Causes of hypotonic 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

The serum tonicity is defined as the osmolar concentration of solutes that do not readily cross the cell membrane (effective osmoles). These solutes are primarily sodium salts in the extracellular space. As a result, the plasma or serum sodium concentration is used as a surrogate for assessing tonicity of the extracellular fluid.

Hyponatremia is commonly defined as a serum sodium concentration below 135 mEq/L, but the definition can vary to a small degree in different clinical laboratories [1,2]. Most patients with hyponatremia have hypotonicity, but there are exceptions (table 1). Hyponatremia without hypotonicity can occur in patients with hyperglycemia, in patients who have accumulated exogenous effective osmoles, and in patients with pseudohyponatremia caused by extreme hyperlipidemia or hyperproteinemia. The causes of hyponatremia without hypotonicity are discussed elsewhere. (See "Causes of hyponatremia without hypotonicity (including pseudohyponatremia)".)

An overview of the causes of hypotonic hyponatremia is presented in this topic. Most of the individual causes of hyponatremia are discussed in detail separately (table 2), as are issues related to the diagnosis and treatment of hyponatremia (algorithm 1 and algorithm 2) [3,4].

- (See "Diagnostic evaluation of adults with hyponatremia".)

- (See "Overview of the treatment of hyponatremia in adults".)

PATHOGENESIS OF AND DEFENSE AGAINST HYPOTONIC HYPONATREMIA

Hypotonic hyponatremia results from the intake (ie, oral, intravenous, other absorption) and subsequent retention of water [3,5-7].

The major defense against hyponatremia is the capacity to excrete large volumes of urine with a low concentration of sodium and potassium (ie, electrolyte-poor water):

- When water is ingested or absorbed causing even slight hypotonicity, both thirst and antidiuretic hormone (ADH; also called vasopressin) release are normally suppressed [8]. ADH is produced by hypothalamic neurons that receive inputs from osmoreceptors that respond to the serum sodium concentration and from baroreceptors that respond to the status of the circulation [9]. Suppression of ADH secretion requires normal functioning of osmoreceptors and the absence of signals from baroreceptors that can stimulate ADH release even when the serum sodium concentration is low.

- Excretion of electrolyte-poor water is accomplished by reabsorbing salt without water in the water-impermeable ascending limb of the loop of Henle and distal convoluted tubule (known as diluting sites) [10]. Excretion of electrolyte-poor water also requires that the renal tubule segments beyond the diluting sites (the later distal tubule segments and collecting duct) are relatively impermeable to water; water impermeability of these sites requires that the epithelium contain very few water channels (aquaporins). High levels of ADH result in insertion of water channels in the collecting duct while low levels of ADH allow these water channels to be removed from the epithelium [5].

Thus, a water load will, in normal individuals, be rapidly excreted as the dilutional fall in serum tonicity suppresses the release of ADH (figure 1), thereby allowing excretion of the excess water in a dilute urine.

The maximum attainable urine volume in normal individuals on a regular diet is in excess of 10 L/day. The normal diluting mechanisms of the kidney can produce urine with an osmolality that is at least as low as 100 mosmol/kg and often as low as 50 mosmol/kg. A typical western diet generates approximately 900 mosmol of solute daily, which is composed of approximately one-half urea (derived from dietary protein) and one-half sodium and potassium salts. On such a diet, urine with an osmolality of 50 mosmol/kg has a sodium plus potassium concentration of approximately 12 mEq/L. Excretion of 900 mosmol of solute at a concentration of 50 mosmol/L will result in 18 L of electrolyte-poor urine. If the diet is lower in salt, potassium, and protein, the

capacity to excrete large volumes of urine will be less. As an example, excretion of 300 mosmol of solute at a concentration of 50 mosmol/L will result in only 6 L of electrolyte-poor urine. However, this still provides an enormous range of protection against the development of hyponatremia since the daily fluid intake in most healthy individuals is less than 2 to 2.5 L/day.

In contrast to the response in normal individuals, patients who develop hyponatremia typically have an impairment in renal water excretion, most often due to an inability to suppress ADH secretion [11]. An uncommon exception occurs in patients with primary polydipsia who can become hyponatremic because they rapidly drink such large quantities of fluid that they overwhelm the excretory capacity of the kidney even though ADH release is appropriately suppressed. (See 'Primary polydipsia due to psychosis' below.)

CLASSIFICATION OF HYPOTONIC HYPONATREMIA

Hyponatremia occurs when water intake exceeds water excretion; it can result from water intake that is large, water excretion that is low, or a combination of these abnormalities. Because excretion of electrolyte-poor water is the normal defense against hyponatremia, we classify the causes of hyponatremia according to the body's ability to excrete dilute urine and, if that is impaired, the reason for the impairment.

Other classification systems divide hyponatremia into hypovolemic, hypervolemic, and euvolemic hyponatremia. However, determining a patient's volume status is often difficult (particularly distinguishing hypovolemia and euvolemia). In addition, classification of hyponatremia by volume status is most helpful in defining the reason for failure to suppress antidiuretic hormone (ADH) secretion. (See 'Impaired urine dilution due to unsuppressed ADH secretion' below.)

Unimpaired urine dilution

Primary polydipsia due to psychosis — Primary polydipsia, a disorder in which there is a primary increase in thirst, is most often seen in patients with psychiatric illnesses [12-17]. As an example, one study of 239 hospitalized patients with mental illness found that 6.6 percent had a history compatible with compulsive water drinking and that one-half of these had intermittent symptoms of hyponatremia due to transient water retention [18].

It is presumed that a central defect in thirst regulation plays an important role in the pathogenesis of polydipsia [15,19]. In some cases, for example, the osmotic threshold for thirst is reduced **below** the threshold for the release of ADH [20]. In contrast to normal subjects in whom the thirst threshold is roughly equal to or a few mosmol/kg **higher** than the threshold for

ADH [21], these patients will continue to drink until the plasma osmolality is less than the threshold level. This may be difficult to achieve, however, since ADH secretion will be suppressed by the fall in plasma osmolality, resulting in rapid excretion of the excess water and continued stimulation of thirst. The mechanism responsible for abnormal thirst regulation in patients with primary polydipsia is unclear.

Normal subjects can excrete more than 400 to 600 mL of urine per hour, a response that is mediated by suppression of ADH secretion and the subsequent formation of a dilute urine with a minimum osmolality between 40 and 100 mosmol/kg. If ADH regulation and kidney function are intact, primary polydipsia should not lead to clinically important disturbances in the plasma sodium concentration without a massive increase in water intake. Thus, the serum sodium concentration is usually normal or only slightly reduced in primary polydipsia since the excess water is readily excreted [13]. These patients may be asymptomatic or present with complaints of polydipsia and polyuria. (See "Evaluation of patients with polyuria".)

Water intake may occasionally exceed 400 to 600 mL per hour, particularly in institutionalized patients with severe psychosis [17] and may produce fatal hyponatremia even though the urine is maximally dilute with an osmolality below 100 mosmol/kg [22,23]. Symptomatic hyponatremia can also be induced with an acute 3- to 4-liter water load. This is sometimes seen in anxious patients preparing for a radiologic examination or in those attempting to dilute their urine to avoid a positive urine drug test [24].

However, some patients with polydipsia who become hyponatremic have a higher urine osmolality than polydipsic patients who remain normonatremic, indicating a concurrent increase in ADH release and/or response [12,19,25,26]. A number of different abnormalities in ADH regulation have been identified in psychotic patients, each of which can impair water excretion. Studies in patients who have had at least one episode of hyponatremia have revealed the following defects [19]:

- Transient stimulation of ADH release during acute psychotic episodes, producing the syndrome of inappropriate ADH secretion (SIADH) [25,27].
- An increase in the net renal response to ADH so that, at the same plasma ADH levels, psychotic patients have a higher urine osmolality and therefore a lower rate of free water excretion than healthy controls [19]. How this occurs is not known.
- Antipsychotic or antidepressant drugs (such as fluoxetine) may also produce SIADH in a few patients. As examples, carbamazepine and fluoxetine can produce hyponatremia with an SIADH-like clinical picture [28,29].

