern and seen with etiologies such as medications or with paraneoplastic processes (*e.g.*, seen in 10%–15% of patients with small cell lung carcinoma[29]). The next most common pattern is referred to as a "reset osmostat," and patients have a lower osmotic threshold for AVP secretion. In these patients, AVP levels suppress but at lower PNa levels, and hyponatremia is very difficult to correct with free water restriction or salt supplementation.[30] The frequency and associated etiologies of the reset osmostat are not clear, but it has been described in numerous patients with causes as diverse as pregnancy (physiological), aging, cerebral hemorrhage, encephalitis, dementia (Lewy body), alcohol use disorder, malnutrition, and others.[31–34] Another form of SIAD is characterized by undetectable AVP levels and is seen with gain-of-function mutations of the V2 receptor (nephrogenic SIAD).[35] This is a rare X-linked condition leading to constant free water absorption in the collecting duct and hyponatremia. While the condition may present in infancy with cerebral edema, there is great phenotypic variability with some mild cases.[36] The last pattern is elevated basal secretion of AVP despite normal regulation by osmolality.[28]

With water retention driven by AVP, intravascular volume increases, leading to secretion of atrial natriuretic peptide and suppression of the renin-angiotensin-aldosterone system. The resulting excretion of sodium in concentrated urine can exacerbate hyponatremia.[1,16,17] With a urine sodium plus potassium concentration >154 mmol/L, intravenous (IV) infusion of isotonic saline can become a source of free water, a phenomenon termed "desalination."[37]

SIAD Symptoms, Morbidity, and Mortality

Hyponatremia makes brain cells swell, triggering an adaptive loss of intracellular solute that eventually allows equality of intracellular and extracellular osmolalities without an increase in cell volume.[38,39] These biological responses are responsible for hyponatremic symptoms and for morbidity and mortality caused by the electrolyte disturbance and its treatment. Symptoms are related to the PNa level and the rapidity of PNa changes and may also reflect underlying neurologic diseases predisposing to SIAD. Severe neurological symptoms from SIAD are most likely to be found in patients whose PNa falls below 125 mmol/L in <48 hours because of postoperative IV fluid or self-induced water intoxication associated with the street drug ecstasy 3,4-methylenedioxymethamphetamine, psychosis, endurance athletic activities, and preparation for colonoscopy.[40–43] Increased intracranial pressure caused by brain swelling

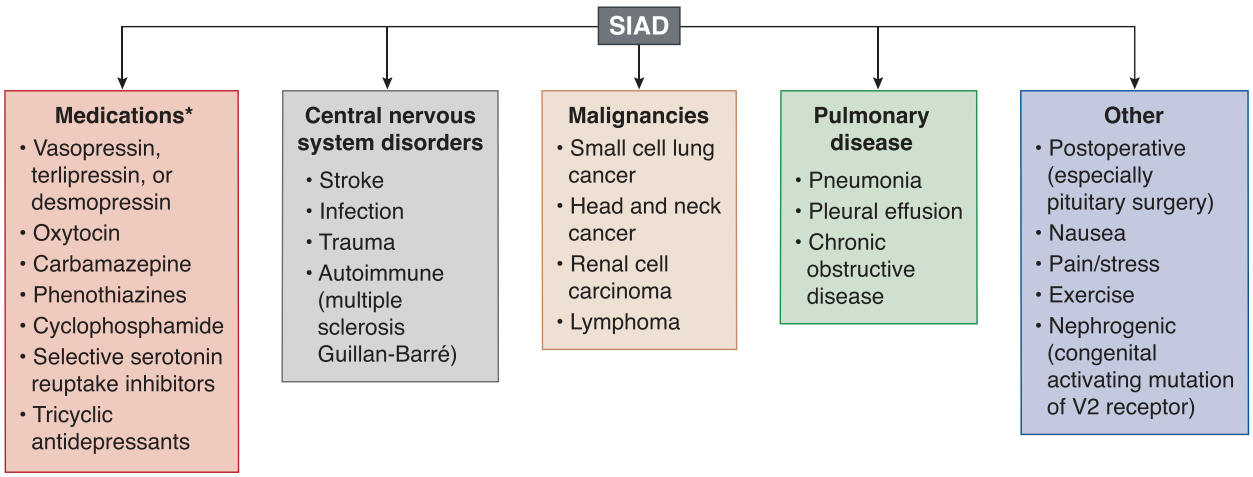

Figure 2. Etiologies of SIAD. *An exhaustive list of medications associated with SIAD can be found in ref. 124. V2, vasopressin type 2.

