Overview of the treatment of hyponatremia in adults

AUTHOR: Richard H Sterns, MD
SECTION EDITOR: Michael Emmett, MD
DEPUTY EDITOR: John P Forman, MD, MSc

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INTRODUCTION

Hyponatremia represents a relative excess of water in relation to sodium. It can be induced by a marked increase in water intake (primary polydipsia) and/or by impaired water excretion due, for example, to advanced kidney failure or persistent release of antidiuretic hormone (ADH). (See "Causes of hypotonic hyponatremia in adults".)

This topic provides an overview of the treatment of adults with hyponatremia, including the pretreatment evaluation, selection of initial and subsequent therapy, goals of therapy, and common pitfalls.

The causes, clinical manifestations, and evaluation of hyponatremia, as well as detailed discussions about specific causes of hyponatremia, are presented in other topics:

- (See "Causes of hypotonic hyponatremia in adults".)
- (See "Manifestations of hyponatremia and hypernatremia in adults".)
- (See "Diagnostic evaluation of adults with hyponatremia".)
- (See "Hyponatremia in children: Etiology and clinical manifestations".)
- (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat".)

- (See "Hyponatremia in patients with heart failure".)
- (See "Hyponatremia in patients with cirrhosis".)
- (See "Diuretic-induced hyponatremia".)
- (See "Hyponatremia and hyperkalemia in adrenal insufficiency".)
- (See "Hyponatremia following transurethral resection, hysteroscopy, or other procedures involving electrolyte-free irrigation".)
- (See "Exercise-associated hyponatremia".)

PRETREATMENT EVALUATION

Our approach to treating patients with hyponatremia depends upon the duration of the hyponatremia, the severity of the hyponatremia, the presence and severity of symptoms, and the presence of preexisting intracranial pathology such as recent traumatic brain injury, recent intracranial surgery or hemorrhage, or an intracranial neoplasm or other space-occupying lesion (algorithm 1). Following initial therapy, the subsequent treatment can vary with the cause of hyponatremia.

Determine the duration of hyponatremia — Therapy for hyponatremia depends in part upon the acuity:

- Acute – If the hyponatremia has developed over a period of less than 48 hours, it is called "acute." Acute hyponatremia usually results from parenteral fluid administration in postoperative patients (who have antidiuretic hormone [ADH] hypersecretion associated with surgery) and from self-induced water intoxication (as in, for example, competitive runners, psychotic patients with extreme polydipsia, and users of ecstasy).
- Chronic – If it is known that hyponatremia has been present for 48 hours or more, or if the duration is unclear (such as in patients who develop hyponatremia at home), it is called "chronic."

The more acute the hyponatremia, the greater the risk of complications (such as cerebral edema and seizures) and the greater the need for aggressive therapy. The more chronic the hyponatremia and the lower the serum sodium concentration, the greater the risk of complications from overaggressive therapy and the greater the need for monitoring to avoid overcorrection.

Determine the severity (degree) of hyponatremia — Although a variety of definitions have been used, we use the following:

- Severe hyponatremia – A serum sodium concentration of <120 mEq/L is "severe hyponatremia." Complications of untreated hyponatremia and complications from overcorrection of hyponatremia are most common among patients with severe hyponatremia.

- Moderate hyponatremia – A serum sodium concentration of 120 to 129 mEq/L is "moderate hyponatremia."

- Mild hyponatremia – A serum sodium concentration of 130 to 134 mEq/L is "mild hyponatremia."

Determine the severity of symptoms — Symptoms due to hyponatremia are typically classified as severe or mild to moderate; some patients are or appear to be asymptomatic:

- Severe symptoms – Severe symptoms of hyponatremia include seizures, obtundation, coma, and respiratory arrest. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Clinical manifestations of acute hyponatremia'.)

  Severe symptoms such as seizures are relatively common in patients with an acute and marked reduction in the serum sodium concentration. Without time for brain adaptation to occur, affected patients can develop severe neurologic manifestations, including coma, brainstem herniation, and death.

  By contrast, seizures and other severe neurologic manifestations are relatively uncommon in patients with chronic hyponatremia (even among those with severely decreased serum sodium concentrations). As an example, a single-center study identified seizures in 3 of 120 patients (2.5 percent) with a serum sodium of 115 to 119 mEq/L, 3 of 54 patients (5.4 percent) with a serum sodium of 110 to 114 mEq/L, and 4 of 39 patients (10 percent) with a serum sodium of less than 110 mEq/L [1]. Similarly, another study reported that seizures occurred in only 7 percent of patients with chronic hyponatremia and a serum sodium of 110 mEq/L or less; by contrast, the incidence of seizures was 30 percent in patients with acute hyponatremia of this severity [2]. However, in patients with chronic hyponatremia, the risk for convulsions may be higher in patients with an underlying seizure disorder and in patients who are withdrawing from alcohol.

- Mild to moderate symptoms – Mild to moderate symptoms of hyponatremia are relatively nonspecific and include headache, fatigue, lethargy, nausea, vomiting, dizziness, gait

disturbances, forgetfulness, confusion, and muscle cramps. They occur most commonly in patients with chronic hyponatremia (present for 48 hours or more) that is severe (serum sodium concentration less than 120 mEq/L) and, in such cases, result from brain adaptations that minimize cerebral edema but alter the composition of brain cells [2-5]. In patients with severe, chronic hyponatremia, these findings are usually **not** associated with impending herniation. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Clinical manifestations of chronic hyponatremia'.)

However, if the serum sodium concentration is extremely low (less than 110 mEq/L), then such symptoms may be a prelude to seizures. In addition, mild to moderate symptoms in patients with acute hyponatremia, even those with sodium concentrations of greater than 120 mEq/L, should be considered ominous and may evolve without warning to seizures, respiratory arrest, and herniation [6]. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Clinical manifestations of chronic hyponatremia'.)

- Asymptomatic – Many hyponatremic patients appear to be asymptomatic. However, "asymptomatic" patients, particularly those with chronic hyponatremia of moderate severity (120 to 129 mEq/L), may have subtle impairments in mentation and gait and an increased risk of falls and fractures [7,8]. Thus, such patients are often offered chronic therapies to normalize the serum sodium concentration in an effort to treat these subtle manifestations [9] and to avoid the possibility that the serum sodium concentration will fall further and produce more serious symptoms. Chronic therapies that are used include oral urea, salt tablets and furosemide, or vasopressin antagonists. However, there is no evidence proving that these therapies decrease the risk of falls and fractures.

Determine the need for hospitalization — Patients at high risk for complications from untreated hyponatremia and those at high risk for complications from overcorrection of hyponatremia should be treated in hospital settings that allow frequent assessments of the patient's neurologic condition, accurate measurements of urine output, and frequent measurements of the serum sodium concentration. Such patients include:

- Those with acute hyponatremia
- Most patients with severe hyponatremia (ie, serum sodium less than 120 mEq/L)
- Most patients with symptomatic hyponatremia

By contrast, patients with mild hyponatremia and asymptomatic patients with moderate hyponatremia usually do not require hospitalization.

Treatment of patients who do not require hospital admission varies according to the cause of hyponatremia. Chronic treatment of these disorders is discussed separately:

- (See "Hyponatremia in patients with heart failure".)
- (See "Hyponatremia in patients with cirrhosis".)
- (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat".)
- (See "Hyponatremia and hyperkalemia in adrenal insufficiency".)

GOALS OF THERAPY

The treatment of hyponatremia in hospitalized patients has four important goals: to prevent further declines in the serum sodium concentration, to decrease intracranial pressure in patients at risk for developing brain herniation, to relieve symptoms of hyponatremia, and to avoid excessive correction of hyponatremia in patients at risk for osmotic demyelination syndrome (ODS) [10].

Our approach to attaining these goals, both during initial therapy (ie, the first six hours after recognition of the electrolyte disturbance) and during subsequent therapy (the first several days), is presented below. (See 'Acute hyponatremia: Initial therapy (first six hours)' below and 'Subsequent therapy (first several days)' below.)

Prevent a further decline in serum sodium — The risk of a further fall in the serum sodium concentration is especially high for the following groups:

- Patients with acute hyponatremia due to self-induced water intoxication (for example, competitive runners, psychotic patients with extreme polydipsia, and users of ecstasy). In such patients, delayed absorption of ingested water from the gastrointestinal tract may produce a further decline in the serum sodium concentration.
- Patients with acute hyponatremia caused by parenteral fluid administration, as in patients with postoperative hyponatremia due to surgery-induced syndrome of inappropriate antidiuretic hormone (SIADH). Large volumes of isotonic fluid produce volume expansion and result in increased sodium excretion in the urine. If antidiuretic hormone (ADH) levels are high, the excretion of this sodium in a concentrated urine will cause the serum sodium to fall further, a phenomenon that has been called "desalination" [11]. Thus, administration of additional isotonic saline should be avoided in such patients.

Prevent brain herniation — Fatal herniation is the most dreaded complication of hyponatremia. Herniation has been reported almost exclusively in the following settings:

- Patients with acute hyponatremia due to massive water ingestion associated with psychosis, competitive exercise, or use of the recreational drug ecstasy
- Women and children with acute postoperative hyponatremia
- Hyponatremic patients with intracranial pathology such as recent traumatic brain injury, recent intracranial surgery or hemorrhage, or an intracranial neoplasm or other space-occupying lesion

In such patients, when the serum sodium concentration falls to less than 130 mEq/L, even mild, nonspecific symptoms (eg, nausea, vomiting, headache, confusion) may rapidly progress to seizures, respiratory arrest, and permanent or fatal brain damage.

Concurrent hypoxemia, which may result from noncardiogenic pulmonary edema or hypoventilation, can exacerbate hyponatremia-induced cerebral edema and lead to a vicious cycle ending in death [6]. Impending herniation can be successfully reversed with a 4 to 6 mEq/L increase in the serum sodium concentration [12].

In contrast to the clinical settings listed above, other patients with hyponatremia have virtually no risk of herniation. Although such patients who are hospitalized with hyponatremia have a high mortality rate, deaths associated with hyponatremia are primarily due to the underlying disease and are rarely caused by cerebral edema. In one study, for example, only 1 of 664 patients with a serum sodium less than 120 mEq/L admitted to a community hospital over the course of 12 years died from cerebral edema, and this patient had coexistent intracranial pathology [13].

Relieve symptoms of hyponatremia — It is important to determine whether or not hyponatremia may be producing symptoms and to relieve those symptoms by raising the serum sodium concentration. Symptoms of hyponatremia are nonspecific, but if the serum sodium is less than 130 mEq/L, we assume that hyponatremia may be responsible. (See 'Determine the severity of symptoms' above and "Manifestations of hyponatremia and hypernatremia in adults", section on 'Hyponatremia'.)

The urgency and, therefore, the aggressiveness of treatment to raise the serum sodium varies depending upon the severity of symptoms, the acuity of hyponatremia, the level of the serum sodium concentration, and the patient's underlying condition. Even the most extreme symptoms can be relieved by a 4 to 6 mEq/L increase in serum sodium during the first 24 hours. Thus, if symptoms persist after an increase of this magnitude, there is no benefit and, in some cases, potential harm from correcting at a faster rate.

Avoid overcorrection — Overly rapid correction of severe, chronic hyponatremia (ie, chronic hyponatremia with a serum sodium concentration below 120 mEq/L and particularly below 115 mEq/L) can lead to a severe and sometimes irreversible neurologic disorder called the osmotic demyelination syndrome (ODS) (figure 1) [2,4,14-17].