- A downward resetting of the osmostat regulating ADH release. As a result, a lower-than-normal plasma sodium concentration is required to completely suppress ADH release and excrete a water load. (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat".)

- Transient ADH release due to nausea [17].

The net effect is that some modestly hyponatremic patients with primary polydipsia do not dilute their urine maximally, as would be expected if ADH were suppressed by hypoosmolality [19]. The likelihood of developing hyponatremia will be increased further by the presence of a cause for enhanced ADH release, such as nausea, stress, or concurrent diuretic therapy [24,30].

Primary polydipsia can also occur with hypothalamic lesions that affect the thirst center, as can be seen with infiltrative diseases such as sarcoidosis [31]. Low dietary solute intake can contribute to the development of hyponatremia by limiting water excretion even if the secretion of ADH is appropriately suppressed. (See 'Low dietary solute intake' below.)

As in any patient with polydipsia and polyuria, the possibility of diabetes insipidus should be considered in patients with psychiatric illness who present with these symptoms in the absence of hyponatremia. If compliance is possible, we recommend a water restriction test to distinguish between primary polydipsia and diabetes insipidus. An alternative in the uncooperative patient is to increase the plasma osmolality via a slow infusion of hypertonic saline with concomitant measurement of copeptin levels. (See "Evaluation of patients with polyuria".)

Measuring the urine osmolality is also important in polydipsic patients who are hyponatremic. Pure primary polydipsia should be associated with appropriate suppression of ADH release and a urine osmolality below 100 mosmol/kg. A higher urine osmolality, which is often present, suggests at least a contributory role for increased ADH release or responsiveness [12,19,26]. (See "Diagnostic evaluation of adults with hyponatremia".)

There is no proven specific therapy for primary polydipsia with or without hyponatremia in psychotic patients. Acutely, limiting water intake will rapidly raise the plasma sodium concentration as the excess water is readily excreted in a dilute urine. The risk of inducing osmotic demyelination in this setting is unclear [32,33].

Over the long term, limiting the use of drugs that cause dry mouth, restricting fluid intake, and frequent weighing (to detect water retention) all may be helpful. Some clinicians have tried the tetracycline derivative demeclocycline, which induces reversible ADH resistance; however, this

agent has not generally been effective [34]. (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat".)

Low dietary solute intake — Malnourished individuals who drink large quantities of beer (beer potomania) and other malnourished patients (including those with low protein-, high water-intake diets; ie, the "tea and toast syndrome") may have a marked reduction in water excretory capacity that is directly mediated by poor dietary intake [35-37]. Ingestion of a normal diet results in the generation and excretion of 600 to 900 mosmol of solute per day (primarily sodium and potassium salts and urea). Thus, if the minimum urine osmolality is 60 mosmol/kg, the maximum urine output will be 10 to 15 L/day (eg, 900 mosmol/day ÷ 60 mosmol/kg = 15 L).

By contrast, beer contains little or no sodium, potassium, or protein to generate solutes for excretion. In addition, the alcohol and carbohydrate load from beer will suppress endogenous protein breakdown and therefore urea excretion. As a result, daily solute excretion may fall below 250 mosmol and, even with maximal urine dilution, this can reduce the daily free water excretion to below 4 L/day (eg, 240 mosmol/day ÷ 60 mosmol/kg = 4 L). Under these conditions, hyponatremia will ensue if more than 4 L/day of water is ingested (as would be the situation with ingestion of 12 average-sized cans of beer).

In addition, many such patients develop nausea or hypovolemia; this may transiently stimulate ADH, thereby impairing urine dilution and predisposing to or exacerbating hyponatremia.

Impaired urine dilution but normal suppression of ADH

Advanced kidney function impairment — The relative ability of the kidney to excrete free water (ie, the free water excretion divided by the glomerular filtration rate [GFR]) is not substantially impaired in patients with mild to moderate reductions in GFR (eg, GFR >15 mL/min) [38]. Thus, normonatremia is usually maintained in such patients.

By contrast, in severe kidney function impairment (eg, GFR <15 mL/min, as in patients with advanced chronic kidney disease or severe acute kidney injury), the minimum urine osmolality rises to as high as 200 to 250 mosmol/kg despite the appropriate suppression of antidiuretic hormone (ADH) [39]. The obligate increase in solute excretion per functioning nephron is thought to be responsible for the inability to maximally dilute the urine.

The impairment in free water excretion in advanced kidney function impairment can lead to the retention of ingested water and the development of hyponatremia. Although the water retention will also lower the serum osmolality, this will be offset at least in part by the elevation in blood urea nitrogen (BUN). As a result, the measured serum osmolality may be normal or even increased despite hyponatremia. However, because urea is an ineffective osmol, the

tonicity of the extracellular fluid is reduced. The tonicity in such patients can be estimated by subtracting the osmotic contribution of urea from the measured serum osmolality (Sosm):

Tonicity = Measured Sosm - (BUN ÷ 2.8)

Dividing the BUN by 2.8 converts mg/dL into mmol/L, which is required when estimating its contribution to osmolality. If the blood urea is measured in units of mmol/L, the formula is:

Tonicity = Measured Sosm - Blood urea concentration

Diuretic-induced hyponatremia — Hyponatremia, which can be severe, is an important complication of therapy with thiazide diuretics [40,41]. (See "Diuretic-induced hyponatremia".)

Thiazide-induced hyponatremia typically develops soon after the onset of thiazide therapy (within the first one to two weeks) and can recur after rechallenge with the diuretic. Occasionally, hyponatremia may occur months or years after initiation of thiazide therapy, usually during an intercurrent illness that can result in inappropriate ADH secretion. (See 'Syndrome of inappropriate ADH secretion (euvolemic hyponatremia)' below.)

Older women with low body weight are most susceptible to thiazide-induced hyponatremia, and this may be exacerbated in these patients by a large fluid intake and a low dietary solute intake. (See 'Low dietary solute intake' above.)

Patients with thiazide-induced hyponatremia are usually clinically euvolemic, exhibiting many of the features found in patients with inappropriate ADH secretion. (See "Diuretic-induced hyponatremia", section on 'Clinical manifestations'.)

The pathogenesis of thiazide-induced hyponatremia is presented elsewhere. (See "Diuretic-induced hyponatremia", section on 'Pathogenesis'.)

Hyponatremia is only rarely induced by loop diuretics since the inhibition of sodium chloride transport in the loop of Henle impairs the generation of the countercurrent gradient and therefore limits the ability of ADH to promote water retention. When hyponatremia does develop during use of loop diuretics, it usually occurs in patients with heart failure or cirrhosis, conditions that by themselves can cause hyponatremia, or because of overdiuresis, resulting in hypovolemia. (See 'Reduced effective arterial blood volume' below.)

Impaired urine dilution due to unsuppressed ADH secretion — Hypotonic hyponatremia is most commonly caused by failure to suppress antidiuretic hormone (ADH) secretion. Direct measurements of ADH are seldom performed and are rarely helpful because clinically available

assays are unreliable. Rather, in the absence of kidney disease or diuretics, unsuppressed ADH is inferred when the urine is not maximally dilute (ie, a urine osmolality <100 mosmol/kg indicates maximal dilution; higher values indicate an effect of ADH).

