Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat

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INTRODUCTION

Hyponatremia in the syndrome of inappropriate antidiuretic hormone secretion (SIADH) results from ADH-induced retention of ingested or infused water. Although water excretion is impaired, sodium handling is intact since there is no abnormality in volume-regulating mechanisms such as the renin-angiotensin-aldosterone system or atrial natriuretic peptide [1].

The treatment of hyponatremia due to SIADH (including the reset osmostat variant) will be reviewed here. The choice of therapy of SIADH is dependent upon a number of factors including the degree of hyponatremia, the presence or absence of symptoms, and, to some degree, the urine osmolality.

The pathogenesis and etiology of the SIADH and a general review of the treatment of hyponatremia due to a variety of causes are discussed separately:

- (See "Pathophysiology and etiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)".)
- (See "Overview of the treatment of hyponatremia in adults".)

PATHOGENESIS

To understand the approach to therapy of hyponatremia in SIADH, it is worthwhile to briefly review the pathogenesis of hyponatremia in this disorder. Among patients with SIADH, the combination of water retention and secondary solute (sodium plus potassium) loss accounts for essentially all of the reduction in serum sodium [2,3].

These changes occur in the following sequence [3,4]:

- Hyponatremia is initially mediated by ADH-induced water retention.
- The ensuing volume expansion activates secondary natriuretic mechanisms, resulting in sodium and water loss and the restoration of near-euvolemia. The net effect is that, with chronic SIADH, sodium loss is more prominent than water retention [3]. However, since there is no impairment in volume regulatory hormones (aldosterone and natriuretic peptides), patients with SIADH are **euvolemic** unless there is a second problem leading to salt loss (eg, vomiting, diarrhea, or diuretic therapy).
- Hyponatremia may also be associated with potassium loss. Since potassium is as osmotically active as sodium, the loss of potassium contributes to the reductions in plasma osmolality and sodium concentration. (See "Overview of the treatment of hyponatremia in adults".)

The lost potassium is derived from the cells and probably represents part of the cell's volume regulatory response [3]. Cells that increase in size due to water entry in hyponatremia lose potassium and other solutes in an attempt to restore cell volume. This adaptation is discussed elsewhere. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Osmolytes and cerebral adaptation to hyponatremia'.)

THERAPIES TO RAISE THE SERUM SODIUM

A number of modalities can be used to correct hyponatremia in SIADH, with fluid restriction, salt administration, urea administration, and vasopressin receptor antagonists being most important [1,5,6]. When treating such patients, attention must be paid to the rate of correction.

There are three components to the treatment of hyponatremia in SIADH:

- Treatment of the underlying disease, if possible
- Initial therapy to raise the serum sodium
- Prolonged therapy in patients with persistent SIADH

Treat the underlying disease — A variety of causes of SIADH can be effectively treated, leading to resolution of the hyponatremia. These include (see "Pathophysiology and etiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)", section on 'Etiology'):

- Hormone replacement in adrenal insufficiency (which can lead to overly rapid correction of the hyponatremia) or hypothyroidism
- Treatment of infections such as meningitis, pneumonia, or tuberculosis
- Cessation of offending drugs, such as selective serotonin reuptake inhibitors or chlorpropamide

Fluid restriction — Fluid restriction is a mainstay of therapy in most patients with SIADH, with a suggested goal intake of less than 800 mL/day [4]. Unfortunately, few patients can adhere to such restriction for prolonged periods.

The associated negative water balance initially raises the serum sodium concentration slowly toward normal and, with maintenance therapy in chronic SIADH, prevents a further reduction in serum sodium. A multinational registry that included 1524 patients with SIADH found that fluid restriction was the most commonly used treatment approach (48 percent) and resulted in a median increase of 2 mEq/L during the first 24 hours of therapy [7]. In a small trial of 46 patients with chronic asymptomatic SIADH, fluid restriction (less than 1 liter daily) increased serum sodium by 3 mEq/L at three days with minimal additional improvement thereafter [8]. (See 'Pathogenesis' above.)

Subarachnoid hemorrhage — Fluid restriction may not be appropriate for hyponatremia associated with subarachnoid hemorrhage (SAH). Patients with SAH are at risk for cerebral vasospasm and infarction, the incidence of which is increased by a fall in blood pressure [9]. Because of the neurologic symptoms associated with the cerebral bleeding, it is typically difficult to determine the role, if any, of the hyponatremia in the pathogenesis of the symptoms. (See "Aneurysmal subarachnoid hemorrhage: Clinical manifestations and diagnosis".)

Hyponatremia in patients with SAH is usually due to SIADH, but is often inappropriately characterized as cerebral salt wasting (CSW), a much less common problem [10]. The two disorders have similar manifestations, and it is only the presence of clear evidence of volume depletion (eg, hypotension, decreased skin turgor, possibly increased blood urea nitrogen/serum creatinine ratio) despite a urine sodium concentration that is not low that suggests that CSW might be present rather than SIADH. (See "Cerebral salt wasting".)

Fluid restriction is a standard component of therapy in SIADH, but may promote cerebral vasospasm in patients with SAH who are usually treated with volume expansion. (See "Aneurysmal subarachnoid hemorrhage: Treatment and prognosis", section on 'Vasospasm and delayed cerebral ischemia'.)

Thus, hyponatremic patients with SAH should be treated with hypertonic (3 percent) saline to both preserve cerebral perfusion and prevent complications from hyponatremia-induced brain swelling. One proposed regimen is an initial infusion rate of 20 mL/h with subsequent dosing being dependent upon serial measurements of serum sodium at six-hour intervals [11]. Fluid therapy in normonatremic patients with SAH is discussed elsewhere. (See "Cerebral salt wasting", section on 'Therapy of SIADH associated with SAH'.)

Intravenous hypertonic saline — Severe, symptomatic, or resistant hyponatremia in patients with SIADH often requires the administration of sodium chloride. If the serum sodium concentration is to be elevated, the electrolyte concentration of the fluid given must **exceed the electrolyte concentration of the urine**, not simply that of the plasma [5].

The calculations that follow are similar to those that are described in greater detail elsewhere. (See "Overview of the treatment of hyponatremia in adults", section on 'Do not use isotonic saline in SIADH'.)

The calculations are based upon two important physiologic principles:

- Sodium and water excretion in the urine are regulated independently: sodium by aldosterone and atrial natriuretic peptide; and water by ADH.
- The urine volume is normally regulated by ADH in response to changes in water intake. When ADH release does not respond to changes in water intake, as usually occurs in SIADH, the urine osmolality is relatively fixed and the urine volume varies with changes in solute excretion. Increasing solute excretion by giving salt or urea will increase the urine volume and tend to raise the serum sodium.