Overly rapid correction of hyponatremia can result from efforts to raise the serum sodium, such as administration of hypertonic saline or vasopressin antagonists, or from elimination of the underlying cause of hyponatremia, such as the administration of saline to patients with true volume depletion, the administration of glucocorticoid therapy in adrenal insufficiency, or water restriction in patients with self-induced water intoxication. (See 'Diagnose and treat the underlying cause of hyponatremia' below.)

Some patients are at particularly high or low risk for ODS (see "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia", section on 'Risk factors for ODS'):

- High risk for ODS – Patients at highest risk for ODS are those with serum sodium concentrations of less than or equal to 105 mEq/L and those with hypokalemia, alcohol use disorder, malnutrition, liver disease, and possibly, hypophosphatemia.

- Low risk for ODS – Patients with acute hyponatremia that developed over a few hours due to a marked increase in water intake, as can occur in marathon runners, patients with primary polydipsia, and users of ecstasy, are probably not at risk for this complication. These patients have not had time for the brain adaptations that reduce the severity of brain swelling but also increase the risk of harm from rapid correction of the hyponatremia. In addition, the risk of osmotic demyelination is low when the initial serum sodium concentration is greater than 120 mEq/L; therefore, there should be little hesitation to treat acute hyponatremia with hypertonic saline even when symptoms are mild and the serum sodium concentration is only slightly below 130 mEq/L. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Osmolytes and cerebral adaptation to hyponatremia'.)

Complications of overly rapid correction of hyponatremia were once called "central pontine myelinolysis (CPM)," but the term "osmotic demyelination syndrome (ODS)" was introduced to describe these complications for several reasons: because demyelination may be more diffuse and does not necessarily involve the pons, because not all patients with posttreatment neurologic symptoms have demonstrable anatomic lesions, and because not all patients with central pontine myelinolysis have experienced a rapid increase in serum sodium (figure 1) [14]. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia".)

Goal rate of correction — Although some correction of hyponatremia is usually indicated in patients with severe hyponatremia, the goal of initial therapy is to raise the serum sodium concentration by 4 to 6 mEq/L in a 24-hour period. In symptomatic patients with acute hyponatremia or in patients with severe symptoms, this goal should be achieved quickly, over six hours or less. Thereafter, the serum sodium can be maintained at a constant level for the remainder of the 24-hour period to avoid overly rapid correction.

If the serum sodium concentration is <120 mEq/L or if there are additional risk factors of ODS (as examples, alcohol use disorder, malnutrition, or advanced liver disease) the **maximum rate of correction** should be 8 mEq/L in any 24-hour period [12,18-20]. In general, the same rate of rise can be continued on subsequent days until the sodium is normal or near normal.

The rationale for these recommendations is as follows:

- A 4 to 6 mEq/L increase in serum sodium concentration appears to be sufficient to reverse the most severe manifestations of hyponatremia [20,21]. In addition, the actual correction often exceeds what is intended, and, therefore, targeting an increase of 4 to 6 mEq/L in 24 hours may help avoid overly rapid correction.

- Most cases of ODS have occurred in patients with severe hyponatremia whose serum sodium concentration was raised by more than 10 to 12 mEq/L within 24 hours or more than 18 mEq/L within 48 hours [2,15]. However, a few cases have been reported after slower correction rates of 9 mEq/L in 24 hours [19,22].

- Because of the inherent imprecision of serum sodium measurements, particularly at very low concentrations, a laboratory report indicating that the serum sodium has increased by 8 mEq/L might reflect a true increase of 10 mEq/L [23]. For this reason, the therapeutic goal should not be too close to rates that can result in patient harm.

- The 24-hour goal may be achieved in the first few hours since it is the daily change, rather than the hourly change, in serum sodium that is associated with ODS. Thus, patients requiring emergency therapy can be corrected rapidly in the first several hours of the 24-hour period.

ACUTE HYPONATREMIA: INITIAL THERAPY (FIRST SIX HOURS)

Our approach to initial therapy of acutely hyponatremic patients (ie, during the first six hours after recognition of the disturbance) depends upon the presence or absence of symptoms (algorithm 1 and table 1).

Because of osmotically driven water flow across the blood-brain barrier, an acute onset of hyponatremia can result in life-threatening cerebral edema. Thus, even mild symptoms in acute hyponatremia present a medical emergency that requires prompt and aggressive treatment with hypertonic saline to prevent brain herniation.

Placement of a central venous catheter before administering hypertonic saline is **not necessary**, and attempts to do so can delay potentially life-saving therapy; 3 percent sodium chloride can be safely administered in a peripheral vein [24-27].

Asymptomatic — In acutely hyponatremic patients with a serum sodium <130 mEq/L who are asymptomatic, we usually treat with a 50 mL bolus of 3 percent saline (ie, hypertonic saline) to prevent the serum sodium from falling further. However, we do not give hypertonic saline if the hyponatremia is already autocorrecting due to a water diuresis. Autocorrection can be suspected if the cause of hyponatremia has been reversed, urine output has increased, and the urine is dilute (specific gravity <1.005, osmolality <200 mosmol/kg, or urine cation concentration [the sum of the urine sodium and potassium concentrations] is less than one-half the serum sodium). Alternatively, autocorrection can be detected by remeasuring the serum sodium. However, the results of this remeasurement must be available expeditiously. A point-of-care sodium analyzer (if available) provides helpful and rapid information about the trajectory of the serum sodium in such patients.

We then monitor the patient for symptoms and remeasure the serum sodium concentration every one to two hours to determine the need for additional therapy.

Patients with self-induced water intoxication may have a further decline in serum sodium, even after presentation, due to delayed absorption of ingested water. In addition, patients who have ingested large volumes of water are volume expanded, which results in increased sodium excretion in the urine. If antidiuretic hormone (ADH) levels are high due to a nonosmotic stimulus such as nausea, the excretion of sodium in a concentrated urine will cause the serum sodium to fall, a phenomenon that has been called "desalination" [11].

Symptomatic (even mild symptoms) — In acutely hyponatremic patients with a serum sodium <130 mEq/L who have any symptoms that might be due to increased intracranial pressure (seizures, obtundation, coma, respiratory arrest, headache, nausea, vomiting, tremors, gait or movement disturbances, or confusion), we treat with a 100 mL bolus of 3 percent saline, followed, if symptoms persist, with up to two additional 100 mL doses (to a total dose of 300 mL); each bolus is infused over 10 minutes. A table summarizing the emergency management of acute hyponatremia in adults is provided (table 1).

An alternative approach, recommended in by European organizations, is to treat with two 150 mL bolus infusions of 3 percent saline, each given over 20 minutes, measuring the serum sodium between infusions [28].

The goal of therapy is to **rapidly** increase the serum sodium by 4 to 6 mEq/L over a period of a few hours. Raising the serum sodium by 4 to 6 mEq/L should generally alleviate symptoms and prevent herniation [11,12,29-34].

Based upon broad clinical experience, the administration of hypertonic saline is the only rapid way to raise the serum sodium concentration and improve neurologic manifestations and outcomes in patients with severe, symptomatic hyponatremia [12,18,21,35-39].

We do not use mannitol and/or vasopressin antagonists (ie, vaptans) in these patients, either in addition to or instead of hypertonic saline. Although mannitol has been used to treat cerebral edema, it is potentially nephrotoxic and can also lower the serum sodium concentration, making it more difficult to monitor the hyponatremia. Vaptans have variable efficacy, and their onset of action is too slow to be recommended in patients with acute hyponatremia.

Patients with mild hyponatremia (serum sodium 130 to 134 mEq/L) should not have symptoms due to hyponatremia, are not at risk for brain herniation, and, therefore, do not require hypertonic saline. However, such patients should undergo monitoring to detect a further decrease in serum sodium (in which case hypertonic saline may become necessary). (See 'Monitoring' below.)

In all patients with acute hyponatremia, we employ additional measures to prevent the serum sodium from further decreasing, such as discontinuing medications that could contribute to hyponatremia and limiting the intake of hypotonic fluids. (See 'Additional measures in all patients' below.)

CHRONIC HYPONATREMIA: INITIAL THERAPY (FIRST SIX HOURS)

Our approach to initial therapy of hyponatremic patients (ie, during the first six hours after recognition of the disturbance) depends upon the severity of the hyponatremia, the presence and severity of symptoms, and the presence of preexisting intracranial pathology such as recent traumatic brain injury, recent intracranial surgery or hemorrhage, or an intracranial neoplasm or other space-occupying lesion (algorithm 1).

Mild hyponatremia (serum sodium 130 to 134 mEq/L) — In patients with mild, chronic hyponatremia (serum sodium 130 to 134 mEq/L), we do not treat with hypertonic saline. Rather,

our initial approach includes general measures that are applicable to all hyponatremic patients (ie, identify and discontinue drugs that could be contributing to hyponatremia; identify and, if possible, reverse the cause of hyponatremia; and limit further intake of water [eg, fluid restriction, discontinue hypotonic intravenous infusions]). (See 'Additional measures in all patients' below.)

Moderate to severe hyponatremia (serum sodium <130 mEq/L) — Our initial therapy in patients with chronic hyponatremia and serum sodium <130 mEq/L depends upon the severity of symptoms (if any), the presence or absence of preexisting intracranial pathology (eg, recent traumatic brain injury, recent intracranial surgery or hemorrhage, or an intracranial neoplasm or other space-occupying lesion), and whether or not the hyponatremia is severe (ie, a serum sodium <120 mEq/L) (algorithm 1).

Severe symptoms or known intracranial pathology — In all patients with severe symptoms of hyponatremia (eg, seizures, obtundation, coma, respiratory arrest), we treat with a 100 mL bolus of 3 percent saline followed, if symptoms persist, by up to two additional 100 mL doses (to a total dose of 300 mL); each bolus is infused over 10 minutes [40]. An alternative approach, recommended by European organizations, is to infuse 150 mL of 3 percent saline followed 20 minutes later by a second 150 mL bolus (if the serum sodium does not increase by 4 to 6 mEq/L after the initial dose) [28].

The presence of moderate to severe hyponatremia in a patient with intracranial pathology (such as recent traumatic brain injury, recent intracranial surgery or hemorrhage, or an intracranial neoplasm or other space-occupying lesion) should raise concern for increased intracranial pressure and possible risk for herniation. Thus, we treat such patients with a 100 mL bolus of 3 percent saline, followed, if symptoms persist, with up to two additional 100 mL doses (to a total dose of 300 mL) over the course of 30 minutes.

The goal of therapy is to rapidly increase the serum sodium by 4 to 6 mEq/L over a period of a few hours. Raising the serum sodium by 4 to 6 mEq/L should generally alleviate symptoms and prevent herniation [11,12,29-34].

Asymptomatic or mild to moderate symptoms and no intracranial pathology — In chronically hyponatremic patients with a serum sodium <130 mEq/L, absent or mild to moderate symptoms (eg, headache, fatigue, nausea, vomiting, gait disturbances, confusion), and no intracranial pathology, our approach depends upon the severity of the hyponatremia.