Release of ADH is a normal response to an inadequate circulation, otherwise known as "reduced effective arterial blood volume." Hyponatremia due to unsuppressed ADH secretion can be found in patients who are clinically hypovolemic (hypovolemic hyponatremia) and in patients with heart failure or cirrhosis who generally have reduced effective arterial blood volume. These patients are often also edematous (hypervolemic hyponatremia). Hypovolemic and hypervolemic hyponatremia are associated with reduced effective arterial blood volume, a decreased ability to excrete sodium, and urine sodium concentrations that are typically low (except when renal sodium loss is the cause of hypovolemia).

Patients with ADH-induced hyponatremia who are neither hypovolemic nor edematous (euvolemic hyponatremia) are said to have SIADH. Patients with euvolemic hyponatremia due to SIADH are able to excrete sodium normally, and urine sodium concentrations are typically high (reflecting dietary and parenteral sodium intake).

Reduced effective arterial blood volume — The term "reduced effective arterial blood volume" (also called effective circulating volume) refers to the volume of arterial blood that is effectively perfusing the tissues. Reduced effective arterial blood volume can occur by various mechanisms: true volume depletion and reduced tissue perfusion due to a low cardiac output (heart failure) or arterial vasodilation (cirrhosis). Hyponatremic patients with reduced tissue perfusion caused by heart failure or cirrhosis are usually edematous. (See "General principles of disorders of water balance (hyponatremia and hypernatremia) and sodium balance (hypovolemia and edema)", section on 'Effective arterial blood volume'.)

Significantly decreased tissue perfusion is a potent stimulus to the secretion of ADH (figure 2), regardless of whether it is due to true hypovolemia, low cardiac output, or arterial vasodilation. This response is mediated by baroreceptors in the carotid sinus, which sense a reduction in pressure or stretch. The reduced effective arterial blood volume stimulus is sufficiently potent to overcome the inhibitory effect of hypotonicity on ADH secretion. Thus, water retention and hyponatremia can develop in patients with any disorder causing reduced effective arterial blood volume.

True volume depletion (hypovolemic hyponatremia) — True volume depletion can be caused by gastrointestinal fluid losses (eg, vomiting or diarrhea), urinary losses (most often due to diuretic therapy but sometimes from aldosterone deficiency or renal salt wasting), skin losses (eg, exudative skin lesions or burns), sequestration of fluid into a "third space" (eg, severe

pancreatitis, crush injuries), or bleeding. (See "Etiology, clinical manifestations, and diagnosis of volume depletion in adults".)

It has been suggested that some patients with neurologic disorders become hyponatremic because of hypovolemia caused by salt wasting resulting from natriuretic peptides released from a damaged brain. Because it is often uncertain whether cases of purported "cerebral salt wasting" are truly hypovolemic, this entity is discussed as a separate category of hyponatremia. (See 'Cerebral salt wasting' below.)

If enough fluid is lost, activation of baroreceptors in the carotid sinus stimulates release of ADH, thereby impairing urinary dilution. If potassium depletion also occurs, it contributes to the decrease in serum sodium concentration. (See 'Determinants of the serum sodium concentration' below.)

Heart failure and cirrhosis (hypervolemic hyponatremia) — Even though the plasma and extracellular volumes may be markedly increased in heart failure and cirrhosis, the pressure sensed at the carotid sinus baroreceptors is generally reduced due to the fall in cardiac output in heart failure and to arterial vasodilatation in cirrhosis [3,42]. Thus, serum ADH levels tend to reflect the severity of the underlying disease, making hyponatremia an important prognostic sign. A serum sodium that is persistently below 130 mEq/L may be a marker of near end-stage heart or liver disease (figure 3). (See "Hyponatremia in patients with heart failure" and "Hyponatremia in patients with cirrhosis".)

By contrast, hyponatremia is an uncommon finding in patients with the nephrotic syndrome unless the GFR is severely reduced. Nephrotic patients usually have relatively normal tissue perfusion and effective arterial blood volume and therefore do not have a clinically important stimulus to ADH secretion. (See "Pathophysiology and treatment of edema in adults with the nephrotic syndrome", section on 'Volume regulatory hormones'.)

Syndrome of inappropriate ADH secretion (euvolemic hyponatremia) — Persistent antidiuretic hormone (ADH) release and water retention can be seen in a variety of disorders that are not associated with true hypovolemia or reduced effective arterial blood volume. This condition is called the SIADH. Major causes include central nervous system (CNS) disease, malignancy, drugs, and recent surgery.

CNS disturbances — Any central nervous system (CNS) disorder, including stroke, hemorrhage, infection, trauma, and psychosis, can enhance ADH release. As in other causes of SIADH, hyponatremia associated with intracranial bleeding, as well as other severe neurologic events, is due to ADH-mediated water retention and to urinary sodium losses. However, with these severe neurologic conditions, there is uncertainty as to whether the sodium losses are a

result of SIADH-induced expansion of the extracellular volume or whether they are caused by salt wasting (ie, cerebral salt wasting), with release of ADH that is secondary to a reduction in extracellular fluid volume. (See 'Cerebral salt wasting' below.)

Malignancies — Ectopic production of ADH by a tumor is most often due to a small cell carcinoma of the lung and is rarely seen with other lung tumors [43]. Less common causes of malignancy-associated SIADH include head and neck cancer, olfactory neuroblastoma (esthesioneuroblastoma), and extrapulmonary small cell carcinomas [44]. Although SIADH is common in patients with small cell lung cancer, in some cases, these tumors secrete ectopic atrial natriuretic peptide (ANP). High ANP levels cause renal salt excretion and can inhibit aldosterone, thereby generating hypovolemia, which can generate hyponatremia in some patients [43,45,46]. In addition, ectopic ANP secretion may exacerbate hyponatremia caused by SIADH by provoking sodium excretion in a concentrated urine, similar to the "desalination" phenomenon (see 'Surgery' below) but without extracellular fluid volume expansion.

Drugs — Certain drugs can enhance ADH release or effect (table 3) [47-49]. Drugs that commonly cause SIADH are chlorpropamide, carbamazepine, oxcarbazepine (a derivative of carbamazepine), high-dose intravenous cyclophosphamide, and selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline).

Many other drugs have been associated with the SIADH. These include vincristine, vinblastine, vinorelbine, cisplatin, thiothixene, thioridazine, haloperidol, amitriptyline, monoamine oxidase inhibitors, melphalan, ifosfamide, methotrexate, opiates, nonsteroidal antiinflammatory agents, interferon alpha, interferon gamma, sodium valproate, bromocriptine, lorcainide, amiodarone, ciprofloxacin, and high-dose imatinib.

Synthetic phenethylamines are widely abused psychoactive substances that include synthetic cathinones (eg, "bath salts") and amphetamines, such as methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). These agents lead to serotonin-mediated hyponatremia, caused by both inappropriate ADH secretion and excessive water intake [50-61] (see 'Primary polydipsia due to psychosis' above). Hyponatremia due to ecstasy and other phenethylamines may be severe, rapid in onset, and often fatal, particularly in women.

Some medications have been associated with hyponatremia by an unknown mechanism. Data from a national population-based registry in Sweden found that newly initiated (≤90 days) calcium channel blockers were associated with a fourfold increase in the risk of being hospitalized with a principal diagnosis of hyponatremia [62].

Surgery — Surgical procedures are often associated with hypersecretion of ADH, a response that is probably mediated by pain afferents [63]. In addition, hyponatremia may

develop after other types of interventional procedures, such as cardiac catheterization [64]. Acute postoperative hyponatremia is responsible for many of the reported cases of death from cerebral edema, almost exclusively in women and young children.

The administration of large volumes of intravenous fluids after surgery is responsible for the condition. This is particularly true if hypotonic fluids are prescribed, but excessive isotonic fluids after surgery can also lower the serum sodium concentration, because high levels of ADH concentrate the urine, allowing administered sodium to be excreted in a volume of urine that is smaller than the infused volume; the result is net electrolyte-free water retention. This phenomenon has been referred to as "desalination" of intravenous fluids.