Suppose a patient with SIADH and a serum sodium of 120 mEq/L has a high, relatively fixed urine osmolality and a urine cation concentration (ie, urine [Na] + urine [K]) of 308 mEq/L, which is twice the cation concentration of isotonic saline. If 1000 mL of isotonic saline is given (containing 154 mEq of

sodium), all of the NaCl will be excreted (because sodium handling is intact), but in only 500 mL of water (154 mEq of urinary sodium in 500 mL equals 308 mEq/L). The retention of one-half of the administered water will lead, ultimately, to a further reduction in the serum sodium concentration even though the serum sodium concentration will temporarily increase because the isotonic saline is hypertonic compared with the patient's serum before infusion of the saline.

This hypothetical example has been confirmed in postoperative patients, many of whom have transient SIADH. In one report, for example, the administration of isotonic saline or lactated Ringer's solution to 22 women who had undergone uncomplicated gynecologic surgery resulted in a fall in the serum sodium concentration by a mean of 4.2 mEq/L in 21 of the patients [12]. During the first 16 hours after the induction of anesthesia, the mean peak urine osmolality was more than 600 mosmol/kg, and the mean urinary sodium plus potassium concentration was almost 300 mEq/L (twice that in plasma). The loss of sodium plus potassium in the urine at a much higher concentration than in the plasma was responsible for the fall in serum sodium.

The response is different if hypertonic saline is given. Each liter of 3 percent saline contains 513 mEq of sodium. If 500 mL of this solution (which contains 257 mEq of sodium) is slowly given to a 60 kg woman with a total body water of approximately 30 liters and a baseline serum sodium of 120 mEq/L, the infused sodium will increase total body sodium plus potassium from 3600 mEq to 3857 mEq, and the infused volume will increase total body water from 30 L to 30.5 L, raising the serum sodium by 6.5 mEq/L. The rise in serum sodium after 500 mL of hypertonic saline will be smaller in a 70 kg man who has a larger total body water of approximately 42 liters. In this setting, the extra 257 mEq of sodium will distribute over 42.5 liters, raising the serum sodium by 4.6 mEq/L.

However, the rise in serum sodium in response to 3 percent saline will partially dissipate over time, because all of the sodium chloride will be excreted (as with isotonic saline), but in a larger volume of urine; as an example, at a urine cation concentration (urine [Na] + urine [K]) of 308 mEq/L, the 257 mEq of sodium that was administered in 500 mL of 3 percent saline will be excreted in approximately 830 mL of urine; leading to net loss of 330 mL of water. The net effect is that sodium balance is unchanged but 330 mL of fluid has been lost, which will result in final elevation in the serum sodium of only 1.3 mEq/L in a 60 kg woman (120 mEq/L at baseline x [30/29.67] = 121.3 mEq/L) and 1 mEq/L in a 70 kg man (120 mEq/L at baseline x [42/41.67] = 121 mEq/L).

Thus, after the administration of hypertonic saline in a hyponatremic patient with a high urine osmolality, there will be an initial large rise in the serum sodium concentration that falls over time as the administered sodium is excreted.

The late reduction in serum sodium is less pronounced (ie, there is a greater persistent elevation in serum sodium) if the urine osmolality and urine sodium plus potassium concentrations are not so high, since more water will follow the excretion of sodium chloride. If, for example, the urine osmolality is close to that of plasma, and the urine cation concentration is 154 mEq/L rather than 308 mEq/L, the 257 mEq of sodium that was administered in 500 mL of 3 percent saline will be excreted in 1688 mL of urine. Thus, the net fluid loss will be 1188 mL (1688 minus 500 mL given), resulting in a final elevation in serum sodium of 5 mEq/L in a 60 kg woman (120 mEq/L at baseline x [30/28.8] = 125 mEq/L) and 3.5 mEq/L in a 70 kg man (120 mEq/L at baseline x [42/40.8] = 123.5 mEq/L).

These calculations illustrate the limited long-term effect of even hypertonic saline in hyponatremic patients with SIADH who have a highly concentrated urine. Thus, in addition to restricting water intake, efforts must also be made in such patients to reduce the urinary concentration (ie, lower the urine osmolality), which can be achieved with a loop diuretic or a vasopressin receptor antagonist.

High solute intake — In normal individuals, the urine output is primarily determined by fluid intake, a relationship that is mediated by changes in the release of antidiuretic hormone that lead to appropriate changes in the urine osmolality. However, when the urine osmolality is fixed, as in SIADH, the urine output is determined by the intake and subsequent urinary excretion of solutes (mostly sodium salts and urea), which has been called the renal solute load. As an example, at a fixed urine osmolality of 600 mosmol/kg in a patient with SIADH, the urine output will be 1 L/day if urinary solute excretion is 600 mosmol/day and 2 L/day if urinary solute excretion is increased to 1200 mosmol/day by a high-sodium, high-protein diet or with the ingestion of salt tablets and/or urea. Such a high-solute diet can be combined with a loop diuretic, which interferes with concentrating ability and lowers the urine osmolality.

Oral salt tablets — The principles described in the above section on intravenous saline also apply to oral salt intake. Suppose the same 60 kg woman with a serum sodium of 120 mEq/L and total body water of approximately 30 L takes in 9 g of salt (154 mEq each of sodium and chloride) in tablet form. All 154 mEq will be excreted since sodium handling is normal, which will increase the urine output by 500 mL if the urine cation concentration (ie, urine [Na] + urine [K]) is 308 mEq/L and by approximately 1000 mL if the urine cation concentration is 154 mEq/L. Using the calculations in the above section, this extra loss of water will tend to raise the serum sodium by 2 mEq/L (120 mEq/L at baseline x [30/29.5] = 122 mEq/L) if the urine cation concentration is 308 mEq/L, and by approximately 4 mEq/L (120 mEq/L at baseline x [30/29] = 124 mEq/L) if the urine cation concentration is 154 mEq/L. (See 'Intravenous hypertonic saline' above.)

Some patients with chronic SIADH have a major underlying illness (such as small cell carcinoma) that may limit compliance with increased dietary salt intake.

Salt plus a loop diuretic — The effect of salt tablets (as with hypertonic saline) can be enhanced if given with a drug that lowers the urine osmolality and increases water excretion. This can be achieved by impairing the renal responsiveness to ADH by the administration of a loop diuretic or a vasopressin receptor antagonist. A loop diuretic (eg, 20 mg of furosemide orally twice a day or 10 to 20 mg of torsemide daily) directly interferes with the countercurrent concentrating mechanism by decreasing sodium chloride reabsorption in the medullary aspect of the loop of Henle [1,13,14].