Patients with moderate hyponatremia (serum sodium 120 to 129 mEq/L) — Patients with moderate hyponatremia (serum sodium 120 to 129 mEq/L) that is chronic and associated with absent or mild or moderate symptoms are often not admitted to the hospital. However, if

such patients are hospitalized, we do not suggest hypertonic saline. In addition, the measures taken to prevent osmotic demyelination syndrome (ODS) in patients with severe hyponatremia (described below) are generally not necessary. Rather, our initial approach in such patients is to take general measures that are applicable to all hyponatremic patients (ie, identify and discontinue drugs that could be contributing to hyponatremia; identify and, if possible, reverse the cause of hyponatremia; and limit further intake of water). (See 'Additional measures in all patients' below.)

However, some patients with moderate hyponatremia have risk factors for ODS (eg, alcohol use disorder, hypokalemia, malnutrition, advanced liver disease) or have arginine vasopressin disorders (formerly called diabetes insipidus) and have desmopressin-induced hyponatremia. These individuals, despite not having severe hyponatremia, can develop ODS, and more care should be taken to avoid overly rapid correction. Such measures are described below. (See 'Patients with severe hyponatremia (serum sodium <120 mEq/L)' below.)

Patients with severe hyponatremia (serum sodium <120 mEq/L) — If the patient has severe, chronic hyponatremia (serum sodium <120 mEq/L), we initiate intravenous 3 percent saline beginning at a rate of 15 to 30 mL/hour, administered via a peripheral vein; we use 3 percent saline (rather than normal saline) in patients **with and without** suspected hypovolemia. An alternative option is to give 1 mL/kg (maximum, 100 mL) boluses of 3 percent saline intravenously every six hours, with dose modification as needed. Some patients may also require desmopressin (dDAVP) to prevent overly rapid correction. (See 'If cause of hyponatremia is rapidly reversible' below.)

There is evidence that 3 percent saline can be safely infused in a peripheral vein [25,26,41], and there is no evidence that it causes vascular thrombosis or extravasation injury. Nevertheless, some hospitals have policies stating that 3 percent saline can only be infused in a central vein. Such policies may cause some clinicians to choose isotonic saline instead of hypertonic saline for patients who are believed to be hypovolemic; however, isotonic saline should be **avoided** in patients with severe hyponatremia. If 3 percent saline cannot be used because of hospital policy restrictions, options include infusion of 1.5 or 2 percent saline but at rates more rapid than suggested for 3 percent saline. (See 'Use of isotonic saline in symptomatic or severe hyponatremia' below.)

There are limited data to inform the choice between slow, continuous infusion and intermittent boluses of 3 percent saline in patients with severe hyponatremia and mild to moderate symptoms. One unblinded trial compared continuous infusion (0.5 mL/kg/hour) with intermittent boluses (2 mL/kg given every six hours) [41]; these doses of 3 percent saline are substantially higher than what we recommend. The two groups had similar rates of symptom

resolution and overcorrection. However, at these doses, therapeutic relowering with 5 percent dextrose in water was required in approximately one-half of the patients, and despite this intervention, overcorrection was frequent. Because most of the patients were at very low risk of developing osmotic demyelination, the safety of these regimens could not be established.

For those with rapidly reversible causes of hyponatremia (as examples, patients with hypovolemia, thiazide-associated hyponatremia, or arginine vasopressin disorders who have desmopressin-induced hyponatremia) who are likely to develop a water diuresis during the course of therapy, or in those who are at high risk of developing ODS, we simultaneously initiate (or continue) desmopressin to prevent overly rapid correction. (See 'If cause of hyponatremia is rapidly reversible' below.)

Rapidly reversible causes of hyponatremia include:

- Hyponatremia due to true volume depletion (in such patients, correction of hypovolemia inhibits secretion of antidiuretic hormone (ADH), thereby leading to a water diuresis)
- Hyponatremia due to adrenal insufficiency (in such patients, administration of adrenal steroids inhibits ADH secretion and produces a water diuresis)
- Hyponatremia due to the syndrome of inappropriate antidiuretic hormone (SIADH; including postsurgical patients or SIADH due to pain or a drug)
- Thiazide-associated hyponatremia

Risk factors for ODS include:

- Serum sodium ≤105 mEq/L
- Concurrent hypokalemia
- Chronic excess alcohol intake
- Acute or chronic hepatic disease
- Malnourishment
- Hypophosphatemia (possible)

Patients with severe hyponatremia are at risk of worsening symptoms if the serum sodium falls further and, conversely, at risk of osmotic demyelination if the serum sodium rises too quickly. The lower the serum sodium concentration, the greater the risk. For reasons discussed below, we prefer 3 percent saline in such patients to treat hyponatremia, even among those who are thought to be hypovolemic. Isotonic saline can be given concurrently (with 3 percent saline), if needed, to correct symptomatic hypovolemia or prerenal azotemia. (See 'Use of isotonic saline

in symptomatic or severe hyponatremia' below and 'Isotonic saline in true volume depletion' below.)

If cause of hyponatremia is rapidly reversible — In patients with reversible causes of severe hyponatremia (serum sodium <120 mEq/L) who are likely to develop a water diuresis during the course of therapy, or who are at high risk of developing ODS, desmopressin can be given proactively at the beginning of therapy with 3 percent saline (ie, before any treatment is given to correct the hyponatremia). Although we prefer 3 percent saline to treat severe hyponatremia in hypovolemic patients, some clinicians use normal saline instead; in such cases, desmopressin should only be given after the serum sodium has been increased by 4 to 6 mEq/L.

Patients with arginine vasopressin disorders (formerly called diabetes insipidus) who develop hyponatremia while taking desmopressin should be considered a high-risk group because they can become hypernatremic if desmopressin is discontinued. Thus, we continue to administer desmopressin to such patients even when the serum sodium is >120 mEq/L. Oral or intranasal outpatient dosing should be converted to the parenteral route to ensure an effective antidiuresis while hyponatremia is being corrected.

When desmopressin is prescribed to prevent overly rapid correction of hyponatremia, we usually use 1 to 2 mcg of desmopressin, intravenously or subcutaneously (our preference), every six to eight hours for a period of 24 to 48 hours (or until the serum sodium has been increased to at least 125 mEq/L), and we simultaneously administer a slow intravenous infusion of hypertonic saline, beginning with a dose of 0.25 mL/kg/hour. A bolus of hypertonic saline can be given at the start of therapy to help relieve troublesome symptoms if these are present. The rate of infusion of hypertonic saline is then adjusted to achieve the desired rate of correction. Desmopressin makes the rate of correction resulting from hypertonic saline more predictable because it prevents an unexpected water diuresis from occurring during the course of therapy.

The effectiveness of this regimen was shown in two retrospective studies of symptomatic patients with severe hyponatremia (serum sodium less than 120 mEq/L) who were treated with hypertonic saline plus desmopressin [22,42]. In one of these studies, 25 patients received 3 percent saline (dose varied depending upon the severity of symptoms, with some patients receiving a 50 mL bolus of 3 percent saline) and desmopressin (1 to 2 mcg intravenously or subcutaneously every eight hours for 24 to 48 hours), aiming for a correction rate of 6 mEq/L/day [42]. The mean increase in serum sodium was 6 mEq/L in the first 24 hours and 4 mEq/L in the second 24 hours; one patient corrected by 11 mEq/L in the first 24 hours, but there were no other instances of overly rapid correction. With this approach, desmopressin is given to eliminate the potential for urinary water losses, in essence creating a state of iatrogenic SIADH that can be managed more predictably with hypertonic saline. The approach can be used to

treat both hypovolemic hyponatremia and SIADH. It is particularly attractive in patients who are at high risk of developing ODS from overly rapid correction of hyponatremia.

We recommend **against** the less frequent desmopressin dosing that is typically used to treat arginine vasopressin disorders (ie, every 12 or 24 hours). These dosing schedules allow escape from the antidiuretic effect and emergence of a water diuresis, possibly resulting in overly rapid correction of hyponatremia.

If desmopressin is used, it is important to restrict free water intake to avoid an unwanted decrease in the serum sodium concentration. For this reason, we do **not** use desmopressin in patients who are at high risk for self-induced water intoxication (eg, psychotic patients).

Some experts prefer to withhold desmopressin initially, giving it only if a water diuresis develops during the course of therapy [19,43]. However, we find this strategy to be labor intensive and often unsuccessful, associated with an unacceptably high incidence of unintentional overcorrection. Once a water diuresis begins, washout of the renal medullary gradient may result in a delay in achieving the full antidiuretic effect of desmopressin.

Other clinicians may choose not to use desmopressin and instead partially replace urinary water losses with intravenous 5 percent dextrose in water to prevent overly rapid correction. However, in our experience, that strategy is less effective and more difficult to manage than using desmopressin. Large doses of 5 percent dextrose will also exacerbate thiamine deficiency, hypokalemia, and hypophosphatemia if these are present.

If the proactive strategy of hypertonic saline with desmopressin is chosen, there is less need for frequent measurements of the serum sodium concentration and urine output; once it has been established that a large urine output has been prevented and that hypertonic saline is increasing the serum sodium concentration at the desired rate, measurements of the serum sodium every six hours are usually sufficient.

If cause of hyponatremia is unlikely to be rapidly reversible — We do **not** use desmopressin in patients who are unlikely to develop a water diuresis during the course of therapy. As examples:

- We do not use desmopressin in edematous patients with heart failure or cirrhosis; desmopressin may increase the amount of hypertonic saline required to achieve the desired increase in serum sodium concentration, and the likelihood of overly rapid correction in such patients is low.

In edematous patients, such as those with heart failure, coadministration of furosemide with hypertonic saline may be required to prevent worsening hypervolemia. Several groups have reported favorable outcomes treating heart failure patients in this manner [44-46].

- Similarly, we do not use desmopressin in patients with recurrent hyponatremia that is caused by chronic SIADH.

Additional measures in all patients — In all patients with a serum sodium concentration below the normal range (ie, <135 mEq/L), regardless of the acuity of the disorder or its associated symptoms, measures should be taken to avoid worsening of the electrolyte disturbance. These include:

- Identify medications taken by the patient that could cause or contribute to hyponatremia. Discontinue those drugs unless there is no reasonable substitute and stopping the medication would cause serious harm.

- Reduce the intake of electrolyte-free water: Restrict fluid intake, eliminate hypotonic intravenous fluids, and/or increase dietary salt intake.

- Identify and treat the cause of hyponatremia (eg, adrenal insufficiency, neuroendocrine tumors) (algorithm 2). (See "Diagnostic evaluation of adults with hyponatremia".)

SUBSEQUENT THERAPY (FIRST SEVERAL DAYS)

In the past, treatment of hyponatremia was targeted at raising the serum sodium to a level perceived to be safe (usually above 120 mEq/L and sometimes above 128 mEq/L) on the first day of treatment in the mistaken belief that this improved the prognosis of severe hyponatremia. There is no evidence to support this practice. Although the eventual goal is normalization of the serum sodium concentration, the therapeutic goal on any given day should **not** be a predefined serum sodium level, as this will often lead to overcorrection of hyponatremia when the serum sodium concentration is very low [4]. Small (4 to 6 mEq/L) daily increases in the serum sodium concentration are sufficient, no matter how low the original serum sodium concentration; larger increases offer no therapeutic advantage and only increase the risk of neurologic complications.

Monitoring — In patients with acute hyponatremia, we monitor the patient for symptoms and remeasure the serum sodium concentration hourly to determine the need for additional

therapy. The frequency of monitoring can be decreased when the serum sodium has been raised by 4 to 6 mEq/L.