impairs cerebral blood flow and can rarely result in herniation. Symptoms of cerebral edema include headache, confusion, nausea, and vomiting. These nonspecific symptoms can progress rapidly to seizures, coma, and respiratory arrest.[40]

When the PNa falls more gradually, adaptive losses of organic osmolytes from brain cells permit survival but may also contribute to symptoms. Hyponatremia is called chronic when it has developed over 48 hours or more.[44] Because the precise duration is seldom known, a more practical definition of chronic can be applied to patients who become hyponatremic outside the hospital, drinking conventional volumes of fluid.[45] Despite the absence of cerebral edema on brain imaging, chronically hyponatremic patients with PNa <125 mmol/L may develop symptoms similar to those of acute hyponatremia (*e.g.*, nausea, vomiting), and at very low levels (usually <110 mmol/L), seizures can occur.[46] Adaptive release of glutamate, an excitatory neurotransmitter, may increase the susceptibility to seizures; depletion of the transmitter from nerve terminals may account for some of the other neurologic symptoms of chronic hyponatremia (lethargy, confusion, gait disturbances, and falls).[47] Chronic hyponatremia causes osteoporosis as well as a higher risk of falling and is a risk factor of fractures in elderly patients.[48,49]

Astrocytes, glial cells that surround brain capillaries and express aquaporins, protect the brain from osmotic swelling; because recovery of lost organic osmolytes is a slow, energy-requiring process occurring over several days, astrocytes are vulnerable to osmotic injury when the PNa is raised rapidly.[44] Apoptosis of astrocytes results in the osmotic demyelination syndrome (ODS), a delayed onset of neurological symptoms developing 1 to several days after rapid correction of severe, chronic hyponatremia.[50] Rapid correction of acute hyponatremia does not result in ODS, presumably because there has not been sufficient time to adapt to the disturbance with a loss of organic osmolytes from brain cells.

Classically, demyelination affects the center of the pons (central pontine myelinolysis [CPM]), resulting in dysphagia, dysarthria, and quadriparesis.[51] The most severely affected patients with CPM are locked in, awake but unable to move or communicate. However, ODS is not limited to CPM, and not all cases of CPM are due to ODS.[52] ODS has a wide spectrum of manifestations, including seizures, behavioral disturbances, and movement disorders, reflecting demyelination outside the pons (extrapontine myelinolysis [EPM]).[53] Partial or complete recovery is common, even in the most severely affected patients, and supportive measures should be continued for several weeks before considering withdrawal of care.[54]

ODS is extremely rare at PNa above 120 mmol/L.[55] Most cases occur at PNa ≤105 mmol/L after correction by >12 mmol/L in 24 hours and/or >18 mmol/L in 48 hours.[45,56–58] A PNa ≤105 mmol/L, alcohol use disorder, malnutrition, hypokalemia, hypophosphatemia, and advanced liver disease are associated with a higher risk of ODS, and there are case reports in such patients after correction by <12 mmol/L per day.[8]

Hyponatremia is associated with a higher risk of hospital death, but deaths are rarely caused by cerebral edema or ODS.[59] Rather, they usually result from the underlying disease responsible for hyponatremia. Lethal diseases result in persistent hyponatremia and slow rates of correction. Slow correction of hyponatremia is associated with mortality, but the association is unlikely to be causal.[60]

Evaluation and Diagnosis of SIAD

The diagnosis of SIAD (Table 1) is based on the presence of antidiuresis (urine osmolality >100 mOsm/kg) despite hypotonic hyponatremia, in the absence of a thiazide diuretic, impaired kidney function, edema, or hypovolemia (Figure 1).[10,61] Although SIAD is usually caused by AVP, the diagnosis is not based on actual measurements of AVP or copeptin, its precursor hormone. AVP is unstable, and commercial assays are unreliable. While copeptin levels are helpful in the evaluation of polyuria, levels overlap extensively in the various causes of hyponatremia.[62]