Exacerbation of SIADH due to desalination is particularly common in patients with postoperative SIADH because such patients are often given large volumes of intravenous fluid. It can also occur in other causes of SIADH when there is an attempt to correct hyponatremia with isotonic saline.

Hyponatremia is a common late complication of transsphenoidal pituitary surgery [65]. (See "Arginine vasopressin deficiency (central diabetes insipidus): Etiology, clinical manifestations, and postdiagnostic evaluation".)

Pulmonary disease — Pulmonary diseases, particularly pneumonia (viral, bacterial, tuberculous), can lead to the SIADH, although the mechanism by which this occurs is not clear [66]. A similar response may infrequently be seen with asthma, atelectasis, acute respiratory failure, and pneumothorax [67].

Hormone deficiency — Both hypopituitarism and hypothyroidism may be associated with hyponatremia and an SIADH picture that can be corrected by hormone replacement. (See "Hyponatremia and hyperkalemia in adrenal insufficiency" and 'Hypothyroidism' below.)

Hypothyroidism — Hyponatremia is sometimes associated with hypothyroidism, particularly in patients with severe primary hypothyroidism and myxedema [68-72]. Thus, thyroid function should be evaluated in any patient with otherwise unexplained hypotonic hyponatremia.

However, because hypothyroidism and hyponatremia are each relatively common disorders in hospitalized patients, their coexistence may not necessarily be causal. Other explanations for hyponatremia should be sought unless hypothyroidism is severe. In patients with severe myxedema, decreased cardiac output can lead to the release of ADH via the carotid sinus baroreceptors, and decreased GFR may also be a contributing cause of hyponatremia [69,70,73]. However, some patients fulfill criteria for SIADH since the urine sodium is not low, as

would be expected if a reduced cardiac output or kidney function impairment were responsible [74].

Some have questioned whether hypothyroidism deserves its traditional listing as a cause of clinically important hyponatremia [75]. Although higher levels of thyroid-stimulating hormone (TSH) are correlated with lower serum sodium concentrations, the magnitude of this association is clinically negligible. However, symptomatic, severe hyponatremia has been reported in patients with metastatic thyroid carcinoma after withdrawal of thyroid hormone replacement to enhance the effect of radioactive iodine [76].

Adrenal insufficiency — The hypersecretion of ADH seen with cortisol deficiency may be in part due to the reductions in systemic blood pressure and cardiac output (via an unknown mechanism) and the interruption of a negative feedback loop in which cortisol suppresses ADH release [77]. Secondary adrenal insufficiency (hypopituitarism), caused by deficient secretion of adrenocorticotropic hormone (ACTH) by the pituitary, presents with euvolemic hyponatremia with biochemical features of SIADH without hyperkalemia or hypovolemia. This is in contrast to primary adrenal insufficiency (Addison disease), in which aldosterone deficiency also generates salt wasting and hypovolemia, which stimulates ADH secretion. These issues are discussed in detail elsewhere. (See "Hyponatremia and hyperkalemia in adrenal insufficiency".)

Cortisol deficiency should be evaluated in all patients with SIADH of unknown etiology.

Hormone administration — Administration of certain hormones, specifically vasopressin (to control gastrointestinal bleeding), desmopressin (dDAVP; to treat von Willebrand disease, hemophilia, or platelet dysfunction), or oxytocin (to induce labor), can induce SIADH [78]. As with vasopressin and desmopressin, oxytocin acts by increasing the activity of the vasopressin-2 (V2; antidiuretic) receptor [79].

HIV infection — Acquired immunodeficiency syndrome (AIDS) or early symptomatic HIV infection is commonly associated with hyponatremia [80]. Although volume depletion (due, for example, to gastrointestinal losses) or adrenal insufficiency may be responsible, many patients have the SIADH. Pneumonia, due to *Pneumocystis jirovecii* or other organisms, CNS infections, and malignant disease, is most often responsible in this setting [80]. (See "Electrolyte disturbances with HIV infection".)

Idiopathic SIADH — Idiopathic syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been described primarily in older adult patients [81]. However, some cases of apparently idiopathic disease were later found to be caused by an occult tumor (most often small cell carcinoma or olfactory neuroblastoma), unsuspected hypopituitarism, and, in older patients, giant cell (temporal) arteritis.

Impaired urine dilution due to nephrogenic SIADH — The clinical picture of syndrome of inappropriate antidiuretic hormone secretion (SIADH) may result from a gain-of-function mutation affecting the gene for the renal V2 receptor [82]. The gene for the V2 receptor is located on the X chromosome, and loss-of-function mutations of the gene are responsible for X-linked nephrogenic diabetes insipidus. (See "Arginine vasopressin resistance (nephrogenic diabetes insipidus): Etiology, clinical manifestations, and postdiagnostic evaluation", section on 'Hereditary AVP-R'.)

This hereditary disorder was first described in male infants but has subsequently been identified in adults, including heterozygous females. Some affected patients are overtly hyponatremic, and some have normal serum sodium concentrations, except when confronted with a large water load. Patients with the first described mutation do not respond to vasopressin antagonists, whereas a second variant results in a vasopressin receptor that can be inhibited by these agents.

Abnormally low osmostat — In some patients, the threshold plasma tonicity that suppresses release of ADH is abnormally low. The body regulates the serum sodium around an altered threshold, which becomes the new set-point for the serum sodium; ADH is suppressed when the serum sodium falls below this value but is released when the serum sodium is above this value.

Acquired reset osmostat of chronic illness — Mild, stable hyponatremia can be found in patients with a variety of chronic illnesses. Severe hyponatremia does not occur, because, when water is ingested, the urine becomes dilute and ingested water is excreted. When the serum sodium concentration rises, the urine becomes more concentrated, as in normal subjects. These responses suggest that hypothalamic osmoreceptors are responding normally but to a lower-than-normal serum sodium concentration. The condition has been called a "reset osmostat." (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat", section on 'Reset osmostat'.)

Genetic reset osmostat — Polymorphisms in the genes encoding the hypothalamic osmoreceptor, transient receptor potential cation channel subfamily V member 4 (*TRPV4*), may cause mild hyponatremia [6]. Affected individuals would be expected to behave as if they have a reset osmostat, with a lower-than-normal serum sodium concentration that regulates normally around that value. The variant hypofunctioning allele could potentially result in unrestricted drinking, and, therefore, more severe hyponatremia, if people harboring the polymorphism were to develop SIADH for another reason. (See "Treatment of hyponatremia: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and reset osmostat", section on 'Reset osmostat'.)

Reset osmostat of pregnancy — The release of human chorionic gonadotropin during pregnancy may be responsible for a mild resetting of the osmostat downward that is responsible for a fall in the serum sodium concentration of approximately 5 mEq/L [83]. (See "Maternal adaptations to pregnancy: Renal and urinary tract physiology".)

Exercise-associated hyponatremia — Individuals who participate in prolonged exercise, such as marathon and ultramarathon runners, can develop potentially severe hyponatremia that is primarily due to excessive water intake combined, in many cases, with impaired water excretion due to persistent ADH secretion (due, for example, to pain or nausea). (See "Exercise-associated hyponatremia".)

A sudden exacerbation of hyponatremia can occur at the end of the race due to delayed absorption of ingested water from the gastrointestinal tract.

Cerebral salt wasting — A rare syndrome has been described in patients with cerebral disease that mimics all of the findings in the SIADH except that salt wasting is thought to be the primary defect, with the ensuing volume depletion causing a secondary rise in ADH release [84]. This distinction is not easy to make, since the true volume status of the patient is often difficult to ascertain. Patients with subarachnoid hemorrhage are typically treated with large volumes of isotonic saline in an effort to preserve cerebral perfusion. Since SIADH is a common complication of subarachnoid hemorrhage, infused saline may provoke a large volume of concentrated, salt-rich urine and hyponatremia due to desalination (see 'Surgery' above). Patients with SIADH and desalination may be misdiagnosed as having cerebral salt wasting.