Patients who are treated for chronic hyponatremia in the hospital should have their serum sodium measured often enough to ensure an appropriate rate of correction and to allow the clinician to react quickly to impending overly rapid correction (eg, every four hours). In addition, the urine output should be monitored, and, if increasing, the urine osmolality, urine sodium, and urine potassium should be measured. An increase in urine output and a decrease in the urine cation concentration can signify that the rate of correction is accelerating, and, in this setting, the serum sodium should be measured more frequently (eg, every two hours). If the risk of overly rapid correction is low, the frequency of measurements can be reduced, but measurements should still be taken at least every 12 hours until the serum sodium is 130 mEq/L or higher.

Subsequent therapy of chronic hyponatremia

Discontinuing hypertonic saline used as initial therapy — Once the daily correction goal of 4 to 6 mEq/L has been achieved, infusion of 3 percent saline should be discontinued for the remainder of the day, and hypertonic potassium solutions or oral potassium therapy should be changed to a hypotonic potassium solution. (See 'Potassium replacement in hypokalemic patients' below.)

If the serum sodium begins to fall again, hypertonic saline can be resumed as needed to preserve the desired increase in serum sodium for the day.

Fluid restriction — Fluid restriction to below the level of urine output is indicated for the treatment of symptomatic or severe hyponatremia in edematous states (such as heart failure and cirrhosis), syndrome of inappropriate antidiuretic hormone (SIADH), and advanced kidney function impairment. Restriction to 50 to 60 percent of daily fluid requirements may be required to achieve the goal of inducing negative water balance [31]. In general, fluid intake should be less than 800 mL/day. In patients with a highly concentrated urine (eg, 500 mosmol/kg or higher), fluid restriction alone may be insufficient to correct hyponatremia.

- (See "Hyponatremia in patients with heart failure", section on 'Fluid restriction'.)
- (See "Hyponatremia in patients with cirrhosis", section on 'Fluid restriction'.)
- (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat", section on 'Fluid restriction'.)

Fluid restriction is also warranted in hyponatremic patients with primary polydipsia in whom increased fluid intake is the primary problem. (See "Causes of hypotonic hyponatremia in adults", section on 'Primary polydipsia due to psychosis'.)

The effectiveness of fluid restriction alone can be predicted by the urine-to-serum cation ratio (the concentration of the urine cations, sodium (Na) and potassium (K), to the serum sodium concentration; ie, the concentrations of the urine [Na] plus the urine [K] divided by the serum [Na]) [47]. A ratio less than 0.5 suggests that the serum sodium concentration will rise with fluid restriction, while a ratio greater than 1 indicates that it will not. Similarly, if fluid must be given or the serum sodium concentration must be raised quickly because of symptomatic hyponatremia, the cation concentration of the administered fluid must exceed the cation concentration of the urine.

Other therapies for chronic hyponatremia

Loop diuretics in patients with a high urine cation concentration — Concurrent use of a loop diuretic may be beneficial in patients with SIADH who have a urine-to-serum cation ratio greater than 1. By inhibiting sodium chloride reabsorption in the thick ascending limb of the loop of Henle, furosemide interferes with the countercurrent mechanism and induces a state of antidiuretic hormone (ADH) resistance, resulting in the excretion of a less-concentrated urine and increased water loss. (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat", section on 'Salt plus a loop diuretic'.)

Oral salt tablets in patients with SIADH — Patients with syndrome of inappropriate antidiuretic hormone (SIADH) secretion who have very mild or absent symptoms and a serum sodium above 120 mEq/L can be treated with oral salt tablets in addition to fluid restriction. Given hourly, salt tablets can substitute for hypertonic saline in nonurgent situations [48]. Oral salt tablets may also be effective in hypovolemic patients who are treated as outpatients (in combination with reversing the cause of hypovolemia).

Calculating the dose of oral salt tablets uses the same principles as intravenous isotonic or hypertonic saline: 9 g of oral salt provides a similar quantity of sodium as 1 L of isotonic saline (154 mEq) but without any water; 1 g of oral salt is equivalent to 35 mL of 3 percent saline. (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat", section on 'Oral salt tablets'.)

Oral salt tablets should not be given to edematous patients (eg, those with heart failure, cirrhosis). (See "Hyponatremia in patients with heart failure" and "Hyponatremia in patients with cirrhosis".)

Urea in patients with SIADH — Urea administered orally or enterally (via a gastric tube) will increase the serum sodium concentration by increasing the excretion of electrolyte-free water [49]. Urea is an alternative to the combination of loop diuretics and oral salt tablets [43]. Favorable short- and long-term outcomes with urea therapy for hyponatremia have been reported in patients with syndrome of inappropriate antidiuretic hormone (SIADH) [50-53]. (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat", section on 'Urea'.)

Urea is available in the United States and Europe either as a palatable, flavored medical food dispensed in 15 g packets or as unflavored urea in bulk containers. The usual dose for maintenance therapy is 15 to 30 g/day.

Potassium replacement in hypokalemic patients — Potassium is as osmotically active as sodium. As a result, giving potassium (usually for concurrent hypokalemia) can raise the serum sodium concentration and osmolality in hyponatremic patients [54-58]. Since most of the potassium that is retained in the body enters the cells, electroneutrality is maintained in one of three ways, each of which will raise the serum sodium concentration:

- Intracellular sodium moves into the extracellular fluid in exchange for potassium.
- Extracellular chloride moves into the cells with potassium; the increase in cell osmolality promotes free water entry into the cells.
- Intracellular hydrogen moves into the extracellular fluid in exchange for potassium. These hydrogen ions are buffered by extracellular bicarbonate and, to a much lesser degree, plasma proteins. This buffering converts the bicarbonate ions to carbon dioxide and water, and the bicarbonate is replaced by the chloride that was infused with potassium (which, as noted, is exchanged for hydrogen ions). The increased intracellular osmolality due to potassium leads to water movement into the cells.

The net effect is that concurrent administration of potassium must be taken into account when estimating the sodium deficit and anticipating the rate of correction of the hyponatremia. This relationship becomes clinically important in the patient with severe diuretic or vomiting-induced hyponatremia who is also hypokalemic.

Suppose, for example, that a patient with hyponatremia has a serum potassium concentration of 2 mEq/L and that it is decided to give 400 mEq of oral potassium during the first day. If the patient is a 70 kg man, the total body water (TBW) will be approximately 40 liters (60 percent of body weight). The administered potassium will raise the serum sodium concentration by approximately 10 mEq/L, which exceeds the upper limit for the rate of safe correction. Thus,

giving potassium chloride alone will correct **both** the hyponatremia and the hypokalemia [54,55]. Giving additional sodium may lead to an overly rapid elevation in the serum sodium concentration and potentially cause osmotic demyelination syndrome (ODS) [57]. (See 'Avoid overcorrection' above.)

By contrast, many commercially available intravenous potassium solutions are hypotonic (10 mmol in 100 mL of water producing a 100 mmol/L solution). This solution will generally **not** increase the serum sodium. However, a more concentrated intravenous potassium solution (eg, 20 mmol in 50 mL of water producing a 400 mmol/L solution) will have the same effect on the serum sodium as 40 mL of hypertonic saline. Oral preparations of potassium chloride will raise the serum sodium as they contain no or little water [42].

Thus, when calculating the impact of a particular regimen on the serum sodium concentration, one must consider the sodium plus potassium concentration of the solution, not simply the sodium concentration. Similar considerations apply to calculating the impact of fluid losses induced by vomiting, diarrhea, or diuretic therapy.

Vasopressin receptor antagonists — An alternative or possible addition to fluid restriction and sodium chloride administration in patients with hyponatremia is the use of an ADH receptor antagonist [59]. There are multiple receptors for the ADH vasopressin: the V1a, V1b, and V2 receptors. The V2 receptors primarily mediate the antidiuretic response, while V1a and V1b receptors principally cause vasoconstriction and mediate adrenocorticotropic hormone (ACTH) release, respectively [18,60].

The vasopressin receptor antagonists produce a selective water diuresis (also called aquaresis) without affecting sodium and potassium excretion. The ensuing loss of free water will tend to correct the hyponatremia. However, thirst increases significantly with these agents, which may limit the rise in serum sodium [9,60].

Some oral formulations, such as tolvaptan, mozavaptan, satavaptan, and lixivaptan, are selective for the V2 receptor, while an intravenous agent, conivaptan, blocks both the V2 and V1a receptors. Only tolvaptan and conivaptan are available in the United States. The US Food and Drug Administration (FDA) warns that tolvaptan should **not** be used in any patient for longer than 30 days and should **not** be given at all to patients with liver disease (including cirrhosis).

We believe that a reasonable exception to this US FDA recommendation can be made for hyponatremic patients with end-stage liver disease who are awaiting liver transplantation. Correction of hyponatremia is desirable in such patients to avoid a rapid perioperative increase in the serum sodium concentration, and the clinical impact of a drug-related exacerbation of

liver injury in this setting is likely to be negligible. (See "Hyponatremia in patients with cirrhosis".)

With respect to conivaptan, there are concerns that the concurrent V1a receptor blockade might lower the blood pressure and increase the risk of variceal bleeding in patients with cirrhosis since vasopressin is used to treat active bleeding in such patients (a V1a effect). There is also a concern that V1a receptor blockade might worsen kidney function in patients with cirrhosis since terlipressin, a V1a receptor agonist, has been used to treat hepatorenal syndrome.

The studies that have evaluated the use of vasopressin receptor antagonists in the different settings in which hyponatremia occurs are presented elsewhere:

- SIADH (see "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat", section on 'Vasopressin receptor antagonists')
- Heart failure (see "Hyponatremia in patients with heart failure")
- Cirrhosis (see "Hepatorenal syndrome", section on 'Terlipressin plus albumin where available' and "Hyponatremia in patients with cirrhosis", section on 'Vasopressin receptor antagonists')

An example of the potential efficacy of these drugs was provided in a combined report of oral tolvaptan in two randomized, double-blind, placebo-controlled, multicenter trials (Study of Ascending Levels of Tolvaptan in Hyponatremia [SALT]-1 and SALT-2) in 448 patients with hyponatremia (mean serum sodium 129 mEq/L) caused by SIADH, heart failure, or cirrhosis [9]. 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 patients with 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 [61]. The mean serum sodium was maintained at more than 135 mEq/L, compared with 131 mEq/L at baseline. The responses were similar in SIADH and heart failure and were 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).

Vasopressin receptor antagonists should **not** be used in hyponatremic patients who are volume depleted in whom volume repletion with saline is the primary therapy. (See 'Isotonic saline in true volume depletion' below.)

There are several potential adverse effects associated with oral V2 receptor antagonists:

- Concerns about the safety of tolvaptan were raised by a multicenter trial (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes [TEMPO] 3:4) that examined its effect on the progression of kidney disease in polycystic kidney disease [62,63]. 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 initially issued a safety warning regarding the use of tolvaptan [64], recommending that liver function tests be promptly performed among patients who report symptoms that suggest liver injury, including fatigue, anorexia, right-upper-quadrant discomfort, dark urine, or jaundice. However, the US FDA subsequently determined that tolvaptan should **not** be used in any patient for longer than 30 days, or at all in patients with liver disease (including cirrhosis), because it may potentially lead to liver failure or death [65]. (See "Autosomal dominant polycystic kidney disease (ADPKD): Treatment".)