Hypotonic hyponatremia is confirmed by mathematically correcting for hyperglycemia (the PNa will fall by approximately 2 mmol/L for each 100 mg/dl higher blood glucose over 100 mg/dl)[63,64] and by excluding cases resulting from exogenous solutes (administration of hypertonic mannitol or Ig solutions or absorption of glycine or sorbitol irrigant) or pseudohyponatremia (hypertriglyceridemia, plasma cell dyscrasia, or lipoprotein X from obstructive jaundice).[65]

Hyponatremia due to edematous conditions (advanced heart failure and liver disease) is clinically obvious, but hyponatremia caused by mild hypovolemia may be difficult to exclude by physical examination; measurement of urine sodium may be helpful if the patient is not on diuretics.[66,67] In untreated SIAD, the urine sodium is ≥30 mmol/L unless dietary sodium intake is extremely low. Hypokalemia, hyperkalemia, and acid–base disturbances are not features of SIAD and suggest hypovolemic hyponatremia. The gold standard for the diagnosis of SIAD is persistent antidiuresis without edema after volume repletion.

A diagnosis of SIAD is like a diagnosis of fever; it reflects an underlying disorder. The cause is often apparent from the patient's medications, an acute medical condition, or a known malignancy, but in some patients, hyponatremia may be the presenting symptom of an unrecognized disease—*e.g.*, a remote episode of traumatic brain injury, unsuspected bronchiectasis, an occult malignancy, or cortisol deficiency. Cortisol inhibits AVP secretion, and in the absence of cortisol, secretion of corticotropin-releasing hormone—a potent AVP secretagogue—increases.[68] In frail, elderly patients, hyponatremia is often idiopathic, and an extensive diagnostic evaluation may not be warranted other than a morning cortisol to exclude secondary adrenal insufficiency, an important treatable disease that presents with features of SIAD.[69] In other patients with chronic or recurrent hyponatremia of unknown etiology, an evaluation might also include computed tomography scans of the chest, head, and nasal sinuses.[10,70,71] If these are unrevealing, a search for AVP-producing neuroendocrine tumors using (68Ga)-DOTATATE PET/computed tomography could be considered.[72,73]

Treatment of SIAD

Treatment of the Underlying Etiology

The primary focus in treating SIAD is to address the underlying cause, such as discontinuing selective serotonin reuptake inhibitors, treating pneumonia, or managing pain and nausea in the postsurgical state. However, in many patients, the cause remains unidentified (as in idiopathic SIAD), or if identified, it cannot be effectively treated (as with metastatic cancer). Below, we will review various therapeutic strategies that can be used. Given the significant morbidity and mortality associated even with mild hyponatremia, we recommend aiming for the normalization of PNa levels whenever possible (Figure 3).

Fluid Restriction

The goal of fluid restriction is to achieve a negative electrolyte-free water balance, where intake is less than output. This strategy is regarded as the first-line therapy for patients with mild or no apparent symptoms of hyponatremia due to SIAD. Nonetheless, hyponatremia in 39%–55% of patients with SIAD will not improve with fluid restriction.[13,74] The (urine sodium+urine potassium)/PNa (Fürst ratio) has been proposed as a way to guide fluid restriction.[75] A study found that a Fürst ratio >1 was significantly associated with lack of response to fluid restriction, but urine sodium >130 mmol/L and urine osmolality >500 mOsm/kg even more strongly correlated.[76] The only trial assessing the efficacy of fluid restriction enrolled 46 patients with SIAD and randomized them to 1 L/d fluid restriction or no treatment for 1 month.[74] After 3 days, PNa increased by 3 mmol/L in the fluid restriction group compared with 1 mmol/L in the no-treatment group ($P = 0.005$). By day 30, PNa increased by 4 mmol/L in the fluid restriction group versus 1 mmol/L in the no-treatment group. Long-term adherence to fluid restriction is challenging because of a downward resetting of the osmotic threshold for thirst in SIAD.[77]