A loop diuretic will be effective if the urine osmolality is more than twice the plasma osmolality, which typically means a urine osmolality above 500 mosmol/kg. Monitoring of the serum potassium is important, particularly in the early stages of therapy. Many patients require potassium chloride supplementation or use of a potassium-sparing diuretic, such as amiloride [14].

Vasopressin receptor antagonists — There are three receptors for vasopressin (ADH): the V1a, V1b, and V2 receptors. The V2 receptors primarily mediate the antidiuretic response, while V1a and V1b receptors primarily cause vasoconstriction and adrenocorticotropic hormone (ACTH) release, respectively [15,16].

The vasopressin receptor antagonists produce a selective water diuresis (aquaresis) without affecting sodium and potassium excretion [15,16]. The ensuing loss of electrolyte-free water will tend to raise the serum sodium in patients with SIADH and may improve mental status in patients with a serum sodium under 130 mEq/L [17]. Thirst increases significantly with these agents, which may limit the rise in serum sodium [17]. (See "Overview of the treatment of hyponatremia in adults", section on 'Vasopressin receptor antagonists'.)

Some oral formulations—tolvaptan, mozavaptan, satavaptan, and lixivaptan—are selective for the V2 receptor, while an intravenous agent, conivaptan, blocks both the V2 and V1a receptors. Tolvaptan should **not** be used for longer than 30 days and should **not** be given to patients with liver disease (including cirrhosis). (See 'Limitations to use of tolvaptan' below.)

Efficacy — Randomized double-blind trials have shown that oral or intravenous vasopressin antagonists (tolvaptan, lixivaptan, and conivaptan) are more effective than placebo in raising the serum sodium of hyponatremic patients both in and out of the hospital [17-23]. Most of the patients studied in these trials had asymptomatic or mildly symptomatic hyponatremia and an average serum sodium concentration that was close to normal (ranging from 127 to 131 mEq/L). The increase in serum sodium relative to placebo in these studies was small (mean, 1 to 5 mEq/L), and there was no evidence that long-term outcomes were improved [24]. Although the incidence of correction of the serum sodium by more than 12 mEq/L in 24 hours with these drugs was low (2 to 4 percent), it is likely that the incidence of overly rapid correction using the definition presented below (more than 8 mEq/L in 24 hours) was considerably higher (see 'Rate of correction' below). In addition, the risk of overly rapid correction would likely be even greater in patients with more severe hyponatremia at baseline. Tolvaptan and conivaptan, but not lixivaptan, are approved for use in the United States. However, the United States Food and Drug Administration (FDA) has issued a safety warning about tolvaptan. (See 'Limitations to use of tolvaptan' below.)

The following studies illustrate the range of findings in SIADH:

- The effectiveness of intravenous conivaptan in SIADH was demonstrated in a randomized placebo-controlled trial of 84 hospitalized patients with euvolemic or hypervolemic hyponatremia (serum sodium 115 to <130 mEq/L) [19]. Compared with placebo, intravenous conivaptan (20 mg loading dose followed by a continuous infusion of either 40 or 80 mg/day for four days) significantly raised the serum sodium concentration by study end (6.3 and 9.4 mEq/L in the 40 and 80 mg/day arms, respectively, versus 0.8 mEq/L for placebo). The effective free water clearance after 24 hours was approximately two liters with both doses compared to minus 300 mL with placebo.

- The efficacy of oral tolvaptan in ambulatory patients was demonstrated in a combined report of two randomized double-blind, placebo-controlled multicenter trials (SALT-1 and SALT-2) consisting of 448 patients with hyponatremia (mean serum sodium 129 mEq/L) caused by the SIADH (190 patients), heart failure, or cirrhosis [17]. Compared with placebo, tolvaptan significantly increased the serum sodium concentration at day 4 (134 to 135 mEq/L versus 130 mEq/L) and day 30 (136 versus 131 mEq/L).

  Among all patients in the SALT trials (ie, not limited to those with cirrhosis) who had a serum sodium below 130 mEq/L at baseline, tolvaptan was also associated with a statistically significant improvement in mental status scores. However, the difference was usually not clinically significant and long-term efficacy is uncertain, since the duration of follow-up was only 30 days.

  In an open-label extension (called SALTWATER), 111 patients were treated with tolvaptan for a mean follow-up of almost two years [25]. The mean serum sodium was maintained at more than 135 mEq/L compared to 131 mEq/L at baseline. The responses were similar in SIADH and heart failure, and more modest in cirrhosis. The main adverse effects were abnormally frequent urination, thirst, dry mouth, fatigue, polyuria, and polydipsia. Adverse effects that were possibly or probably related to tolvaptan led to discontinuation of therapy in six patients (5.4 percent).

However, there are significant limitations to the use of tolvaptan. (See 'Limitations to use of tolvaptan' below.)

Use of conivaptan — Since conivaptan requires intravenous administration, it is only useful in the treatment of SIADH in patients who are hospitalized. Its potential role varies with the severity of the hyponatremia:

- Patients with mild to moderate hyponatremia and minimal or no symptoms can be effectively and safely treated with the modalities described above (eg, fluid restriction and salt tablets). Conivaptan will more rapidly raise the serum sodium concentration, but it is unclear that is an important advantage in such patients unless it might shorten the duration of hospitalization.
- Among patients with more severe hyponatremia or mild to moderate symptoms, conivaptan can be given alone or in combination with hypertonic saline.
- Among patients with severe symptomatic hyponatremia, conivaptan can be given in combination with hypertonic saline. Since the effect of conivaptan on free water clearance begins as early as one to two hours, it may permit a more rapid initial elevation in serum sodium. (See 'Intravenous hypertonic saline' above.)

As described below, attention must be paid to avoid overly rapid correction of the hyponatremia. (See 'Rate of correction' below.)

Limitations to use of tolvaptan — Although tolvaptan effectively raises the serum sodium concentration in patients with SIADH, as demonstrated in the SALT trials cited above [17], there are important limitations to its use:

- Concerns about the safety of tolvaptan were raised by a multicenter trial (TEMPO 3:4) that examined its effect on the progression of kidney disease in polycystic kidney disease [26,27]. A greater than 2.5-fold increase in liver enzymes was more common among patients who received tolvaptan compared with placebo. Based upon these data, the US FDA issued safety warnings regarding the use of tolvaptan [28,29], recommending: that liver function tests be promptly performed among patients who report symptoms that suggest liver injury (eg, fatigue, anorexia, right upper quadrant discomfort, dark urine, jaundice); that tolvaptan should **not** be used in any patient for longer than 30 days; and that tolvaptan should **not** be used at all in patients with liver disease (including cirrhosis) because it may potentially lead to liver failure or death [29]. (See "Autosomal dominant polycystic kidney disease (ADPKD): Treatment", section on 'Tolvaptan'.)
- There may be overly rapid correction of the hyponatremia, which can lead to irreversible neurologic injury. Because of the risk of overcorrection, hospitalization is required for the initiation or reinitiation of therapy. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia" and "Overview of the treatment of hyponatremia in adults".)