- Overly rapid correction of the hyponatremia may occur, which can lead to irreversible neurologic injury. In the SALT trials, 1.8 percent of patients exceeded the study goal of limiting daily correction to 12 mEq/L [9]. However, only 30 of the 223 patients enrolled in these trials had a serum sodium <130 mEq/L [66]. In a subsequent study, the incidence of overly rapid correction due to tolvaptan in patients with SIADH who had a serum sodium <130 mEq/L was 33 percent (when using a threshold of >8 mEq/L per 24 hours to define overly rapid correction); the incidence was 25 percent using a threshold of 12 mEq/L per 24 hours [67]. Overcorrection was even more common when the serum sodium was <120 mEq/L. Because of frequent overcorrection after 15 mg of tolvaptan (the only dose available in the United States), many countries now market a 7.5 mg tablet [66]. (See 'Avoid overcorrection' above.)

- These drugs increased thirst, which may limit the rise in serum sodium [9].

Another important limiting factor is the prohibitive **cost** of tolvaptan, which is as high as USD $300 per tablet in some areas.

Approach to impending overcorrection — In view of the often severe and permanent adverse consequences of ODS, prevention is essential. Prevention and treatment of overly rapid correction and ODS are discussed in detail elsewhere. (See "Osmotic demyelination syndrome

(ODS) and overly rapid correction of hyponatremia", section on 'Prevention and treatment of ODS'.)

The risk for overly rapid correction is higher if the cause of impaired water excretion is likely to be reversible (eg, in hypovolemic patients), thereby resulting in a water diuresis that can produce an abrupt rise in the serum sodium. An increase in urine output and a decrease in the urine cation concentration can signify a water diuresis that will accelerate the rate of correction.

Avoidance of overly rapid correction (more than 8 mEq/L in any 24-hour period) is often difficult in patients with self-induced water intoxication (as with psychotic patients who have primary polydipsia, exercise-associated hyponatremia, and ecstasy use). These patients tend to autocorrect since ADH is physiologically suppressed, permitting rapid excretion of large volumes of free water. However, the acute onset of hyponatremia in these disorders is associated with a low risk of ODS due to overly rapid correction. (See 'Avoid overcorrection' above.)

Diagnose and treat the underlying cause of hyponatremia — In addition to the specific therapies that are aimed at correcting the hyponatremia, therapy should also be directed at the underlying disease. Determining the cause of hyponatremia is presented elsewhere (algorithm 2). (See "Diagnostic evaluation of adults with hyponatremia".)

There are several circumstances in which the underlying cause of hyponatremia can be corrected quickly; the risk of overly rapid correction is high in such settings (see 'Avoid overcorrection' above):

- The administration of saline (isotonic or hypertonic) to patients with true volume depletion and prevention of further volume losses. In this setting, restoration of euvolemia will suppress the release of ADH (which has a half-life of only 15 to 20 minutes), thereby allowing rapid excretion of the excess water. (See 'Isotonic saline in true volume depletion' below.)

- The administration of glucocorticoids to patients with adrenal insufficiency, which will directly suppress the release of ADH. (See "Hyponatremia and hyperkalemia in adrenal insufficiency".)

- Relatively rapid reversal of SIADH. This can occur when the cause of SIADH is self-limited disease (eg, nausea, pain, surgery) or with the cessation of certain drugs that cause SIADH (eg, desmopressin [dDAVP], selective serotonin reuptake inhibitors such as fluoxetine or sertraline). (See "Pathophysiology and etiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)", section on 'Etiology'.)

- Discontinuation of thiazide diuretics. Elimination of the diuretic restores the ability to excrete maximally dilute urine.

There are a number of other causes of hyponatremia that can be corrected in which the serum sodium rises more slowly. This is most often seen with thyroid hormone replacement in patients with hypothyroidism and by gradually reversing the cause of SIADH by, for example, the treatment of tuberculosis or meningitis or the cessation of long-acting drugs. (See "Causes of hypotonic hyponatremia in adults" and "Pathophysiology and etiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)", section on 'Etiology'.)

APPROACHES THAT WE TYPICALLY AVOID

Use of isotonic saline in symptomatic or severe hyponatremia — Isotonic saline has a limited role in the management of symptomatic or severe hyponatremia (serum sodium <120 mEq/L). It is primarily used to correct hyponatremia in patients with minimal or no symptoms and serum sodium concentrations of >120 mEq/L who are at low risk of complications from untreated hyponatremia or from overly rapid correction of hyponatremia. Isotonic saline is also indicated in patients who are overtly hypovolemic with hypotension, prerenal azotemia, or orthostatic symptoms.

The degree to which isotonic saline will raise the serum sodium concentration in hyponatremic patients varies with the cause of the hyponatremia. As illustrated by the following discussion, the response to isotonic saline differs with the cause of hyponatremia.

Isotonic saline in true volume depletion — In states of true volume depletion (eg, diarrhea, vomiting, diuretic therapy), the administered sodium and water will initially be retained. In this setting, isotonic saline corrects the hyponatremia by two mechanisms:

- It slowly raises the serum sodium by approximately 1 mEq/L for every liter of fluid infused since isotonic saline has a higher sodium concentration (154 mEq/L) than the hyponatremic plasma.

- By correcting the hypovolemia, it removes the stimulus to antidiuretic hormone (ADH) release, thereby allowing the excess water to be excreted in a dilute urine. At this time, the serum sodium concentration may return rapidly toward normal; in some patients, overly rapid correction of hyponatremia can lead to the severe neurologic disorder osmotic demyelination syndrome (ODS) [54,68]. The management of such patients is discussed separately. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of

hyponatremia", section on 'Patients who have exceeded correction limits (rescue strategy)'.)

Isotonic saline is indicated in patients who are overtly hypovolemic with hypotension, prerenal azotemia, or orthostatic symptoms. Although isotonic saline will raise the serum sodium in hyponatremic patients with true hypovolemia, we concurrently give hypertonic saline if the hyponatremia is acute or severe and symptomatic. Isotonic saline will initially raise the serum sodium more slowly than hypertonic saline (until near-euvolemia is attained and ADH secretion is suppressed). In addition, some patients with hypovolemia may have coexistent syndrome of inappropriate ADH (SIADH) due to stress and will not respond well to isotonic saline. Thus, hypertonic saline will be predictably more effective in rapidly alleviating symptoms of severe hyponatremia. After euvolemia is established, the slow correction in patients receiving isotonic saline may accelerate due to suppression of ADH, leading to a marked water diuresis. This rapid rise in serum sodium in patients who were, until that point, correcting slowly may produce an excessive 24-hour increase in the serum sodium. Initial therapy with a combination of hypertonic saline and desmopressin (dDAVP) can quickly improve symptoms of hyponatremia while preventing overly rapid correction.

Do not use isotonic saline in edematous patients — Isotonic saline should **not** be used to treat hyponatremia associated with edematous disorders. Unlike patients with true volume depletion, saline will not result in the excretion of dilute urine. Rather, infused saline will be retained, resulting in a minimal increase in serum sodium concentration (1 mEq/L per liter of infused saline) and exacerbating edema.

Do not use isotonic saline in SIADH — In contrast to hypovolemia, the response to administered isotonic saline is different in a hyponatremic patient with syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Assuming the patient is euvolemic, the administered sodium is excreted in the urine because the response to aldosterone and atrial natriuretic peptide is normal. However, the water is retained because of the persistent action of ADH. Thus, when 1 liter of isotonic saline is administered to a patient with SIADH, the sodium is excreted in the urine while some of the water is retained, worsening the hyponatremia.

A few simple calculations can illustrate this point. Suppose a patient with SIADH and hyponatremia has a high, relatively fixed urine osmolality and a urine cation concentration (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 sodium chloride 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 to a further reduction in the serum sodium concentration even though the

serum sodium concentration will temporarily increase because the isotonic saline is hypertonic to the patient.

Using a hypothetical 60 kg woman with a serum sodium of 110 mEq/L and the equations that are presented below (see 'Approaches that we typically avoid' above), the effect of 500 mL of retained water can be calculated. For these calculations, the initial total body water (TBW) is assumed to be 50 percent of body weight (30 L), and the baseline total exchangeable cations are assumed to equal the product of TBW and the serum sodium concentration (30 L x 110 mEq/L = 3300 mEq). With these assumptions:

New serum sodium (SNa) = Total exchangeable cations ÷ TBW
= 3300 mEq (same as baseline) ÷ 30.5 L (500 mL increase)
= 108 mEq/L

Support for possible harm from isotonic saline was provided in a report of 22 women who underwent uncomplicated gynecologic surgery and had been treated with modest volumes of only isotonic saline or near-isotonic Ringer's lactate [11]. At 24 hours after induction of anesthesia, the serum sodium fell by a mean of 4.2 mEq/L. Fatalities from severe hyponatremia have been reported following the administration of large volumes of isotonic fluid after surgery [11].

Use of predictive formulas — Several formulas have been proposed to estimate the direct effect of a given fluid (eg, normal saline or hypertonic saline) on the serum sodium concentration. However, these formulae do not consider the effect of treatment of volume and composition of the urine output. As example, in the absence of any urine output, the following calculations apply:

Sodium deficit = TBW x (desired SNa - actual SNa)

Increase in SNa after 1 L infusate = (Infusate [Na] - SNa) ÷ (TBW + 1) [31]

The TBW, rather than extracellular fluid volume, is used in these formulas since, although the administered sodium will stay in the extracellular space, water moves from the intracellular to extracellular space in response to the administered sodium to equalize the osmolality of the two fluid compartments. Potassium added to the solution should be included in the formula (ie, "Infusate [Na + K]" rather than "Infusate [Na]") since potassium is as osmotically active as sodium and will therefore contribute to the elevation in serum sodium (see 'Potassium replacement in hypokalemic patients' above):

Increase in SNa after 1 L infusate = (Infusate [Na + K] - SNa) ÷ (TBW + 1)

Because TBW in liters is approximately 0.5 x body weight in kg and because each mL of 3 percent (hypertonic) saline contains 0.5 mEq of sodium, a simplified version of the formula predicts:

1 mL/kg body weight of 3 percent saline = 1 mEq/L increase in SNa

However, these formulas have a number of limitations and **cannot be used** to accurately predict the magnitude of change in serum sodium [69-71].

When hypertonic saline is given, the increase in serum sodium is often greater than that predicted by the formula [72,73]. As an example, in a series of 62 patients with a baseline serum sodium of 112 mEq/L who were treated with hypertonic saline, 74 percent had a rise in serum sodium greater than expected from the above formulas. In addition, the maximum recommended rate of correction at 24 and 48 hours was exceeded in 11 and 10 percent, respectively [72]. Inadvertent overcorrection was due to a documented water diuresis in 40 percent of patients, which, as mentioned above, can occur when saline therapy corrects hypovolemia, thereby removing the hypovolemic stimulus to the release of ADH and permitting rapid excretion of the excess water.