Hypertonic Saline 3% with or without Desmopressin

Hypertonic saline 3% 100 ml IV bolus up to three times is indicated in patients with SIAD experiencing severe symptoms of hyponatremia (*i.e.*, seizures or coma), with the goal of increasing PNa by 6 mmol/L urgently (*e.g.*, within 1–2 hours).[78] Hypertonic saline establishes an osmotic gradient across the blood–brain barrier, pulling water from the brain's intracellular space into the intravascular space, thereby reducing cerebral edema. Bolus administration raises PNa more quickly compared with slow infusion, though overcorrection rates are similar.[79,80] Hypertonic saline can be administered safely through a peripheral IV line.[81] In patients with transient SIAD (*e.g.*, postoperative state), rapid correction because of large water diuresis is also a concern. Desmopressin, an AVP agonist, has been suggested as a method to limit water diuresis, preventing rapid correction.[82] A systematic review of 17 studies between case reports and case series involving 80 patients with PNa <125 mmol/L recognized three strategies for desmopressin use:

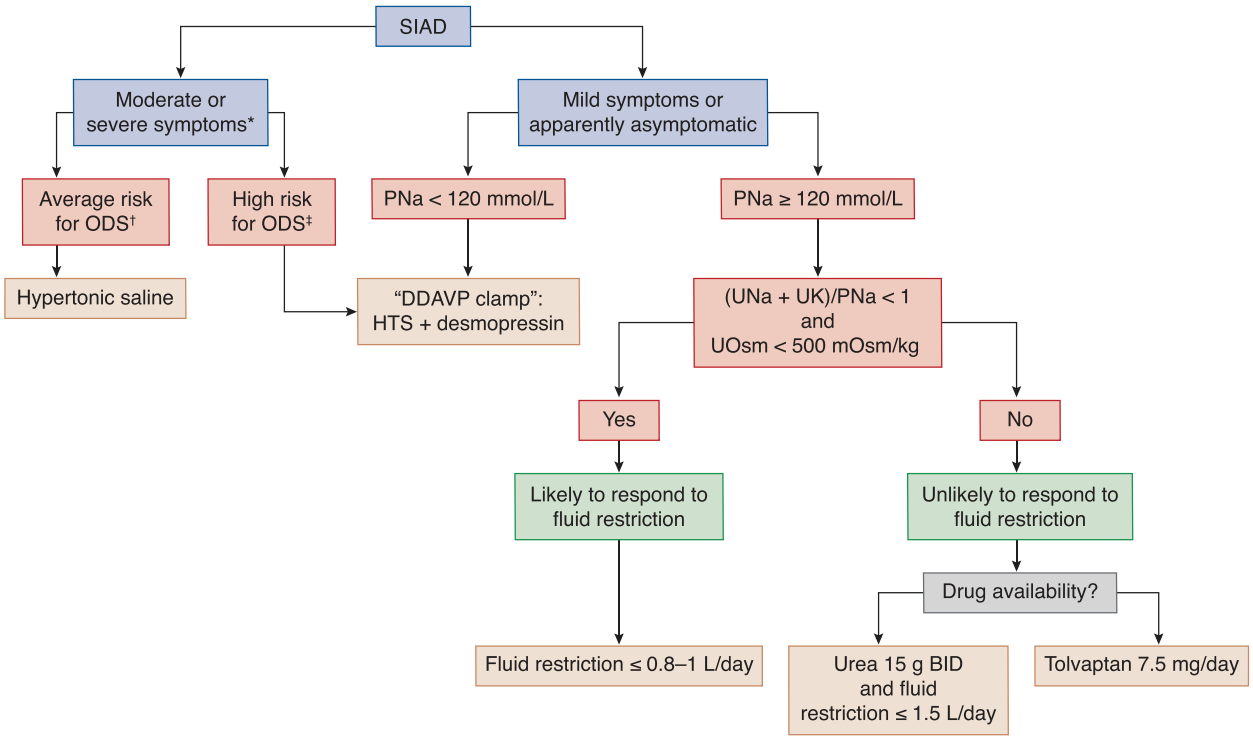

Figure 3. Initial treatment of SIAD. *Patients with moderate-to-severe symptoms of hyponatremia should receive hypertonic saline 3% bolus to achieve a goal of correction of 6 mmol/L within 1 hour. †For patients at average risk of ODS, guidelines recommend a correction limit of 10–12 mmol/L in 24 hours and 18 mmol/L in 48 hours. ‡For patients at high risk of ODS (PNa ≤105 mmol/L, advanced liver disease, alcohol use disorder, malnutrition, hypokalemia, and hypophosphatemia), a correction limit of 8 mmol/L in 24 hours is recommended. HTS, hypertonic saline; ODS, osmotic demyelination syndrome; UK, urine potassium.

proactive or desmopressin clamp (combined with hypertonic saline from the outset of correction), reactive (started before imminent overcorrection), and rescue (started after overcorrection had occurred).[83] The proactive strategy is the only strategy not endorsed by current guidelines. A recent trial of 49 patients with severely symptomatic hyponatremia (47% with SIAD) found no significant differences in overcorrection rates between proactive and reactive strategies.[84]

Loop Diuretics and Salt Tablets