Calculation of the fractional excretion of uric acid (FEUA) before and after correction of hyponatremia has been proposed as a way of distinguishing SIADH from cerebral salt wasting [85]. According to this theory, before correction of hyponatremia, FEUA is >11 percent in both SIADH and salt wasting. Conversely, after correction of hyponatremia, a FEUA that remains >11 percent is said to indicate salt wasting, caused by impaired proximal tubule sodium reabsorption, whereas a FEUA <11 percent identifies patients with SIADH. However, serial measurements of FEUA have not been validated with a consistent, rigorous, and convincing gold standard for identifying salt wasting [86-88]. For this reason, the diagnostic validity of these measurements is unproven.

The pathogenesis, manifestations, and treatment of cerebral salt wasting are discussed separately. (See "Cerebral salt wasting".)

DETERMINANTS OF THE SERUM SODIUM CONCENTRATION

Understanding the factors that determine the serum sodium concentration is required to appreciate how they promote the development of hyponatremia and what the composition of intravenous fluids must be to correct the hyponatremia.

In the following discussion, the term "tonicity" (also called the effective plasma osmolality) refers to the osmotic activity of solutes that do not easily cross cell membranes and therefore determine the transcellular distribution of water.

The extracellular and intracellular fluids are in osmotic equilibrium since water moves freely across most cell membranes. As a result, plasma tonicity is equal to the effective intracellular osmolality and to the effective osmolality of the total body water (TBW). These relationships can be summarized by the following equation:

$$\text{Plasma tonicity} = \frac{\text{Osmotically active solute (Extracellular + Intracellular)}}{\text{TBW}}$$

Soluble sodium cations (Na) and their associated extracellular anions are the primary effective extracellular solutes, and soluble potassium cations (K) and their associated intracellular anions are the primary intracellular solutes; these solutes are the major determinants of the effective plasma osmolality. Notably, a large fraction of the body's sodium and, to a lesser extent, potassium is not free in solution [6]. These cations not in solution are bound to anionic sites on proteoglycans in bone, cartilage, and connective tissue. The number of anionic sites on these macromolecules may vary in response to, as yet undefined, physiological stimuli. Flux between bound and soluble electrolytes may occur, and bound sodium is a potential reservoir for soluble solute. It is the soluble solute and not the bound solute that contribute to tonicity.

Plasma tonicity (effective plasma osmolality) can therefore be expressed as:

$$\text{Plasma tonicity} \approx \frac{([2 \times \text{Soluble Na}] + [2 \times \text{Soluble K}])}{\text{TBW}}$$

The multiplier 2 accounts for the osmotic contributions of the anions accompanying sodium and potassium. In the absence of large amounts of other osmotically active solute in the extracellular fluid, the above equation can be simplified to:

$$2 \times \text{Plasma Na} \approx \frac{([2 \times \text{Soluble Na}] + [2 \times \text{Soluble K}])}{\text{TBW}}$$

and then to:

$$\text{Plasma Na} \approx \frac{\text{Soluble (Na + K)}}{\text{TBW}}$$

As shown in the figure, this relationship applies over a wide range of plasma or serum sodium concentrations (figure 4) [89].

Glucose is the other major extracellular solute that can generate "tonicity." However, in the absence of marked hyperglycemia, glucose present in a much lower molar concentration than sodium (eg, 5 mmol/L [90 mg/dL] versus 140 mmol/L) is not a major determinant of plasma tonicity.

Urea is considered an ineffective osmole since it freely equilibrates across cell membranes. When the plasma concentration of an ineffective osmole changes, the solute rapidly moves into or out of cells to equalize the concentrations. Thus, in contrast to water shift induced by changes in the plasma sodium concentration, changes in the plasma urea concentration usually result in little or no water shift into or out of cells (dialysis disequilibrium is an exception to this rule). (See "Dialysis disequilibrium syndrome".)

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".)

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

- Hyponatremia is commonly defined as a serum sodium concentration below 135 mEq/L, but the definition can vary to a small degree in different clinical laboratories. Most patients with hyponatremia have hypotonicity, but there are exceptions (table 1). (See 'Introduction' above.)

- Hypotonic hyponatremia results from the intake (either oral or intravenous) and subsequent retention of water. The major defense against hyponatremia is the capacity to excrete large volumes of urine with a low concentration of sodium and potassium (ie, electrolyte-poor water). Thus, a water load will, in normal individuals, be rapidly excreted as the dilutional fall in serum tonicity suppresses the release of antidiuretic hormone (ADH) (figure 1), thereby allowing excretion of the excess water in a dilute urine. In contrast to the response in normal individuals, patients who develop hyponatremia typically have an impairment in renal water excretion, most often due to an inability to suppress ADH secretion. An uncommon exception occurs in patients with primary polydipsia who can become hyponatremic because they rapidly drink such large quantities of fluid that they overwhelm the excretory capacity of the kidney even though ADH release is appropriately suppressed. (See 'Pathogenesis of and defense against hypotonic hyponatremia' above.)

- We classify the causes of hypotonic hyponatremia according to the body's ability to excrete dilute urine and, if that is impaired, the reason for the impairment (table 2) (see 'Classification of hypotonic hyponatremia' above):

  - Patients with hyponatremia who have unimpaired urine dilution include those with primary polydipsia due to psychosis and in those with a low dietary solute intake (ie, a "tea and toast diet" or "beer potomania"). (See 'Unimpaired urine dilution' above.)

- Patients who have hyponatremia due to impaired urine dilution (but with normal suppression of ADH) include those with advanced kidney function impairment and those with thiazide-induced hyponatremia. (See 'Impaired urine dilution but normal suppression of ADH' above.)

- Patients with hyponatremia caused by to impaired urine dilution due to unsuppressed ADH secretion may have reduced effective arterial blood volume (ie, true volume depletion, heart failure, or cirrhosis) or may be euvolemic (ie, the syndrome of inappropriate ADH secretion [SIADH], which can result from a variety of etiologies). (See 'Impaired urine dilution due to unsuppressed ADH secretion' above and "Pathophysiology and etiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)".)

- Hyponatremic patients with impaired urine dilution due to nephrogenic SIADH have a gain-of-function mutation affecting the gene for the renal V2 vasopressin receptor. (See 'Impaired urine dilution due to nephrogenic SIADH' above.)

- Patients with hyponatremia due to reset osmostat have a threshold plasma tonicity that suppresses release of ADH that is abnormally low. The body regulates the serum sodium around this altered threshold, which becomes the new set-point for the serum sodium; ADH is suppressed when the serum sodium falls below this value but is released when the serum sodium is above this value. Reset osmostat may be acquired in patients with chronic illness, may be due to human chorionic gonadotropin in pregnant women, or may result from a genetic mutation. (See 'Abnormally low osmostat' above.)

- Individuals who participate in exercise (especially but not limited to prolonged athletic events such as marathon and ultramarathon running) can develop potentially severe hyponatremia that is primarily due to excessive water intake combined, in many cases, with impaired water excretion due to persistent ADH secretion. (See 'Exercise-associated hyponatremia' above.)

- A rare syndrome has been described in patients with cerebral disease that mimics all of the findings in the SIADH except that salt wasting is thought to be the primary defect, with the ensuing volume depletion causing a secondary rise in ADH release. (See 'Cerebral salt wasting' above.)