By contrast, in patients with persistent SIADH secretion, the administered sodium will be excreted in the urine, and some of the water will be retained; as a result, the increase in serum sodium after 3 percent saline will be less than that predicted by formulas, and the serum sodium may actually fall after isotonic saline. Suppose, for example, a 60 kg woman with SIADH and hyponatremia (serum sodium of 110 mEq/L) has a high, relatively fixed urine osmolality and a urine cation concentration (urine [Na] + urine [K]) of 308 mEq/L, which is twice the cation concentration of isotonic saline. If 1000 mL of hypertonic saline (513 mEq/L) is given, all of the sodium chloride will be excreted but now in 1665 mL of urine (513 ÷ 308 mEq/L). Thus, after the administration of hypertonic saline, there will be an initial large rise in the serum sodium concentration, followed by reduction toward baseline after the administered sodium has been excreted. At this time, the rise in the serum sodium due to the net loss of 665 mL of water can be calculated. For these calculations, the initial TBW is assumed to be 50 percent of body weight (30 L), and the baseline total exchangeable cations are assumed to equal the product of TBW and the serum sodium concentration (30 L x 110 mEq/L = 3300 mEq). With these assumptions:

New SNa = Total exchangeable cations ÷ TBW
= 3300 mEq (same as baseline) ÷ 29.3 L (665 mL loss)
= 113 mEq/L

The 3 mEq/L rise in serum sodium is considerably less than that predicted by the formulas above, which, if used, would have erroneously predicted the following effects of 1000 mL of hypertonic saline:

(Infusate [Na] - SNa) ÷ (TBW + 1) = 13 mEq/L
or
1 mL/kg body weight of 3 percent saline = 17 mEq/L

Predictive formulas can, however, be valuable adjuncts to therapy. If the increase in serum sodium is more than predicted by the formula, one should suspect that an increase in water excretion has occurred because the original cause for water retention has ended (eg, euvolemia has been restored in a patient with hypovolemic hyponatremia or desmopressin has worn off in a patient with desmopressin-induced hyponatremia). Such a deviation of the actual increase in serum sodium from the predicted increase should prompt strict monitoring of urine output and, in many cases, replacement of water losses or treatment with desmopressin to stop them.

In addition, if serial measurements of urine chemistries (urine sodium, potassium, and creatinine) and urine volume are available, a predictive formula including these data can be useful:

$$\text{Predicted serum } [Na^+] = \frac{\text{Total body } (Na^+ + K^+) + \text{Net } (Na^+ + K^+) \text{ balance}}{\text{TBW} + \text{Net fluid balance}}$$

An online calculator is available to apply the formula, which is based on careful balance studies and serial measurements of body sodium, potassium, and water content, performed in the 1950s [71]. However, rather than an actual measurement of TBW, the value is estimated from the patient's sex, weight, age, and height. Total body $(Na^+ + K^+)$ equals the current serum $[Na^+]$ multiplied by estimated TBW. Net $(Na^+ + K^+)$ balance (changing the numerator) and net fluid balance (changing the denominator) are calculated from volumes and $(Na^+ + K^+)$ concentrations of intravenous fluids and urine. The calculator allows a comparison of the expected change in serum sodium with its actual change (which should be measured

frequently). As with other formulas, differences between observed and expected values suggest a change in urine output and composition, which should be reevaluated.

DISCHARGE FROM THE HOSPITAL AND OUTPATIENT MANAGEMENT

Patients with mild hyponatremia and asymptomatic patients with moderate hyponatremia can be managed as outpatients. The severity of hyponatremia and the severity of symptoms are presented above. (See 'Determine the severity (degree) of hyponatremia' above and 'Determine the severity of symptoms' above.)

If hyponatremia persists at the time of discharge, patients who were treated in the hospital for severe hyponatremia or symptomatic moderate hyponatremia will require continued therapy as outpatients.

However, the following should be considered before discharging a patient who required inpatient treatment for hyponatremia:

- Patients should remain in the hospital long enough to assure that there is no longer a risk of injury from hyponatremia itself or from rapid correction of the electrolyte disturbance. Generally, this is true of patients whose serum sodium has been raised above approximately 125 mEq/L.

- If the patient still has a potentially reversible cause of hyponatremia (eg, recent administration of desmopressin [dDAVP] to prevent overcorrection), then the clinician should review the patient's risk factors for osmotic demyelination and the rate of rise in serum sodium that occurred in the preceding 24 hours since the rate of rise during the 24 hours after discharge may result in excessive correction.

  Take, for example, a patient being treated with desmopressin as an inpatient to avoid overly rapid correction of hyponatremia; the patient's serum sodium increased from 117 to 125 mEq/L during the preceding 24 hours (an increase of 8 mEq/L, which is in the acceptable range). If desmopressin is withdrawn, the ensuing water diuresis could produce a rise in serum sodium during the subsequent 24 hours that is substantially greater than 8 mEq/L, and that also exceeds the safe 48-hour correction limit, putting the patient at risk for osmotic demyelination syndrome (ODS). Thus, this patient should be monitored as an inpatient for the next 24 hours after withdrawal of desmopressin, rather than being discharged, and water losses should be replaced, if necessary, to avoid excessive correction.

- Tolvaptan, if used, should be started while patients are hospitalized and **not** at the time of discharge or in the outpatient setting. In addition, the appropriate dose of tolvaptan should be determined in the hospital while carefully monitoring the patient's urine output. If tolvaptan is ineffective, then other strategies should be used for outpatient management of the hyponatremia. If tolvaptan successfully increases the patient's serum sodium, then discharge should be delayed until it is established that the patient is able to replace their water losses induced by the drug. Thereafter, the need for continued tolvaptan therapy should be reassessed every 30 days.

Outpatient management of patients who no longer require hospital admission varies according to the cause of hyponatremia. Chronic treatment of these disorders is discussed separately:

- (See "Hyponatremia in patients with heart failure".)
- (See "Hyponatremia in patients with cirrhosis".)
- (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat".)
- (See "Hyponatremia and hyperkalemia in adrenal insufficiency".)

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 topics (see "Patient education: Hyponatremia (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Hyponatremia represents a relative excess of water in relation to sodium. It can be induced by a marked increase in water intake (primary polydipsia) and/or by impaired water excretion resulting from advanced kidney failure or from persistent release of antidiuretic hormone (ADH) (algorithm 2). (See 'Introduction' above.)

Evaluation prior to therapy

- Our approach to treating patients with hyponatremia depends upon the duration of the hyponatremia, the severity of the hyponatremia, the presence and severity of symptoms, and the presence of preexisting intracranial pathology such as recent traumatic brain injury, recent intracranial surgery or hemorrhage, or an intracranial neoplasm or other space-occupying lesion (algorithm 1) (see 'Pretreatment evaluation' above):
  - Therapy for hyponatremia depends, in part, upon the duration (see 'Determine the duration of hyponatremia' above):
    - Acute – If the hyponatremia has developed over a period of less than 48 hours, it is called "acute." Acute hyponatremia usually results from parenteral fluid administration in postoperative patients (who have ADH hypersecretion associated with surgery) and from self-induced water intoxication (as in, for example, competitive runners, psychotic patients with extreme polydipsia, and users of ecstasy).
    - Chronic – If it is known that hyponatremia has been present for 48 hours or more, or if the duration is unclear (such as in patients who develop hyponatremia at home), it is called "chronic."
  - We use the following categories of hyponatremia severity (see 'Determine the severity (degree) of hyponatremia' above):
    - Severe hyponatremia – A serum sodium concentration of <120 mEq/L is "severe hyponatremia." Complications of untreated hyponatremia and complications from

overcorrection of hyponatremia are most common among patients with severe hyponatremia.

- Moderate hyponatremia – A serum sodium concentration of 120 to 129 mEq/L is "moderate hyponatremia."

- Mild hyponatremia – A serum sodium concentration of 130 to 134 mEq/L is "mild hyponatremia."

- Symptoms due to hyponatremia are typically classified as severe or mild to moderate; some patients are, or appear to be, asymptomatic (see 'Determine the severity of symptoms' above):

  - Severe symptoms – Severe symptoms of hyponatremia include seizures, obtundation, coma, and respiratory arrest. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Clinical manifestations of acute hyponatremia'.)

  - Mild to moderate symptoms – Mild to moderate symptoms of hyponatremia are relatively nonspecific and include headache, fatigue, lethargy, nausea, vomiting, dizziness, gait disturbances, forgetfulness, confusion, and muscle cramps.

- Patients with acute hyponatremia, most patients with severe hyponatremia (ie, serum sodium less than 120 mEq/L), and most patients with symptomatic hyponatremia should be treated in hospital settings that allow frequent assessments of the patient's neurologic condition, accurate measurements of urine output, and frequent measurements of the serum sodium concentration. By contrast, patients with mild hyponatremia and asymptomatic patients with moderate hyponatremia usually do not require hospitalization. (See 'Determine the need for hospitalization' above.)

Initial treatment

- The treatment of hyponatremia in hospitalized patients has four important goals: to prevent further declines in the serum sodium concentration, to decrease intracranial pressure in patients at risk for developing brain herniation, to relieve symptoms of hyponatremia, and to avoid excessive correction of hyponatremia in patients at risk for osmotic demyelination syndrome (ODS). Although some correction of hyponatremia is usually indicated in patients with severe hyponatremia, the goal of initial therapy is to raise the serum sodium concentration by 4 to 6 mEq/L in a 24-hour period. In symptomatic patients with acute hyponatremia or in patients with severe symptoms, this goal should be

achieved quickly, over six hours or less. In patients with chronic, severe hyponatremia, the **maximum rate of correction** should be 8 mEq/L in any 24-hour period. (See 'Goals of therapy' above and 'Goal rate of correction' above.)

Our approach to initial therapy of hyponatremic patients (ie, during the first six hours after recognition of the disturbance) is as follows (algorithm 1 and table 1):

- **Acute hyponatremia** – In patients with acute hyponatremia and a serum sodium <130 mEq/L (see 'Acute hyponatremia: Initial therapy (first six hours)' above):
  - We treat **asymptomatic** patients with a 50 mL bolus of 3 percent saline (ie, hypertonic saline) to prevent the serum sodium from falling further. We then monitor the patient for symptoms and remeasure the serum sodium concentration hourly to determine the need for additional therapy. However, we do not give these patients hypertonic saline if the hyponatremia is already autocorrecting due to a water diuresis. (See 'Asymptomatic' above.)
  - We treat patients who have **any symptoms** that might be due to increased intracranial pressure (seizures, obtundation, coma, respiratory arrest, headache, nausea, vomiting, tremors, gait or movement disturbances, or confusion) with a 100 mL bolus of 3 percent saline, followed, if symptoms persist, with up to two additional 100 mL doses (to a total dose of 300 mL) over the course of 30 minutes. A table summarizing the emergency management of acute hyponatremia in adults is provided (table 1). (See 'Symptomatic (even mild symptoms)' above.)
- **Chronic hyponatremia** – In patients with chronic hyponatremia and a serum sodium <130 mEq/L (see 'Chronic hyponatremia: Initial therapy (first six hours)' above and 'Moderate to severe hyponatremia (serum sodium <130 mEq/L)' above):
  - In patients with **severe symptoms** of hyponatremia (eg, seizures, obtundation, coma, respiratory arrest) or in those with **known intracranial pathology** (such as recent traumatic brain injury, recent intracranial surgery or hemorrhage, or an intracranial neoplasm or other space-occupying lesion), we treat with a 100 mL bolus of 3 percent saline followed, if symptoms persist, by up to two additional 100 mL doses (to a total dose of 300 mL). (See 'Severe symptoms or known intracranial pathology' above.)
  - In patients who are **asymptomatic** or have **mild to moderate symptoms** (eg, headache, fatigue, nausea, vomiting, gait disturbances, confusion) and who have **moderate hyponatremia** (serum sodium 120 to 129 mEq/L), we generally take

only those measures that are broadly applicable to all hyponatremic patients (ie, identify and discontinue drugs that could be contributing to hyponatremia; identify and, if possible, reverse the cause of hyponatremia; and limit further intake of water). (See 'Patients with moderate hyponatremia (serum sodium 120 to 129 mEq/L)' above and 'Additional measures in all patients' above.)