  In the SALT trials, 1.8 percent of patients exceeded the study goal of limiting daily correction to 12 mEq/L [17]. However, few patients in these studies had serum sodium levels that were low enough to make them susceptible to overcorrection. Other studies reveal much higher rates of overcorrection with tolvaptan use in SIADH than was reported in the SALT trials [30]. As examples:

  - In two large reports of tolvaptan-treated patients with SIADH, correction rates greater than 12 mEq/L in 24 hours occurred in 12 percent of patients whose median serum sodium was 127 mEq/L and in 22 percent of patients whose median serum sodium was less than 121 mEq/L [31,32].
  - In a study of 28 patients with serum sodium levels <130 mEq/L due to SIADH, tolvaptan (15 mg daily) corrected the serum sodium by more than 12 mEq/L within 24 hours in 25 percent of patients and corrected the sodium by more than 8 mEq/L within 24 hours in 33 percent of patients [33].

  Lower tolvaptan doses are likely to be associated with a reduced risk of overcorrection [30,34].
- Thirst is increased, which may limit the rise in serum sodium [17].
- The cost of tolvaptan may be prohibitive (as high as USD $300 per tablet in some areas).
- The drug is not approved to treat serious neurologic symptoms. In addition, patients in the Phase III pivotal studies were excluded if their serum sodium was less than 120 mEq/L.

Given the important limitations to the use of tolvaptan, it should only be considered in the rare patient whose serum sodium concentration cannot be maintained above 120 mEq/L or who has persistent neurologic symptoms thought to be due to chronic hyponatremia despite treatment with other measures. In such cases, chronic outpatient management with tolvaptan can be prescribed to maintain the serum sodium above 120 mEq/L after first raising the serum sodium to this level as an inpatient using hypertonic saline.

Urea — Another way to increase urinary solute excretion and enhance water excretion in patients with SIADH is the administration of urea [35-39]. Urea is reported to be generally well tolerated and has been used chronically in ambulatory patients. Despite the absence of controlled trials supporting their use, European practice guidelines recommend urea while discouraging the use of vaptans (eg, tolvaptan) for the management of chronic hyponatremia due to SIADH [40], a recommendation that has generated controversy [41]. Urea has seldom been used because it has not been readily available in pharmacies; as an example, in a multinational registry that included 1524 patients with SIADH, urea was used in only 10 patients [42]. However, oral urea can now be obtained as a premixed medical food dispensed in 21 g packets containing 15 g of urea per packet.

The increase in serum sodium concentration that occurs after urea administration depends upon the urine osmolality. As an example, excretion of 30 g (500 milliosmoles) of urea in urine with an osmolality of 500 mosmol/kg will result in the loss of 1 liter of water, which will increase the serum sodium of a 60 kg woman with a baseline serum sodium of 120 mEq/L by approximately 4 mEq/L (120 mEq/L at baseline x [30/29] = 124 mEq/L) [43]. At a urine osmolality of 250 mosmol/kg, the serum sodium concentration will increase twice as much (approximately 8 mEq/L).

Efficacy of urea — Urea has not been studied in placebo-controlled trials. However, in an open-label study, the effectiveness of oral urea was examined in 13 outpatients with hyponatremia (125±3 mEq/L) due to SIADH who had completed a previous trial of oral vasopressin antagonists (satavaptan or tolvaptan) [44]. Hyponatremia corrected in these 13 patients (to a mean serum sodium 135±3 mEq/L) during one year of therapy with satavaptan or tolvaptan and recurred (126±5 mEq/L) when these drugs were stopped. Treatment of these patients with urea (15 to 30 g daily) for one year corrected hyponatremia as effectively as the vaptans (to a mean serum sodium of 135±2 mEq/L). In a second study of 36 patients with SIADH due to cancer (mean serum sodium 123±4 mEq/L), 15 to 30 g of oral urea without fluid restriction resulted in a 5±3 mEq/L increase in serum sodium after 24 hours and 33 of 36 patients attained a normal serum sodium within 60 days of treatment [45].

Demeclocycline or lithium — Demeclocycline and lithium act on the collecting tubule cell to diminish its responsiveness to ADH, thereby increasing water excretion [1,46-48]. In patients with bipolar disorder who are treated with chronic lithium therapy, nephrogenic diabetes insipidus develops in up to 20 to 40 percent [48]. (See "Renal toxicity of lithium", section on 'Nephrogenic diabetes insipidus'.)

Demeclocycline (300 to 600 mg twice a day) is more predictably effective [46] and more often used than lithium for the treatment of hyponatremia in SIADH. However, both drugs can be nephrotoxic; demeclocycline can cause nausea, vomiting, and photosensitivity and costs USD $10 to $20 per tablet, and lithium has a variety of neuropsychiatric side effects.

The author and reviewers of this topic rarely use demeclocycline in such patients and do not use lithium. The impairment in concentrating ability with demeclocycline takes several days to one week to become apparent.

RATE OF CORRECTION

Among hospitalized patients, the severity of neurologic symptoms attributable to hyponatremia determines the initial rate of correction (see "Manifestations of hyponatremia and hypernatremia in adults"):

- Patients with severe neurologic symptoms, which primarily occur with acute and marked reductions in serum sodium (usually to below 120 mEq/L), require rapid initial correction, often with hypertonic saline. However, overly rapid correction should be avoided since it can lead to the late onset of neurologic complications from osmotic demyelination. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia".)
- Most patients with SIADH and chronic moderate hyponatremia (serum sodium 120 to 129 mEq/L) appear asymptomatic, and slow correction of the hyponatremia is recommended. Some of these "asymptomatic" patients have subtle neurologic manifestations that may be improved by raising the serum sodium. These include reduced scores on tests of mental, social, and physical functioning and, in older adult patients, unsteadiness and falls [17,49]. (See 'Asymptomatic hyponatremia' below.)

The optimal rate of correction is discussed in detail elsewhere. Summarized briefly, the rate of correction of chronic hyponatremia should be less than 8 mEq/L in any 24-hour period [15,50,51]. An initial rate of correction of 4 to 6 mEq/L in the first two to four hours may be beneficial in patients with severe symptoms (eg, seizures). This requires careful monitoring of the serum sodium concentration (initially every two to three hours) until the patient is stable. (See "Overview of the treatment of hyponatremia in adults".)