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Topic 2374 Version 40.0

GRAPHICS

Measured serum osmolality and sodium in causes of hyponatremia

Condition	Measured serum osmolality	Serum sodium by autoanalyzer	Serum sodium by direct ion-selective electrode
Normal patient	Normal	Normal	Normal
Hypotonic hyponatremia	Low	Low	Low
Hyperglycemia or intravenous mannitol or immune globulin	High	Low	Low
Absorbed surgical irrigants	Normal*	Low	Low
Pseudohyponatremia due to hyperlipidemia or hyperproteinemia	Normal	Low	Normal

Bedside blood gas analyzers measure serum sodium using a direct ion-selective electrode. Occasionally, laboratories will have an autoanalyzer that uses a direct ion-selective electrode.

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* After absorption of large volumes of 1.5% glycine, the serum osmolality may be only slightly reduced, with an extremely low serum sodium concentration.

Courtesy of Richard H Sterns, MD.

Graphic 116018 Version 2.0

Major causes of hypotonic hyponatremia

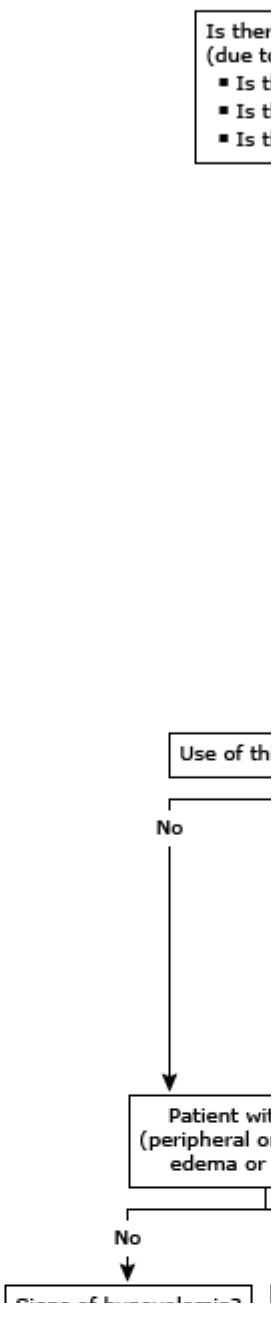
Disorders in which ADH levels are not elevated
Primary polydipsia due to psychosis
Low dietary solute intake (beer drinker's potomania, tea and toast diet)
Disorders with impaired urine dilution but normal suppression of ADH
Advanced renal impairment
Diuretic-induced hyponatremia
Disorders with impaired urine dilution due to unsuppressed ADH secretion
Reduced effective arterial blood volume
True volume depletion (hypovolemic hyponatremia)
Heart failure and cirrhosis (hypervolemic hyponatremia)
Addison's disease
SIADH (euvolemic hyponatremia)
CNS disturbances
Malignancies
Drugs
Surgery
Pulmonary disease
Hormonal deficiency (secondary adrenal insufficiency and hypothyroidism)*
Hormone administration (vasopressin, desmopressin, oxytocin)
Acquired immunodeficiency syndrome
Impaired urine dilution due to abnormal V2 receptor (nephrogenic SIADH)
Abnormally low osmostat
Acquired reset osmostat of chronic illness
Genetic reset osmostat
Reset osmostat of pregnancy
Exercise-induced hyponatremia
Cerebral salt wasting

ADH: antidiuretic hormone; SIADH: syndrome of inappropriate ADH secretion; CNS: central nervous system; V2: vasopressin receptor 2.

* Although sometimes placed in a separate category, we include secondary adrenal insufficiency due to hypopituitarism as a cause of SIADH because it presents with similar clinical manifestations as other causes of the syndrome. Hypothyroidism must be severe to cause clinically important hyponatremia.

Graphic 77603 Version 11.0

Determining the cause of hyponatremia in adults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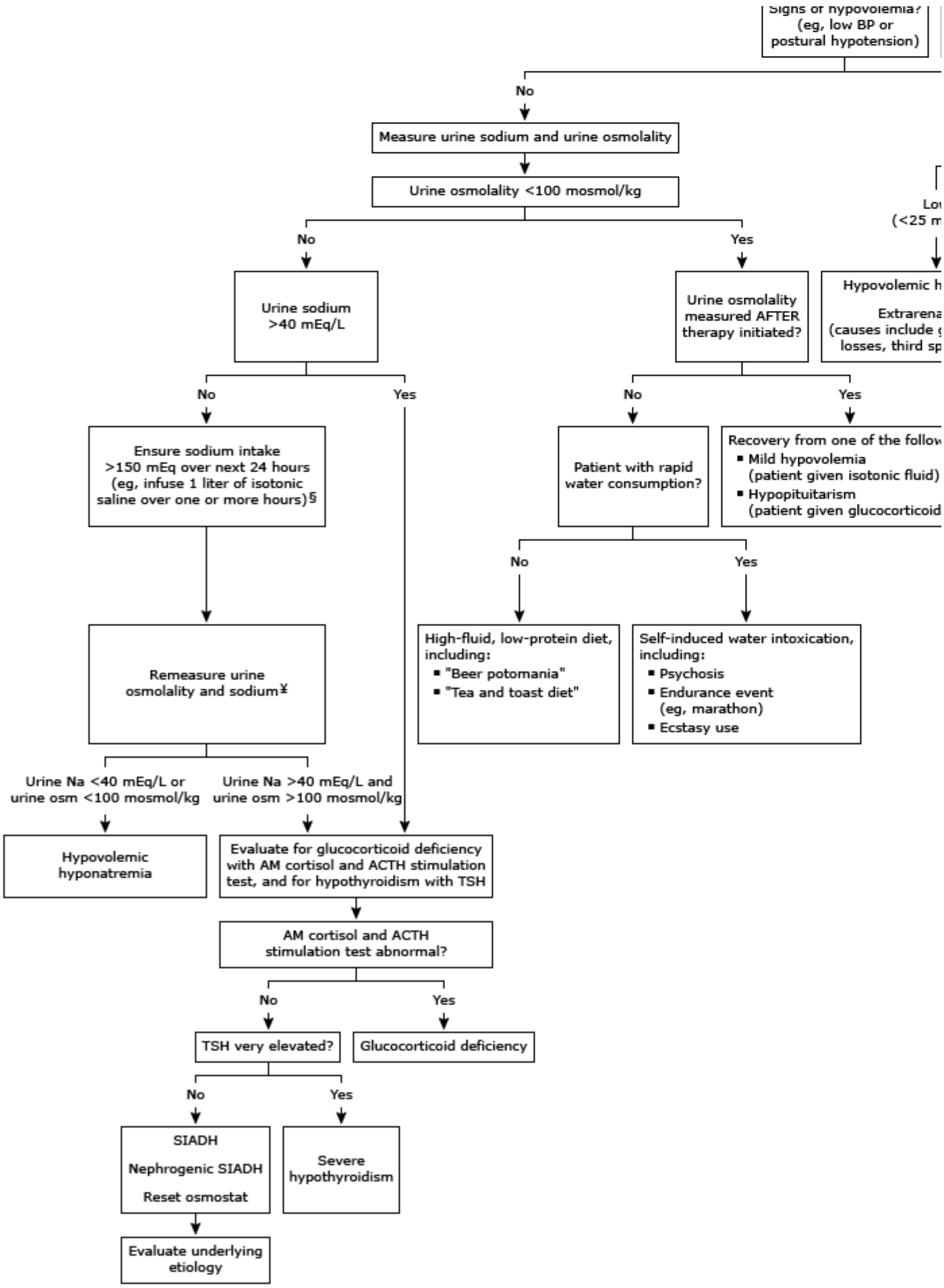

Signs of hypovolemia? (eg, low BP or postural hypotension)
No
Measure urine sodium and urine osmolality
Urine osmolality <100 mosmol/kg
No
Yes
Urine sodium >40 mEq/L
Urine osmolality measured AFTER therapy initiated?
Hypovolemic h
Extrarena
(causes include
losses, third sp
No
Yes
No
Yes
Ensure sodium 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.