- In patients who are **asymptomatic** or have **mild to moderate symptoms** (eg, headache, fatigue, nausea, vomiting, gait disturbances, confusion) and who have **severe hyponatremia** (serum sodium <120 mEq/L), we typically initiate intravenous 3 percent saline beginning at a rate of 0.25 mL/kg/hour. In addition, among those with reversible causes of hyponatremia who are likely to develop a water diuresis during the course of therapy, or in those who are at high risk of developing ODS, we simultaneously initiate desmopressin (dDAVP) to prevent overly rapid correction. (See 'Patients with severe hyponatremia (serum sodium <120 mEq/L)' above.)

Subsequent treatment

- In patients with acute hyponatremia, we monitor the patient for symptoms and remeasure the serum sodium concentration hourly to determine the need for additional therapy. The frequency of monitoring can be decreased when the serum sodium has been raised by 4 to 6 mEq/L. Patients who are treated for chronic hyponatremia in the hospital should have their serum sodium measured often enough to ensure an appropriate rate of correction and to allow the clinician to react quickly to impending overly rapid correction (eg, every four hours). (See 'Monitoring' above.)

- Hypertonic saline should be discontinued once the daily correction goal of 4 to 6 mEq/L has been achieved. If the serum sodium begins to fall again, hypertonic saline can be resumed as needed to preserve the desired increase in serum sodium for the day. (See 'Discontinuing hypertonic saline used as initial therapy' above.)

- Fluid restriction to below the level of urine output is indicated for the treatment of symptomatic or severe hyponatremia in edematous states (such as heart failure and cirrhosis), syndrome of inappropriate ADH (SIADH), advanced kidney impairment, and primary polydipsia. In patients with a highly concentrated urine (eg, 500 mosmol/kg or higher), fluid restriction alone may be insufficient to correct hyponatremia. (See 'Fluid restriction' above.)

- Depending upon the etiology of hyponatremia, other therapies may include loop diuretics, oral salt tablets, urea, potassium supplementation, or vasopressin receptor antagonists.

(See 'Other therapies for chronic hyponatremia' above.)

- In addition to the specific therapies that are aimed at correcting the hyponatremia, therapy should also be directed at the underlying disease. Determining the cause of hyponatremia is presented elsewhere (algorithm 2). (See "Diagnostic evaluation of adults with hyponatremia".)

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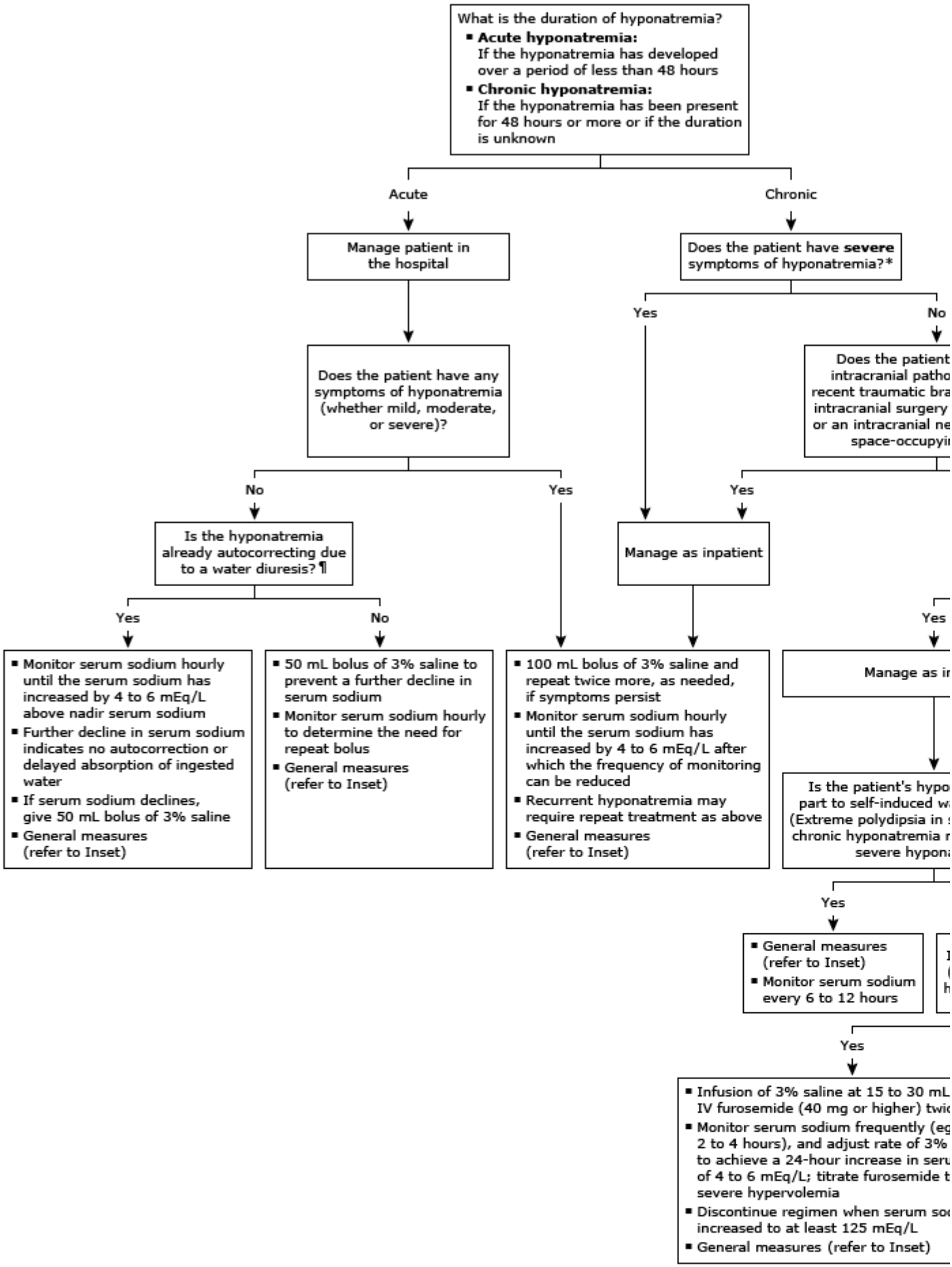
Topic 2350 Version 47.0

GRAPHICS

Treatment of adults with moderate to severe hyponatremia (serum sodium <130 mEq/L)


What is the duration of hyponatremia?
Acute hyponatremia: If the hyponatremia has developed over a period of less than 48 hours
Chronic hyponatremia: If the hyponatremia has been present for 48 hours or more or if the duration is unknown
Acute
Chronic
Manage patient in the hospital
Does the patient have severe symptoms of hyponatremia?*
Yes
No
Does the patient have any symptoms of hyponatremia (whether mild, moderate, or severe)?
Does the patient
intracranial patho
recent traumatic bra
intracranial surgery
or an intracranial ne
space-occupyi
No
Yes
Yes
Is the hyponatremia already autocorrecting due to a water diuresis? ¶
Manage as inpatient
Yes
No
Yes
Monitor serum sodium hourly until the serum sodium has increased by 4 to 6 mEq/L above nadir serum sodium
Further decline in serum sodium indicates no autocorrection or delayed absorption of ingested water
If serum sodium declines, give 50 mL bolus of 3% saline
General measures (refer to Inset)
50 mL bolus of 3% saline to prevent a further decline in serum sodium
Monitor serum sodium hourly to determine the need for repeat bolus
General measures (refer to Inset)
100 mL bolus of 3% saline and repeat twice more, as needed, if symptoms persist
Monitor serum sodium hourly until the serum sodium has increased by 4 to 6 mEq/L after which the frequency of monitoring can be reduced
Recurrent hyponatremia may require repeat treatment as above
General measures (refer to Inset)
Yes
Manage as i
Is the patient's hypo
part to self-induced w
(Extreme polydipsia in
chronic hyponatremia
severe hypon
Yes
General measures (refer to Inset)
Monitor serum sodium every 6 to 12 hours
Yes
Infusion of 3% saline at 15 to 30 mL
IV furosemide (40 mg or higher) twi
Monitor serum sodium frequently (eg
2 to 4 hours), and adjust rate of 3%
to achieve a 24-hour increase in seru
of 4 to 6 mEq/L; titrate furosemide t
severe hypervolemia
Discontinue regimen when serum so
increased to at least 125 mEq/L
General measures (refer to Inset)

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

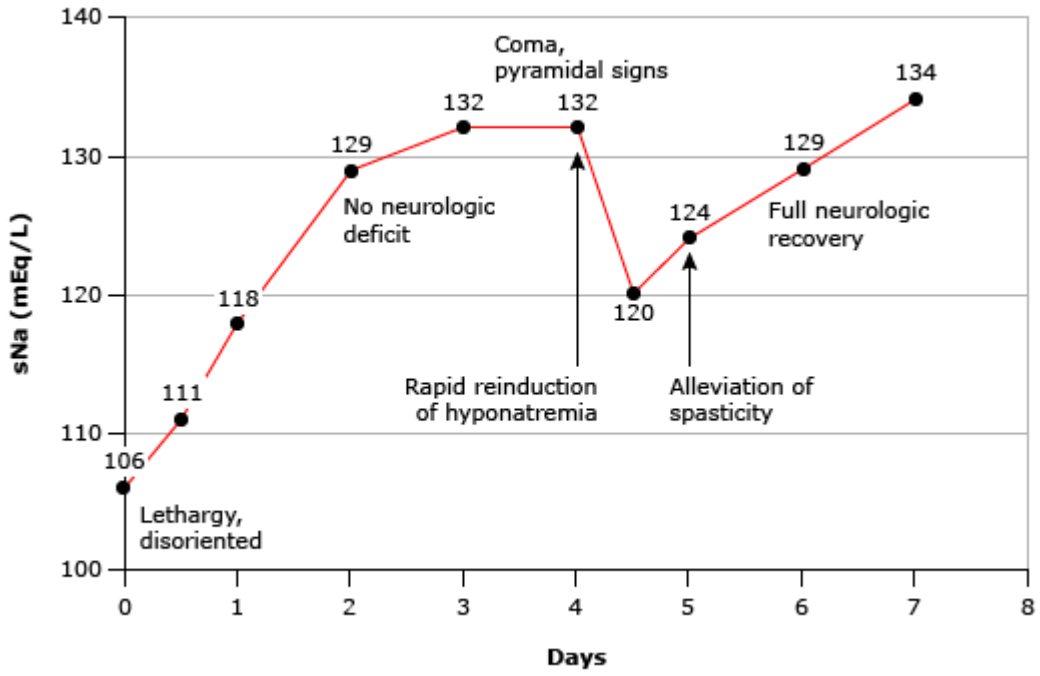
* Severe symptoms of hyponatremia include seizures, obtundation, coma, and respiratory arrest.

¶ 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, in the following 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 urine sodium and potassium concentration) that is lower than the serum sodium.

Δ Vomiting, nausea, fatigue, lethargy, confusion, forgetfulness, headache, dizziness, gait disturbance, muscle cramps.

Graphic 115886 Version 5.0

Delayed appearance of osmotic demyelination and relowering of the serum sodium



Neurologic symptoms of osmotic demyelination syndrome (ODS) typically occur 2 to 6 days after correction of the hyponatremia. In this patient, severe hyponatremia was corrected too quickly (23 mEq/L in 48 hours), and coma developed 2 days later. The serum sodium was quickly relowered and then slowly corrected. Neurologic symptoms improved, which may have been due to relowering of the serum sodium or may have represented spontaneous resolution.