If the SIADH resolves while the patient is hyponatremic, ADH secretion will be suppressed by the hypoosmolality, and a water diuresis will ensue. Excretion of a maximally dilute urine will rapidly increase the serum sodium concentration. In selected patients with severe hyponatremia who are correcting too rapidly, prevention of further short-term elevation in serum sodium or even relowering of the serum sodium may be warranted. These issues are discussed separately. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia", section on 'Patients who

have exceeded correction limits (rescue strategy)'.)

CHOICE OF THERAPY

The choice of therapy in patients with hyponatremia due to SIADH varies with the severity of hyponatremia and the presence or absence of symptoms (algorithm 1). In addition, patients with a reset osmostat do not require correction of the hyponatremia, since they are asymptomatic and have a stable serum sodium. (See 'Reset osmostat' below.)

Symptomatic hyponatremia — Among patients with symptomatic hyponatremia, the approach varies with the severity of the neurologic symptoms.

Severe symptoms — Severe symptoms from hyponatremia (eg, seizures, inability to communicate, and/or coma) are most likely to occur in patients in whom the serum sodium has fallen below 120 mEq/L in less than 48 hours, leading to potentially fatal cerebral edema. Most such cases have been due to the administration of hypotonic intravenous fluids to premenopausal women with postoperative SIADH (figure 1) [52]. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Susceptibility of premenopausal women'.)

In patients with severe hyponatremic symptoms and in symptomatic patients with underlying intracranial disease who cannot tolerate even minor degrees of brain swelling due to hyponatremia, the serum sodium must initially be raised quickly to prevent possibly irreversible neurologic injury. Based upon broad clinical experience, the administration of hypertonic saline is the only rapid way to raise the serum sodium and improve neurologic manifestations in patients with severe symptomatic hyponatremia (algorithm 1) [53].

One regimen that can achieve this goal was initially described in hyponatremic athletes participating in endurance events, such as marathon races [13,54,55]. It consists of 100 mL of 3 percent saline given as an intravenous bolus, which will raise the serum sodium by approximately 1.5 mEq/L in men and 2 mEq/L in women. The rise in serum sodium will pull water out of the brain, decreasing the degree of cerebral edema.

If neurologic symptoms persist or worsen, a 100 mL bolus of 3 percent saline can be repeated one or two more times at 10-minute intervals. The rationale for this approach is that, in patients with symptomatic hyponatremia, rapid increases in serum sodium of 4 to 6 mEq/L can reverse severe symptoms such as seizures [4,13,56]. (See "Overview of the treatment of hyponatremia in adults".)

Hypertonic saline given as intravenous boluses can increase the serum sodium and improve neurologic symptoms more quickly than slower, continuous infusions [57].

For the reasons noted above, there is **no role** for the use of isotonic saline in symptomatic patients with hyponatremia due to SIADH. (See 'Intravenous hypertonic saline' above and "Exercise-associated hyponatremia", section on 'Use of hypertonic saline'.)

If the symptoms resolve, careful monitoring with measurement of the serum sodium concentration every two to three hours is required for two reasons:

- A potential complication of hypertonic saline therapy is overly rapid correction of the hyponatremia, particularly in patients with self-limited or reversible SIADH. The usual goal (the desired rate of increase) is an elevation in serum sodium of 4 to 6 mEq/L per day, and the limit (the rate of increase that should not be exceeded) is 8 mEq/L/day (see 'Rate of correction' above). If symptoms have resolved but the rise in serum sodium is substantially less than the 24-hour goal, further therapy in addition to fluid restriction may consist of a slow infusion of hypertonic saline (eg, 10 to 30 mL per hour) with careful monitoring of the serum sodium.

  In patients with severe hyponatremia who are correcting too rapidly, prevention of further short-term elevation in the serum sodium or even relowering of the serum sodium may be warranted. How this can be achieved is discussed elsewhere. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia", section on 'Patients who have exceeded correction limits (rescue strategy)'.)

- In patients with a highly concentrated urine (eg, above 500 mosmol/kg), the serum sodium will come back down toward baseline as the administered sodium is excreted in the urine unless further therapy is given (see 'Intravenous hypertonic saline' above). In such patients, the urine osmolality can be reduced by administration of a loop diuretic (eg, furosemide 20 mg orally twice a day).

Mild-to-moderate symptoms — Less severe neurologic symptoms (eg, dizziness, gait disturbances, forgetfulness, confusion, and lethargy) can be seen in patients with a serum sodium concentration below 120 mEq/L that develops over more than 48 hours, in patients with a lesser degree of hyponatremia that develops over less than 48 hours, and in patients with chronic moderate hyponatremia (serum sodium 120 to 129 mEq/L). Some of these patients may benefit from hypertonic saline, but do not require the aggressive approach suggested in the preceding section for those with severe neurologic symptoms.

Initial hypertonic saline therapy using either a continuous infusion or a 50 to 100 mL bolus followed by a continuous infusion to raise the serum sodium by 3 to 4 mEq/L may be justified in the first three to four hours in patients with distressing symptoms (eg, confusion and lethargy). In the calculations described above, 500 mL of hypertonic saline initially raised the serum sodium by 6.5 mEq/L in a 60 kg woman and 4.6 mEq/L in a 70 kg man. Thus, raising the serum sodium by 4 mEq/L in four hours would require approximately 300 mL of hypertonic saline in the woman and 400 mL in the man. These calculations are only estimates and the serum sodium should be measured at two to three hours. The total elevation in serum sodium in the first 24 hours should be no more than 8 mEq/L. (See 'Intravenous hypertonic saline' above.)

Patients with less severe symptoms can be treated with less aggressive therapy, such as fluid restriction, oral salt tablets, or urea.

Once the symptoms have resolved, further therapy is similar to that in patients with SIADH who have asymptomatic hyponatremia, with the caveat of avoidance of overly rapid correction. (See 'Asymptomatic hyponatremia' below and 'Rate of correction' above.)

Maintenance therapy — Unless the SIADH is reversible (eg, postoperative or due to a drug that can be discontinued), effective therapy of symptomatic hyponatremia must be followed by maintenance therapy to prevent a subsequent reduction in serum sodium and possible symptom recurrence. The goal serum sodium is discussed below. (See 'Asymptomatic hyponatremia' below.)

One or more of the above therapeutic modalities may be required. The usual sequence of maintenance therapy is as follows:

- Fluid restriction – The suggested goal fluid intake in hyponatremic patients with SIADH is less than 800 mL/day [4]. Unfortunately, few patients can adhere to such restriction for prolonged periods. Patients with a recent subarachnoid hemorrhage should not be treated with fluid restriction, as this can be deleterious. (See 'Fluid restriction' above and 'Subarachnoid hemorrhage' above.)