Loop diuretics inhibit sodium-potassium-2 chloride cotransporter, reducing sodium chloride delivery to the medulla, hence decreasing the osmotic gradient for water reabsorption in the collecting duct resulting in hypotonic urine.[85] Salt tablets supplement sodium chloride losses caused by diuretics because their use without diuretics and after the typical regimen of 6 g/d has insufficient solute load (198 mOsm/d) to result in significant osmotic diuresis. By contrast, 30 g/d of urea provides 500 mOsm/d (the equivalent of 15 1-g NaCl tablets).[86] A recent trial randomized 92 patients with SIAD to fluid restriction alone, fluid restriction with furosemide, and fluid restriction with furosemide and salt tablets.[87] PNa increased by 5 mmol/L after 4 days across all groups, with a nonsignificant trend toward more AKI and hypokalemia in the furosemide groups. However, more data are needed regarding this approach, and clinicians should obtain blood chemistries frequently while implementing this therapy.

Vasopressin Antagonists

Two vasopressin antagonists (vaptans) are available: conivaptan (IV, antagonizes both V1 and V2 receptors) and tolvaptan (oral, V2 receptor selective antagonist). Both increase PNa by blocking AVP actions in the collecting duct. The SALT-1 and SALT-2 trials, conducted in Europe and the United States, respectively, enrolled 448 patients with hyponatremia (42.4% with SIAD) and showed that tolvaptan significantly improved PNa compared with placebo over a course of 30 days.[88] Most of the adverse events related to tolvaptan included thirst, dry mouth, and increased urination. An extension of the SALT trials, the SALTWATER study, followed 111 patients for a median of 1.9 years and reported normalization of PNa in 57% patients, with only six patients discontinuing tolvaptan because of side effects described above.[89] Concerns about liver damage from vaptans emerged from the TEMPO 3:4 trial, a trial of tolvaptan in autosomal dominant polycystic kidney disease, which used much higher doses and for significantly longer times than those typically used for hyponatremia.[90] Consequently, the US Food and Drug Administration (FDA) advises against tolvaptan use in patients with liver disease and limits its use to 30 days.[91] Similarly, other studies have established the efficacy and safety of conivaptan.[92] Conivaptan's use is limited to 4 days because of its strong inhibition over CYP3A4.[93] Despite being the only drug class FDA approved to treat hyponatremia, vaptan use remains limited because of high cost and risk of rapid correction. Indeed, 28.6% and 39.3% of patients with SIAD who received 15 mg of tolvaptan corrected their PNa by >12 mmol/L per day and >8 mmol/L per day, respectively.[94] Some studies suggest a lower starting dose of tolvaptan (*e.g.*, 7.5 mg/d) may reduce the risk of overcorrection.[95–97] If overcorrection occurs with vaptans, desmopressin may not be effective because of V2 receptor blockade and instead dextrose 5% should be used.[93]