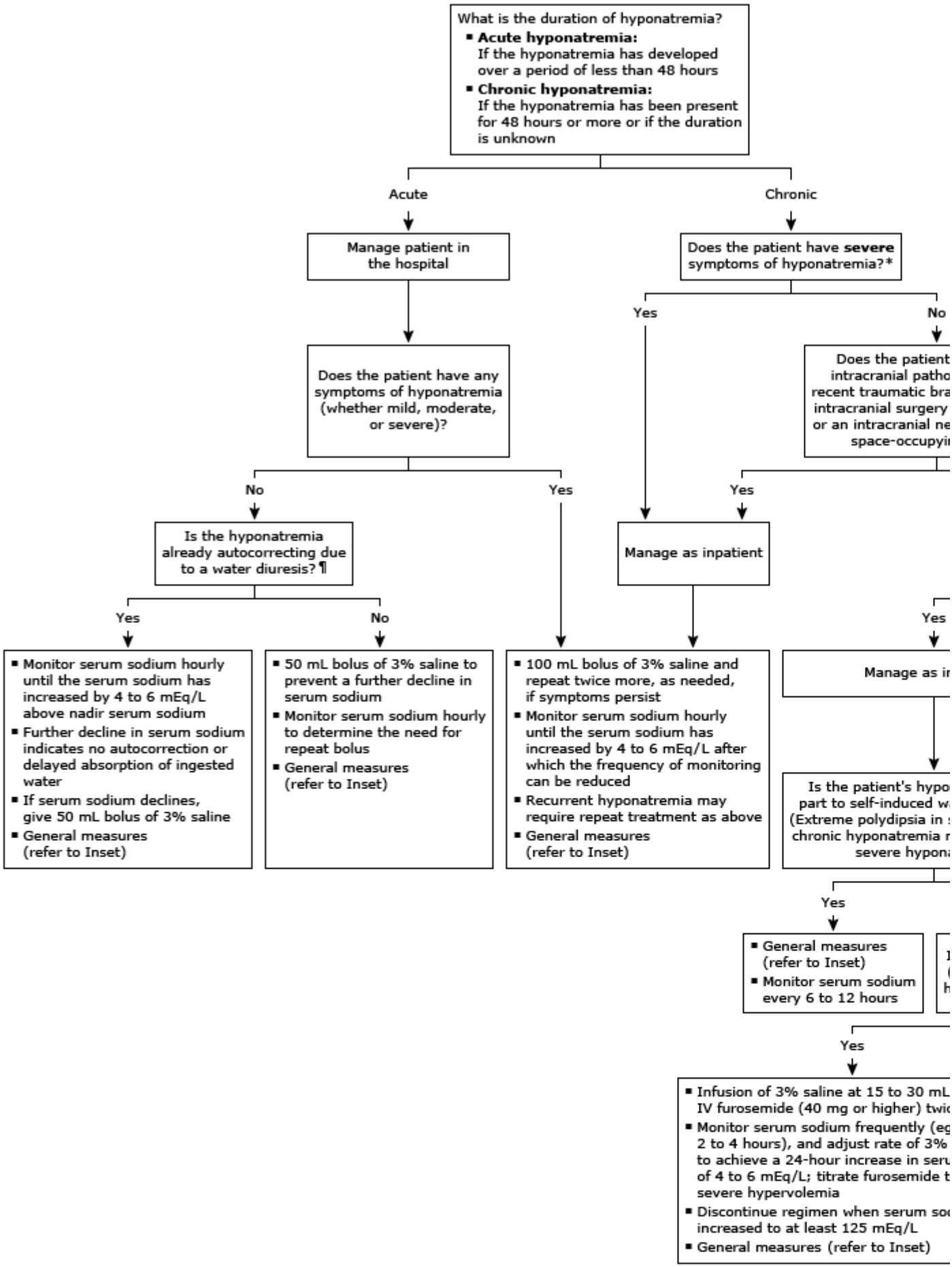
◇ Patients with hypovolemic hyponatremia due to diuretics may have a low urine sodium if the effect of the diuretic has worn off.

§ 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

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.

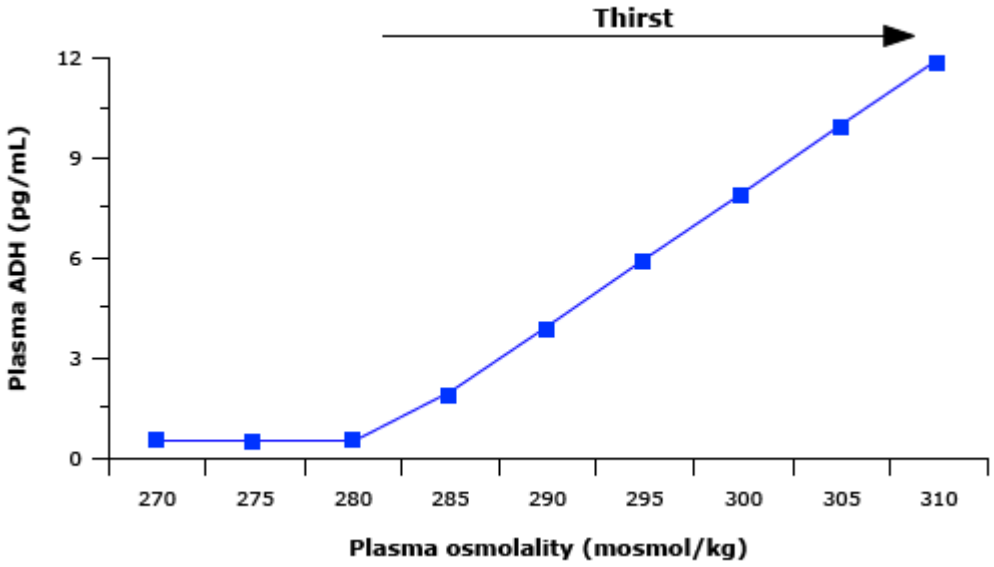
* Severe symptoms of hyponatremia include seizures, obtundation, coma, and respiratory arrest.

¶ 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

Osmotic regulation of ADH release and thirst



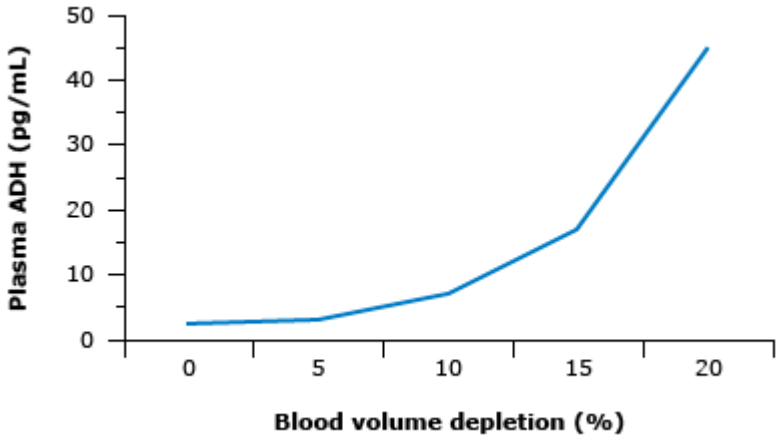
Relation between plasma ADH concentration and plasma osmolality in normal humans in whom the plasma osmolality was changed by varying the state of hydration. The osmotic threshold for thirst is a few mosmol/kg higher than that for ADH.

ADH: antidiuretic hormone.