- Oral salt – In patients with SIADH, administering oral salt will increase the urine output; the usual initial dose is 3 g or one-half teaspoon three times daily, resulting in a total dose of 9 g per day. Smaller doses of oral salt are unlikely to be effective [58]. Since sodium handling is normal and the urine osmolality is relatively fixed in SIADH, increasing oral salt intake will, in a dose-dependent fashion, increase the urine volume. (See 'Oral salt tablets' above.)

- Oral urea – In patients with SIADH who can tolerate its bitter taste, administering oral urea will increase urine output; the usual dose is 15 to 30 g per day. Increasing oral urea will, in a dose-dependent fashion, increase the urine volume. In the calculations described above, the intake of 15 g of urea would be expected to increase the urine output by approximately 500 mL if the urine osmolality is 500 mosmol/kg and by 1000 mL at a urine osmolality of 250 mosmol/kg.

- Loop diuretics to reduce the urine osmolality – In patients with more severe SIADH (urine osmolality more than twice the plasma osmolality), the efficacy of both fluid restriction and increased salt intake will be reduced (see 'Intravenous hypertonic saline' above). If further therapy is necessary, the next step is to increase urinary water excretion by impairing the mechanism of urinary concentration. This can be achieved by loop diuretic therapy. Torsemide (10 to 20 mg orally) is long acting and can be administered once daily; furosemide, if chosen, should be given twice daily (eg, 20 mg orally twice a day) since once-daily dosing can result in unopposed antidiuresis once the effect of the medication has diminished [58].

  Loop diuretic therapy can produce hypokalemia [58], often requiring potassium supplementation, and hypovolemia, since the diuretic response is higher in patients with SIADH who usually have normal or near-normal kidney function and are not sodium avid. (See 'Salt plus a loop diuretic' above.)

For the reasons described above, we do not use tolvaptan, demeclocycline, or lithium for maintenance therapy in patients with asymptomatic hyponatremia. (See 'Limitations to use of tolvaptan' above and 'Demeclocycline or lithium' above.)

Asymptomatic hyponatremia — Patients with chronic moderate hyponatremia (serum sodium 120 to 129 mEq/L) are typically asymptomatic on routine history. Before considering therapy, any reversible cause of SIADH should be addressed. (See 'Treat the underlying disease' above.)

Patients with asymptomatic hyponatremia have often been treated only with fluid restriction if the cause of the SIADH cannot be corrected. However, some of these seemingly asymptomatic patients have subtle neurologic manifestations that can interfere with the quality of life and that may be improved by raising the serum sodium as illustrated by the following observations:

- In the SALT trials described above, tolvaptan improved scores on tests of mental, social, and physical functioning among patients with a baseline serum sodium below 130 mEq/L [17]. However, the difference in mental status testing in the SALT trials was usually not clinically significant and long-term efficacy is uncertain, since the duration of follow-up was only 30 days. (See 'Vasopressin receptor antagonists' above and "Manifestations of hyponatremia and hypernatremia in adults", section on 'Subtle manifestations in mild to moderate chronic hyponatremia'.)

- In a study of older adult patients who presented to the emergency department, those with asymptomatic chronic hyponatremia (serum sodium between 120 and 129 mEq/L) compared to normonatremic controls had an increased incidence of falls that may have resulted from marked impairments in gait and attention [49]. Improvement was seen with repeat testing after treatment of the hyponatremia.

These observations suggest that some, and perhaps many, apparently asymptomatic patients with moderate chronic hyponatremia (serum sodium 120 to 129 mEq/L) have subtle reversible neurologic manifestations and that aiming for a goal serum sodium of 130 mEq/L or higher might be beneficial. Data demonstrating efficacy for routine attainment of this goal are not available.

If it is elected to aim for a serum sodium of 130 mEq/L or higher in chronically hyponatremic patients with SIADH who do not have overt evidence of neurologic dysfunction, we begin with fluid restriction and, if necessary, add oral salt tablets or urea, and then, if necessary, a loop diuretic in patients with a urine osmolality more than twice that of the plasma. (See appropriate sections above.)

Given the limitations cited above, we do not recommend the use of tolvaptan, demeclocycline, or lithium to achieve this goal in asymptomatic patients. (See 'Limitations to use of tolvaptan' above and 'Demeclocycline or lithium' above.)

RESET OSMOSTAT

In normal individuals, plasma antidiuretic hormone (ADH, arginine vasopressin) levels are very low when the plasma osmolality is below 280 mosmol/kg, thereby permitting excretion of ingested water, and increase progressively as the plasma osmolality rises above 280 mosmol/kg (figure 2).

Hyponatremia due to downward resetting of osmostat is one form of the SIADH [1,59-62]. (See "Pathophysiology and etiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)", section on 'Patterns of ADH secretion'.)

Downward resetting of the osmostat can also occur in hypovolemic states (in which the baroreceptor stimulus to ADH release is superimposed upon osmoreceptor function), quadriplegia (in which effective volume depletion may result from venous pooling in the legs), psychosis, tuberculosis, and chronic malnutrition [1,59]. The serum sodium concentration also falls by approximately 5 mEq/L in normal pregnancy. No therapy is required. (See "Maternal adaptations to pregnancy: Renal and urinary tract physiology".)

The presence of a reset osmostat should be suspected in any patient with apparent SIADH who has mild hyponatremia (usually between 125 and 135 mEq/L) that is stable over many days despite variations in sodium and water intake. The diagnosis can be confirmed clinically by observing the response to a water load (10 to 15 mL/kg given orally or intravenously). Normal subjects and those with a reset osmostat should excrete more than 80 percent of the water load within four hours, while excretion will be impaired in the SIADH [1].

Identification of a reset osmostat is important because the above therapeutic recommendations for the SIADH may not apply [1,59,63]. These patients have mild to moderate asymptomatic hyponatremia in which there is downward resetting of the threshold for both ADH release and thirst. Since osmoreceptor function is normal around the new baseline, attempting to raise the serum sodium concentration will increase ADH levels and make the patient thirsty, a response that is similar to that seen with fluid restriction in normal subjects.

Thus, attempting to raise the serum sodium concentration may be unnecessary (given the apparent lack of symptoms and lack of risk of more severe hyponatremia) and likely to be ineffective (due to increased thirst). Treatment should be primarily directed at the underlying disease, such as tuberculosis [64].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hyponatremia" and "Society guideline links: Fluid and electrolyte disorders in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients

who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) (The Basics)" and "Patient education: Hyponatremia (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Among patients with SIADH, hyponatremia is caused by the combination of ADH-induced water retention and secondary solute loss. With chronic SIADH, overall solute loss is more prominent than water retention. (See 'Pathogenesis' above.)
- The treatment of hyponatremia in SIADH involves treatment of the underlying disease and therapies to raise and maintain the serum sodium. Causes of SIADH that can be effectively treated include adrenal insufficiency and hypothyroidism, infections such as meningitis, pneumonia, or tuberculosis, and drug-induced disease. (See 'Treat the underlying disease' above.)