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sNa: serum sodium.

Graphic 76131 Version 16.0

Acute* hyponatremia in adults: Rapid overview of emergency management

Definitions and general principles

- Acute hyponatremia is **known** or (in cases of self-induced water intoxication) can be presumed to have developed over the prior 48 hours. If the duration is unclear, hyponatremia should **NOT** be considered acute, and this rapid overview should not be applied.
- Severe hyponatremia is defined as a serum concentration <120 mEq/L.
- Moderate hyponatremia is defined as a serum concentration from 120 to 129 mEq/L (ie, <130 mEq/L).

Common causes

- Parenteral fluid administration (eg, post-operative).
- Water intoxication (eg, distance runners; psychotic patients with extreme polydipsia; users of MDMA (ie, 3,4-methylenedioxymethamphetamine or "Ecstasy").

Clinical features

- Unlike with chronic hyponatremia, ***any*** symptoms, whether mild or severe, that may be associated with increased intracranial pressure constitute an emergency. Examples include: confusion, gait or movement disturbances, tremor, nausea, vomiting, headache, seizures, obtundation, coma, respiratory arrest.

Diagnostic evaluation

- When possible, focused physical examination should include assessment of respirations, orthostatic blood pressure, pupil size and light reflex, volume status (eg, skin turgor, oral mucosa, edema), and neurologic function (eg, mental status, gait, reflexes, focal deficits).
- Obtain the following laboratory studies: serum creatinine; serum electrolytes (sodium, potassium, bicarbonate); serum glucose; urine sodium, urine potassium, urine osmolality, urine creatinine.

Initial management

- Treat all acutely hyponatremic patients manifesting ***any*** symptoms possibly due to increased intracranial pressure (see list above) with a 100 mL bolus of 3% hypertonic saline infused over 10 minutes.
- Treat acutely hyponatremic patients who are **not** symptomatic with a 50 mL bolus of 3% hypertonic saline infused over 10 minutes **unless** there is evidence of autocorrection (increasing output of dilut urine and/or evidence that serum sodium concentration is increasing without treatment).
- Goal of therapy is an increase in serum sodium by 4 to 6 mEq/L over a few hours.
- Stop all other intravenous (IV) fluid infusions.
- If the patient is seizing and response to hypertonic saline infusion is delayed, can give a rapid-acting benzodiazepine (eg, lorazepam 4 mg IV).
- If symptoms persist after first bolus, up to two additional 100 mL doses of 3% saline may be given, each infused over 10 minutes (maximum total dose 300 mL).

- Obtain repeat measurements of serum sodium every one to two hours. A rapid, point-of-care sodium analyzer can be used if available. Serum sodium may decline further after presentation in patients with self-induced water intoxication.
- Monitor urine output.

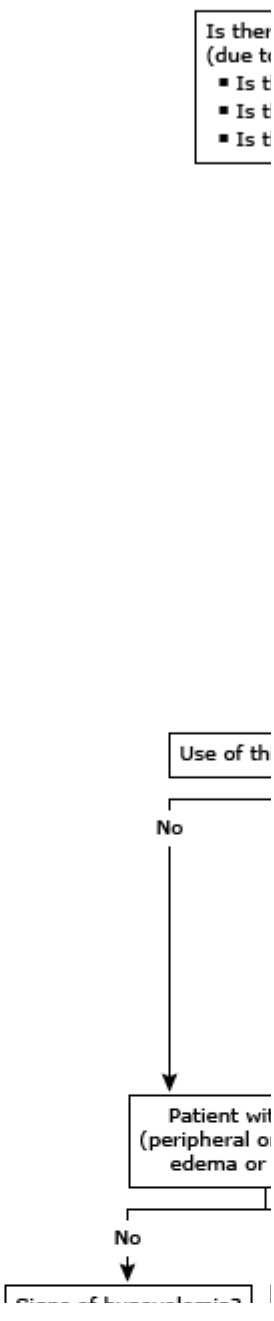
Disposition

- Patients with acute hyponatremia should be hospitalized. Those who manifest or remain at risk for severe complications should be closely monitored in a critical care setting.

* **Chronic** hyponatremia is much less likely to cause seizures and other severe complications. Correction of **chronic** hyponatremia must be performed more **gradually** than acute to avoid osmotic demyelination. Refer to UpToDate topics discussing chronic hyponatremia.

Graphic 143120 Version 3.0

Determining the cause of hyponatremia in adults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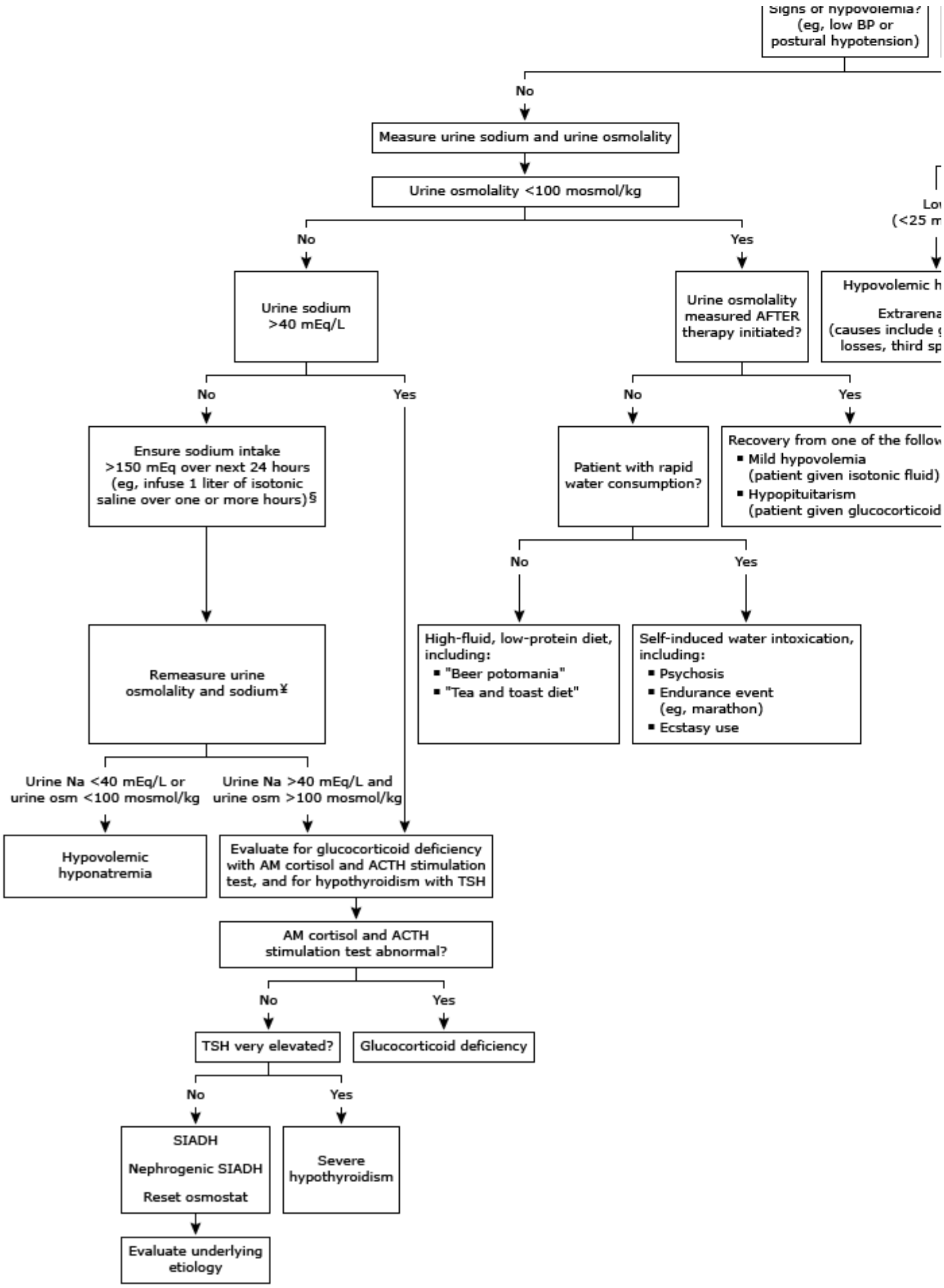
Signs of hypovolemia? (eg, low BP or postural hypotension)
No
Measure urine sodium and urine osmolality
Urine osmolality <100 mosmol/kg
No
Yes
Urine sodium >40 mEq/L
Urine osmolality measured AFTER therapy initiated?
Hypovolemic h
Extrarena
(causes include
losses, third sp
No
Yes
No
Yes
Ensure sodium intake >150 mEq over next 24 hours (eg, infuse 1 liter of isotonic saline over one or more hours)§
Patient with rapid water consumption?
Recovery from one of the follow
Mild hypovolemia (patient given isotonic fluid)
Hypopituitarism (patient given glucocorticoid
No
Yes
High-fluid, low-protein diet, including:
"Beer potomania"
"Tea and toast diet"
Self-induced water intoxication, including:
Psychosis
Endurance event (eg, marathon)
Ecstasy use
Remeasure urine osmolality and sodium¥
Urine Na <40 mEq/L or urine osm <100 mosmol/kg
Urine Na >40 mEq/L and urine osm >100 mosmol/kg
Hypovolemic hyponatremia
Evaluate for glucocorticoid deficiency with AM cortisol and ACTH stimulation test, and for hypothyroidism with TSH
AM cortisol and ACTH stimulation test abnormal?
No
Yes
TSH very elevated?
Glucocorticoid deficiency
No
Yes
SIADH
Nephrogenic SIADH
Reset osmostat
Severe hypothyroidism
Evaluate underlying etiology

IVIG: intravenous immune globulin; TURP: transurethral resection of the prostate; BP: blood pressure; ACTH: adrenocorticotropic hormone; ADH: antidiuretic hormone; TSH: thyroid-stimulating hormone; SIADH: syndrome of inappropriate antidiuretic hormone secretion.

* A simple and convenient correction of the serum sodium for hyperglycemia is as follows: Add 2 mEq/L to the serum sodium for every 100 mg/dL (5.55 mmol/L) of serum glucose above the normal value.

¶ Impaired water excretion in renal failure occurs if there is severe impairment in glomerular filtration rate. Patients with mild-to-moderate impairment in glomerular filtration rate are typically able to excrete water loads. The measured plasma osmolality may be high in patients with renal failure because of high urea concentrations. However, urea is an ineffective osmole, and such patients have hypotonic hyponatremia even if the plasma osmolality is normal.

Δ Thiazide-induced hyponatremia may be protracted. An extensive evaluation for other etiologies can be delayed for several weeks in mildly hyponatremic patients.

◇ Patients with hypovolemic hyponatremia due to diuretics may have a low urine sodium if the effect of the diuretic has worn off.

§ If the serum sodium is 125 mEq/L or less, we do not give isotonic saline. In such patients, the evaluation can be delayed until the sodium is slowly raised to higher levels.

¥ Although patients with hyponatremia due to heart failure or cirrhosis will usually have edema that is clinically apparent, hypovolemia may not always be apparent by clinical exam. Thus, in a patient who appears to be euvolemic but whose urine chemistries are consistent with hypovolemia, infusion of isotonic saline (eg, 1 liter over one hour) can be helpful.

Graphic 101823 Version 6.0