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

Graphic 65195 Version 5.0

Hypovolemic stimulus to ADH release



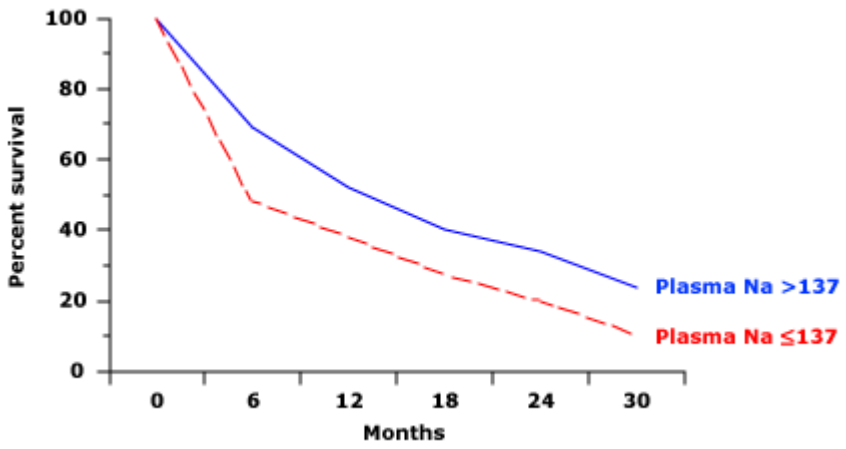
Relationship of plasma ADH concentrations to isosmotic changes in blood volume in the rat. Much higher ADH levels can occur with hypovolemia than with hyperosmolality, although a relatively large fall in blood volume is required before this response is initiated.

ADH: antidiuretic hormone.

Data from: Dunn FL, Brennan TJ, Nelson AE, et al. J Clin Invest 1973; 52:3212.

Graphic 58012 Version 3.0

Hyponatremia associated with reduced survival in patients with severe chronic heart failure



Survival over time in patients with severe chronic heart failure and a left ventricular ejection fraction less than 30% who, at study entry, had either a normal plasma sodium concentration (greater than 137 mEq/L, solid line) or hyponatremia (plasma sodium less than or equal to 137 mEq/L, dashed line). Survival was significantly reduced in the patients with hyponatremia. The survival rate was very low (approximately 15% at 12 months) in those with a baseline plasma sodium concentration less than or equal to 130 mEq/L.

Data from: Lee WH, Packer M. Circulation 1986; 73:257.

Graphic 55554 Version 3.0

Drugs associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Antidepressants
SSRIs
Tricyclic
MAOI
Venlafaxine
Antiseizure medications
Carbamazepine
Sodium valproate
Lamotrigine
Antipsychotics
Phenothiazines
Butyrophenones
Anticancer drugs
Vinca alkaloids
Platinum compounds
Ifosfamide
Melphalan
Cyclophosphamide
Methotrexate
Pentostatin
Antidiabetic drugs
Chlorpropamide
Tolbutamide
Vasopressin analogues
Desmopressin
Oxytocin
Terlipressin
Vasopressin

Miscellaneous
Opiates
MDMA (ecstasy)
Levamisole
Interferon
NSAIDs
Clofibrate
Nicotine
Amiodarone
Proton pump inhibitors
Monoclonal antibodies
Linezolid

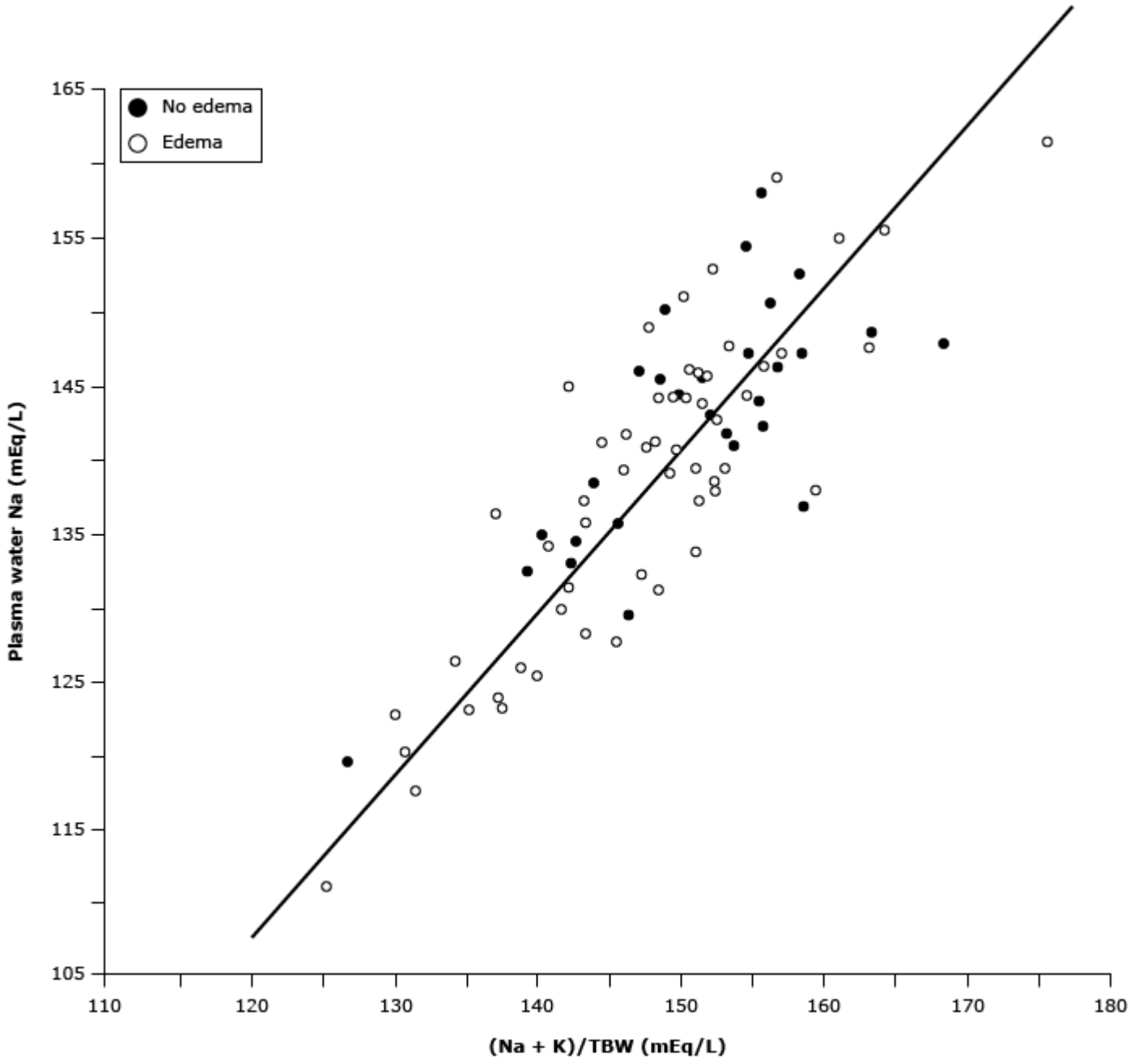
SSRIs: selective serotonin reuptake inhibitors; MAOI: monoamine oxidase inhibitor; MDMA: 3,4-methylenedioxymethamphetamine; NSAIDs: nonsteroidal antiinflammatory drugs.

Adapted from:

1. *Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Neprhol Dial Transplant 2014; 29 Suppl 2:i1.*
2. *Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis 2008; 52:144.*

Graphic 118898 Version 5.0

Determinants of the plasma sodium concentration



Among both normal subjects and patients with a variety of diseases, there is a very close correlation between the plasma water sodium concentration and the ratio of total body exchangeable solutes (primarily Na salts in the extracellular fluid + K salts in the cells) to the TBW. The exchangeable portion is used since approximately 30% of the body Na and a smaller fraction of the body K are bound in areas such as bone where they are "nonexchangeable" and therefore osmotically inactive.

Na: sodium; K: potassium; TBW: total body water.

Adapted from Edelman I, Leibman J, O'Meara MP, et al. J Clin Invest 1958; 37:1236, by copyright permission of the American Society for Clinical Investigation.

Graphic 71817 Version 4.0