Therapies to raise the serum sodium

- Fluid restriction is the mainstay of the treatment of most patients with SIADH, with a suggested goal intake of less than 800 mL/day; patients with subarachnoid hemorrhage are an exception since fluid restriction may promote cerebral vasospasm. (See 'Fluid restriction' above.)
- In addition to fluid restriction, the therapy of SIADH-associated hyponatremia often requires the administration of sodium chloride, either as oral salt tablets or intravenous saline. When using intravenous saline, the electrolyte concentration of the administered fluid must be greater than the electrolyte concentration of the urine. This usually requires the use of hypertonic saline. Isotonic saline is infrequently effective and often leads to further lowering of the serum sodium. (See 'Intravenous hypertonic saline' above and 'Oral salt tablets' above.)
- Among patients with a urine osmolality more than twice the plasma osmolality (which typically means a urine osmolality above 500 mosmol/kg), a loop diuretic may be used to reduce urinary concentration, thereby increasing water excretion. (See 'Salt plus a loop diuretic' above.)
- The vasopressin receptor antagonists produce a selective water diuresis without affecting sodium and potassium excretion. Intravenous conivaptan (which is used in hospitalized patients) and oral tolvaptan are available and approved for use in patients with hyponatremia due to SIADH. The utility of tolvaptan therapy is limited by concerns about hepatotoxicity, excessive thirst, prohibitive cost (at least in the United States), and the potential for overly rapid correction of the hyponatremia which has led to the necessity for hospitalization for the initiation of therapy. Because of potential hepatotoxicity, tolvaptan should **not** be used for longer than 30 days and should **not** be given to patients with liver disease (including cirrhosis). (See 'Vasopressin receptor antagonists' above.)
- The rate of correction of chronic hyponatremia should be less than 8 mEq/L in any 24-hour period. The serum sodium concentration should be checked at two to three hours initially and then every three to four hours until the patient is stable. In selected patients with severe hyponatremia who are correcting too rapidly, prevention of further short-term elevation in serum sodium or even relowering of the serum sodium may be warranted. (See 'Rate of correction' above and "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia", section on 'Patients who have exceeded correction limits (rescue strategy)'.)

Choosing the appropriate therapy — The choice of therapy in patients with hyponatremia due to SIADH varies with the severity of hyponatremia and the presence or absence of symptoms.

- Among patients with severe symptomatic hyponatremia who present with seizures or other severe neurologic abnormalities or with symptomatic hyponatremia in patients with intracerebral diseases, we recommend urgent intervention with hypertonic saline rather than other therapies (**Grade 1C**). An effective initial regimen is 100 mL of 3 percent saline given as an intravenous bolus, which should raise the serum sodium concentration by approximately 1.5 mEq/L in men and 2 mEq/L in women, thereby reducing the degree of cerebral edema. If neurologic symptoms persist or worsen, a 100 mL bolus of 3 percent saline can be repeated one or two more times at 10-minute intervals. (See 'Severe symptoms' above.)
- Some patients have less severe neurologic manifestations and a serum sodium concentration below 120 mEq/L that develops over more than 48 hours, a lesser degree of hyponatremia that develops over less than 48 hours, or chronic moderate hyponatremia (serum sodium 120 to 129 mEq/L). Initial therapy in these patients depends in part upon the severity of symptoms.

- For patients with confusion and lethargy, we recommend the initial administration of hypertonic saline therapy to raise the serum sodium (**Grade 1C**). The goal is to raise the serum sodium 1 mEq/L per hour for three to four hours. The serum sodium should be measured at two to three hours and the subsequent infusion rate should be adjusted to achieve a rate of correction of no more than 8 mEq/L in any 24-hour period.

- For patients who have only mild symptoms (eg, forgetfulness, gait disturbance), we suggest initial therapy with fluid restriction and oral salt tablets rather than hypertonic saline. (See 'Mild-to-moderate symptoms' above.)

- Maintenance therapy in patients who initially had symptomatic hyponatremia may prevent a subsequent reduction in serum sodium and possible symptom recurrence. We suggest fluid restriction to less than 800 mL/day. If the serum sodium is persistently less than 130 mEq/L, we add oral salt tablets (or oral urea) and, if necessary in patients with a urine osmolality more than twice that of the plasma, a loop diuretic (eg, torsemide 10 to 20 mg orally once daily or furosemide 20 mg orally twice daily). We would not use tolvaptan, demeclocycline, or lithium in asymptomatic patients given the limitations cited above. (See 'Maintenance therapy' above and 'Demeclocycline or lithium' above.)

- Among asymptomatic patients with SIADH, we initiate therapy with fluid restriction. Oral salt tablets may be added, and then, if necessary in patients with a urine osmolality more than twice that of the plasma, a loop diuretic. (See 'Asymptomatic hyponatremia' above.)

- Hyponatremia with a reset osmostat pattern is a variant of the SIADH and should be suspected in any patient with mild to moderate hyponatremia (usually between 125 and 135 mEq/L) that is stable over time despite variations in sodium and water intake. The therapeutic recommendations for SIADH do not apply to patients with reset osmostat. Treatment should be primarily directed at the underlying disease. (See 'Reset osmostat' above.)

Goal serum sodium — We suggest a goal serum sodium of 130 mEq/L or higher in patients with SIADH because of the possible presence of subtle neurologic manifestations and falls when the serum sodium is between 120 and 129 mEq/L (**Grade 2C**). (See 'Asymptomatic hyponatremia' above.)