Urea

Urea, a by-product of protein catabolism, acts as an osmotic diuretic in SIAD, but unlike mannitol, it results in positive sodium balance, which is beneficial because hyponatremia of SIAD involves both electrolyte-free water retention and sodium loss.[98] The typical urea dose is 15–60 g/d given with meals.[99] Multiple observational studies suggest urea is effective and safe in SIAD.[100–106] A recent systematic review of 26 studies involving 462 patients reported a median PNa increase of 9.6 mmol/L and 4.9 mmol/L over 5 days and over the first 24 hours, respectively, with few adverse events, including distaste and dysgeusia with no ODS cases.[107] In fact, in experimental animals, urea seems to be protective against ODS.[108] Two small studies showed similar efficacy between urea and vaptans[109,110]; tolvaptan-treated patients achieved a higher PNa at 12 hours compared with urea-treated patients but with no statistical difference at 24 and 48 hours.[109] Urea is considered a dietary supplement by the FDA.[99]

Sodium-Glucose Cotransporter-2 Inhibitors

Sodium-glucose cotransporter-2 inhibitors, such as empagliflozin, work by inducing glucosuria, which leads to increased electrolyte-free water excretion. Two small trials suggest sodium-glucose cotransporter-2 inhibitors are effective and safe in SIAD. In the first randomized controlled trial, 88 patients with SIAD treated with empagliflozin had a significantly higher increase in PNa compared with placebo.[111] Empagliflozin was well tolerated, with no hypoglycemia or hypotension events. In a second smaller trial of 14 patients with SIAD, improvement in PNa and neurocognitive function was seen with empagliflozin.[112]

Other Therapies

One gram of dietary protein generates approximately 0.34 g (5.6 mmol) of urea, and a high-protein diet could generate enough urea to produce osmotic diuresis. A small clinical trial has recently shown that high-protein diets can be effective in the treatment of SIAD.[113] Demeclocycline, a tetracycline derivative, inhibits adenylate cyclase and decreases aquaporin 2 expression, resulting in a reversible nephrogenic diabetes insipidus.[114] A systematic review concluded that demeclocycline is effective in approximately 60% of patients with SIAD but has unpredictable onset and significant adverse effects, including nephrotoxicity,[115] leading the European guidelines to recommend against its use.[7] Apelin, an endogenous peptide, has aquaretic effects by inhibiting AVP release and decreasing kidney aquaporin 2 expression.[116] It has shown promise in the treatment of hyponatremia in animal models of SIAD but remains under investigation.[117] Urea transport proteins UT-A1, UT-A3, and UT-B play a critical role in urinary concentration as demonstrated by the occurrence of urinary concentration defects observed in knockout mice with

deletions in these proteins.[118] A UT-A1 inhibitor has been shown to be effective in increasing PNa in an animal model of SIAD without apparent toxicity.[119]

Relowering of PNa after Rapid Correction

For patients at average risk of ODS, guidelines recommend a PNa correction limit of 10–12 mmol/L in 24 hours and 18 mmol/L in 48 hours.[8] For patients with risk factors of ODS, experts advise a conservative limit of 8 mmol/L in 24 hours, heeding the risk of overcorrection; a larger than intended rise in PNa can follow excessive doses of hypertonic saline, but more often it results from a large, spontaneous water diuresis that emerges once the underlying cause of hyponatremia resolves.[8,52] Animal studies and case reports suggest that when correction limits are inadvertently exceeded, reducing PNa with desmopressin and dextrose 5% to a level just below the limit can prevent ODS.[120–122] This approach is supported by current guidelines for managing overly rapid correction of hyponatremia.

Summary

SIAD is the most common etiology of hyponatremia and requires careful clinical evaluation supplemented with laboratory testing. Ideally, the condition is best treated with withdrawal of causative etiologies or effective treatment of underlying conditions. Treatment rests on counteracting the antidiuresis, which can be achieved through several strategies dependent on the chronicity and severity of hyponatremia.

Disclosure

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/JSN/E979.

Funding

None.

Author Contributions

Conceptualization: Helbert Rondon-Berrios, Mitchell H. Rosner, Richard H. Sterns.
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Writing – original draft: Helbert Rondon-Berrios, Mitchell H. Rosner, Richard H. Sterns.
Writing – review & editing: Helbert Rondon-Berrios, Mitchell H. Rosner, Richard H. Sterns.

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