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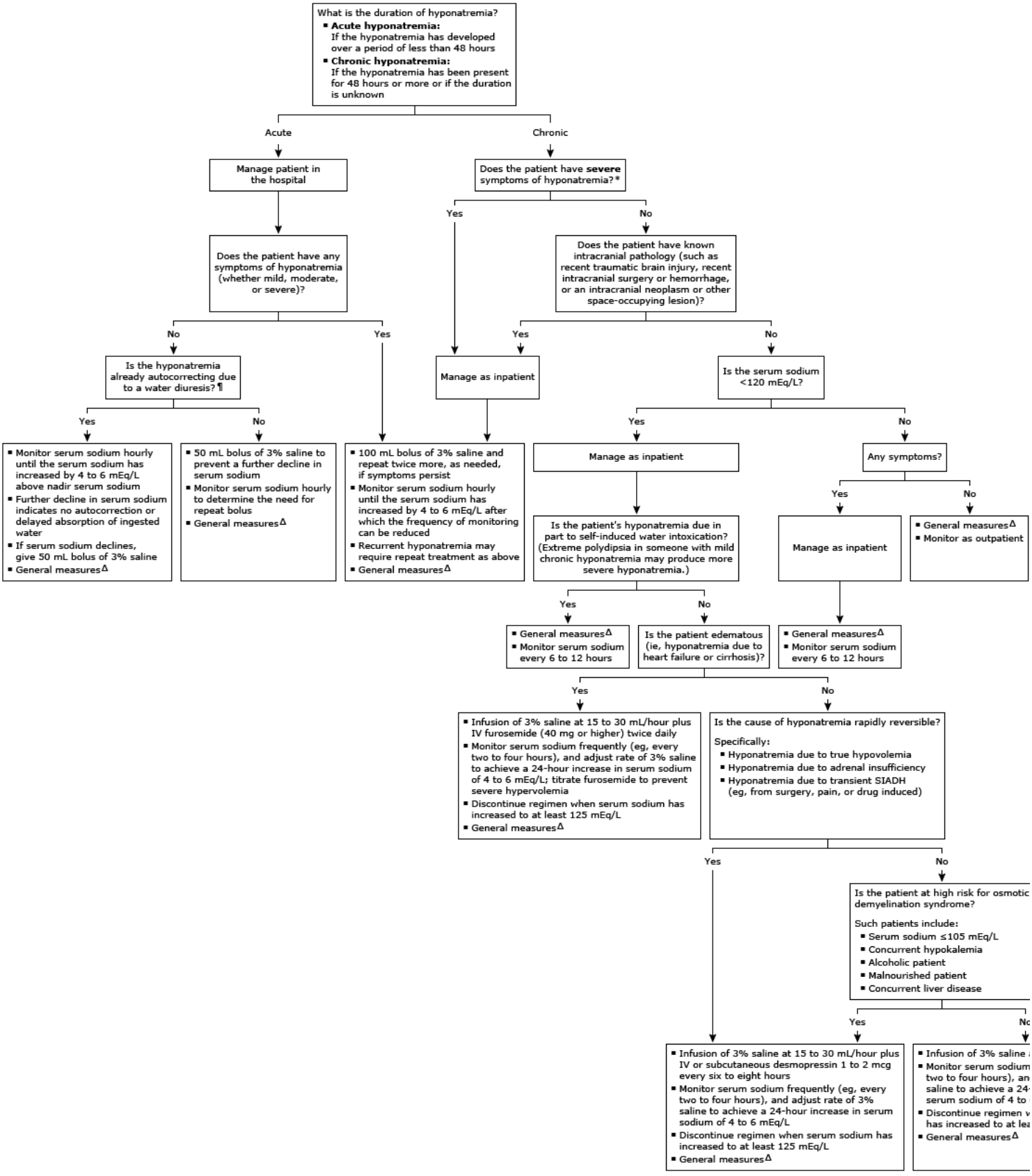
Topic 2357 Version 28.0

GRAPHICS

Overview of the initial treatment of adults with moderate to severe hyponatremia (serum sodium <130 mEq/L)



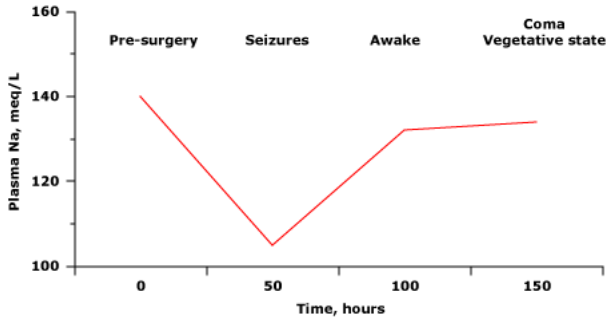
IV: intravenous; SIADH: syndrome of inappropriate antidiuretic hormone secretion.

* Severe symptoms of hyponatremia include seizures, obtundation, coma, and respiratory arrest.
¶ Autocorrection of hyponatremia is present if the serum sodium is rising spontaneously without intervention or treatment. Autocorrection should be suspected, even before a spontaneous rise in serum sodium is noted hyponatremic patients: those with a rapidly reversible cause of hyponatremia who have a brisk urine output and those with a urine output that is increasing over time and a urine cation concentration (ie, the sum of the potassium concentration) that is lower than the serum sodium.
Δ General measures include the following:

- Identify and treat the underlying cause of hyponatremia.
- Identify drugs taken by the patient that could contribute to hyponatremia. Discontinue those drugs unless there is no reasonable substitute and stopping the medication would cause serious harm.
- Reduce intake of electrolyte-free water (impose fluid restriction, eliminate IV hypotonic fluids, increase dietary salt).
- Other therapies in patients with SIADH and chronic hyponatremia include loop diuretics, oral salt tablets, and urea. (Refer to UpToDate topics on treatment of hyponatremia and treatment of SIADH.)

Graphic 115886 Version 2.0

Course of osmotic demyelination in hyponatremia

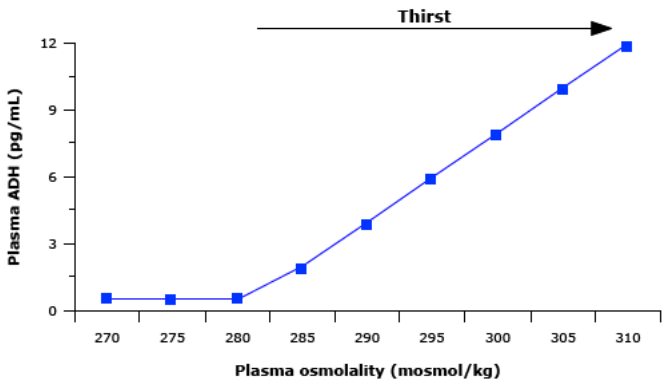


Clinical course in seven previously healthy women show developed postoperative hyponatremia and seizures presumably due to cerebral edema. Rapid correction of the plasma sodium concentration was associated with late deterioration into coma or a permanent vegetative state that may have been due to osmotic demyelination.

Data from: Arieff AI. N Engl J Med 1986; 314:1529.

Graphic 76471 Version 2.0

Osmotic regulation of ADH release and thirst



Relation between plasma ADH concentration and plasma osmolality in normal humans in whom the plasma osmolality was changed by varying the state of hydration. The osmotic threshold for thirst is a few mosmol/kg higher than that for ADH.

ADH: antidiuretic hormone.

Data from Robertson GL, Aycinena P, Zerbe RL. Neurogenic disorders of osmoregulation. Am J Med 1982; 72:339.

Graphic 65195 Version 5.0

Contributor Disclosures

Richard H Sterns, MD Nothing to disclose **Michael Emmett, MD** Consultant/Advisory Boards: AstraZeneca [Hyperkalemia]. **John P Forman, MD, MSc** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy