Etiology and evaluation of hypernatremia in adults

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INTRODUCTION

The term "tonicity," also called "effective osmolality," refers to the activity of solutes that do not easily cross cell membranes (effective osmoles) and therefore determine the transcellular distribution of water. Because sodium and its anions make up most of the effective osmoles in the extracellular fluid, a high plasma sodium concentration (hypernatremia) indicates hypertonicity and a decrease in cell volume [1,2]. In most cases, hypernatremia results from water depletion. This develops when water losses are not replaced because water is unavailable, when the urge to drink is impaired, or because patients cannot seek water for themselves. Abnormally large unreplaced water losses (as an example, due to an arginine vasopressin disorder [formerly called diabetes insipidus]) result in a rapid onset of hypernatremia. However, even with large water losses, hypernatremia will not develop if thirst is intact and water is available. (See 'The importance of thirst' below.)

Although hypernatremia is most often due to water loss, it can also be caused by the intake of salt without water or the administration of hypertonic sodium solutions [3]. (See 'Sodium overload' below.)

Hypernatremia due to water depletion is called **dehydration**. This is different from **hypovolemia**, in which both salt and water are lost [3]. (See "General principles of disorders of water balance (hyponatremia and hypernatremia) and sodium balance (hypovolemia and edema)".)

The causes and evaluation of hypernatremia will be reviewed in this topic (table 1). The treatment of patients with hypernatremia is discussed separately. (See "Treatment of hypernatremia in adults".)

Prior to discussing the etiology and evaluation of hypernatremia, it is helpful to review the determinants of the plasma sodium concentration.

DETERMINANTS OF THE PLASMA SODIUM CONCENTRATION

To appreciate why hypernatremia develops and how it responds to treatment, the factors that determine the plasma sodium concentration must be understood.

Solute concentrations (or osmolalities) in the extracellular and intracellular fluids must be equal because water moves freely across most cell membranes. Owing to Na-K-ATPase, which pumps sodium out of cells in exchange for potassium, sodium is largely extracellular, and potassium is intracellular. However, because osmotic gradients are quickly abolished by water movement, body fluids can be conceptualized as a single "tub" containing sodium, potassium, and water. Thus, one would expect the concentration of sodium in plasma water to equal the concentration of sodium plus potassium in total body water (TBW) [4]. This theoretical relationship was proven to be true by experiments that used isotopes to measure body contents of sodium, potassium, and water in patients with a wide range of plasma sodium concentrations (figure 1).

Approximately 30 percent of total body sodium is bound to large polyanionic molecules called proteoglycans, which make up the ground substance of bone, cartilage, and connective tissue [1]. The amount of bound sodium can vary, and long-term balance studies demonstrate that excess sodium can accumulate in body tissues without altering the serum sodium concentration and without expanding extracellular fluid volume [5-7]. For clinical purposes, bound sodium can be ignored, although this introduces an error in formulas that predict the serum sodium. However, this error is overshadowed by errors that result from other sources: inaccuracies in estimating TBW from total body weight, problems accounting for the intake and loss of electrolytes and water, and rapid changes in urinary losses [7,8].

Considering just the portions of body sodium and potassium that are unbound and free in solution, the relationship between the plasma sodium concentration and body electrolyte and water contents is described by the following simple equation, where Na is sodium and K is potassium:

$$\text{Plasma Na concentration} = \frac{\text{Total body (Na + K)}}{\text{TBW}}$$

The plasma sodium concentration is altered by net sodium and potassium balance (which affects the numerator of the equation) and water balance (which affects the denominator of the equation). To understand changes that occur in the plasma sodium concentration, one must consider the overall tonicity of fluids that are taken in as well as the overall tonicity of fluids that are lost from the body. Just like the plasma sodium concentration, which is determined by the concentrations of sodium and potassium in body water, the tonicity of other fluids, including intravenous fluids, urine, gastrointestinal fluids, and sweat, are also determined by their concentrations of sodium plus potassium.

The effects of an intravenous fluid or loss of bodily fluids on the plasma sodium concentration depend upon the tonicity of the fluid (determined by the sodium and potassium concentration) and **not** the osmolality of the fluid. As an example, 5 percent dextrose in water (D5W) has an osmolality close to that of normal plasma; the osmolality of D5W allows it to be infused without causing hemolysis, but D5W will lower the plasma sodium concentration because it contains no electrolytes. Similarly, the effect of urinary losses on the plasma sodium concentration depends upon the urine sodium and potassium concentrations and not urine osmolality (which depends in part upon other electrolytes, urea, and glucose). Large volume losses of isosmolar or hyperosmolar urine, for example, may raise the plasma sodium if the urine is relatively electrolyte free.

Application to hypernatremia — Hypernatremia is most often due to unreplaced water loss but can also be induced by the administration of hypertonic saline or the ingestion sodium chloride. The intake of potassium without water will have the same effect on the serum sodium as the intake of sodium without water. As an example, the administration of potassium to treat hypokalemia will raise the serum potassium concentration. However, most of the administered potassium will enter the cells, which will cause the osmotic movement of water from the extracellular fluid into the cells, resulting in a small increase in serum sodium unless there is concurrent water intake.

The importance of the sodium plus potassium in lost body fluids as a determinant of the serum sodium concentration (figure 1) can be illustrated by considering the composition of various gastrointestinal fluids:

- Patients with secretory diarrheas (cholera, VIPoma) have a sodium plus potassium concentration in the diarrheal fluid that is similar to the plasma sodium concentration

[9,10]. Loss of this fluid will lead to both a fall in extracellular fluid volume and potassium depletion but will not directly affect the serum sodium concentration.

- By contrast, many viral and bacterial enteritides and the osmotic diarrhea induced by lactulose (to treat hepatic encephalopathy) or charcoal-sorbitol (to treat a drug overdose) are associated with an isosmotic diarrheal fluid that has a sodium plus potassium concentration between 40 and 100 mEq/L [9,11,12]; organic solutes, which do not affect the serum sodium concentration, make up the remaining osmoles. Unreplaced loss of this fluid will tend to induce hypernatremia because water is being lost in excess of sodium plus potassium [11,13]. Similar considerations apply to urinary losses during an osmotic diuresis induced by glucose, mannitol, or urea [14,15] (see below).

- The sodium plus potassium concentration in vomitus and sweat is similar to that in nonsecretory forms of diarrhea [16-18]. In one study, for example, the sodium plus potassium concentration in gastric fluid was well below that of the plasma, averaging approximately 50 to 55 mEq [16]. Thus, loss of this fluid will tend to raise the serum sodium even though the fluid is isosmotic to plasma. Hydrochloric acid accounts for most of the gap between the osmolality of gastric fluid and the contributions of sodium and potassium [16]. The loss of hydrochloric acid has no effect on the serum sodium.

Thus, when considering either the etiology or treatment of hypernatremia, it is the **sodium plus potassium** concentration in the fluid lost or the fluid given, **not the osmolality**, that determines the effect on the serum sodium. In patients who are both hypernatremic and hypokalemic, the addition of potassium to the administered fluid will diminish the amount of electrolyte-free water that is given, thereby limiting the reduction in serum sodium. (See "Treatment of hypernatremia in adults", section on 'If concurrent electrolyte replacement is necessary'.)

THE IMPORTANCE OF THIRST

Hypernatremia can be produced by either the administration of hypertonic sodium solutions or, much more commonly, by the loss of electrolyte-free water [19-24]. However, salt intake and water loss seldom result in hypernatremia because the ensuing rise in plasma tonicity stimulates both the release of arginine vasopressin (AVP, also called antidiuretic hormone) and thirst, thereby minimizing further water loss and increasing water intake [19,24,25]. The decrease in water loss and increase in water intake then lower the serum sodium concentration back to normal. (See "General principles of disorders of water balance (hyponatremia and hypernatremia) and sodium balance (hypovolemia and edema)".)

This regulatory system is so efficient that the plasma osmolality is maintained within a range of 1 to 2 percent despite wide variations in sodium and water intake. Even patients with an AVP disorder (formerly called diabetes insipidus) maintain a near-normal serum sodium concentration by appropriately increasing water intake to replace large urinary water losses caused by diminished AVP effect.

As a result, hypernatremia is seen primarily in patients who cannot experience or respond to thirst normally due to impaired mental status (eg, older adult or critically ill patients) and in infants who can experience thirst but require others to provide fluid intake [19-23,26]. In a retrospective review of 103 hospitalized adults who had hypernatremia on admission or developed it after admission, 86 percent lacked free access to water, 94 percent received less than 1000 mL of electrolyte-free water per day, and many had impaired water conservation due to decreased concentrating ability (primarily due to diuretic therapy) [21]. Older adult patients also appear to have diminished osmotic stimulation of thirst via an unknown mechanism [27,28].

Hospitalized patients, whether old or young, can become hypernatremic as a result of an inadequate fluid prescription and/or impaired thirst [21,29]. The above retrospective review included 85 adults with hospital-acquired hypernatremia, 94 percent of whom received less than one liter of electrolyte-free fluid per day [21]. Many hospitalized older adult patients also develop volume depletion because of sodium and water losses due to diuretics, vomiting, or diarrhea coupled with reduced intake.

Individuals who are alert and have access to water should not develop hypernatremia. Alert patients who are not thirsty despite a serum sodium concentration of 150 mEq/L or more have, by definition, a hypothalamic lesion affecting the thirst center. (See 'Hypothalamic lesions affecting thirst or osmoreceptor function' below.)

ETIOLOGY OF HYPERNATREMIA

There are three mechanisms by which hypernatremia can occur: unreplaced water loss, which is by far the most common cause; water loss into cells; and sodium overload. However, persistent hypernatremia should not occur in patients who are alert, have an intact thirst mechanism, and have access to water.

Unreplaced water losses — The loss of solute-free water will, if unreplaced, lead to an elevation in the serum sodium concentration. As described above, the serum sodium concentration and osmolality are determined by the ratio between total body effective osmoles

(primarily sodium and potassium salts) and the total body water (TBW) (figure 1). Loss of fluid with a **sodium plus potassium concentration less than that in the plasma** will, if the water loss is not replaced, raise the serum sodium concentration [13]. (See 'Determinants of the plasma sodium concentration' above and 'Application to hypernatremia' above.)

There is a variety of sources of electrolyte-free water loss that can lead to hypernatremia [24]. These include skin, gastrointestinal, and urinary losses.

Skin losses — Water loss from the skin consists of both insensible (transepidermal by diffusion) and sensible (sweat) losses and is important for thermoregulation. Under normal conditions, the volume of sweat is approximately 500 to 700 mL/day in adults. However, sweat losses are increased dramatically by fever, exercise, and exposure to high temperatures.

Sweat is derived from the extracellular fluid, and most of the sodium is then removed by the sweat glands. The normal mean sweat sodium concentration is approximately 38 to 45 mEq/L (range 24 to 65 mEq/L), and the mean sweat potassium concentration is approximately 5 mEq/L [30,31]. As the rate of sweat production increases, the serum sodium concentration rises since sweat is hypotonic to plasma (ie, lower sodium plus potassium concentration), which will promote free water loss [30,32,33].

The obligatory water loss from sweat and transdermal evaporative losses must be replaced to avoid hypernatremia. As an example, exclusively breast-fed neonates with a weight loss of more than 10 percent of birth weight are at risk for hypernatremia if inadequate breast-feeding fails to replace ongoing insensible water losses [34,35].

In contrast to water loss in sweat or from evaporation, water that enters alveolar air and is eliminated by breathing does **not** result in net water loss from the body [36]. Partial pressures of water and CO_2 are nearly identical in alveolar air in patients with a normal arterial pCO_2, and thus are eliminated in a 1:1 ratio. Because water and CO_2 are produced in a 1:1 ratio by metabolism of carbohydrates and fatty acids, the loss of water through respiration is equal to its metabolic production.

Gastrointestinal losses — Both upper and lower gastrointestinal losses can result in hypernatremia when water intake is limited. As mentioned above, loss of gastric secretions (due to vomiting or drainage), and small intestinal secretions, have a sodium plus potassium concentration well below that in the plasma and will therefore promote the development of hypernatremia. Similar considerations apply to osmotic diarrheas but not to secretory diarrheas, which have a sodium plus potassium concentration similar to that in the plasma, the loss of which will not directly affect the serum sodium concentration. (See 'Application to hypernatremia' above.)

Urinary losses — Free water loss in the urine can lead to hypernatremia if not replaced. This is most often a problem in patients with an arginine vasopressin disorder or an osmotic diuresis.

AVP deficiency or resistance (central or nephrogenic diabetes insipidus) — Decreased release of arginine vasopressin (AVP, also called antidiuretic hormone) or renal resistance to its effect (AVP deficiency and AVP resistance, respectively) causes the excretion of a relatively dilute urine. Most patients with an arginine vasopressin disorder have a normal thirst mechanism [37]. As a result, they typically present with polyuria and polydipsia, and a high-normal serum sodium concentration, which is required to stimulate thirst. (See "Arginine vasopressin deficiency (central diabetes insipidus): Etiology, clinical manifestations, and postdiagnostic evaluation" and "Arginine vasopressin resistance (nephrogenic diabetes insipidus): Etiology, clinical manifestations, and postdiagnostic evaluation" and "Evaluation of patients with polyuria".)

However, marked and symptomatic hypernatremia can occur in patients with an AVP disorder if a central lesion impairs both AVP release and thirst, in infants and young children who cannot independently access free water, in the postoperative period in patients with an unrecognized AVP disorder, and in older adult patients with AVP resistance caused by lithium therapy [38-41]. (See 'Adipsic diabetes insipidus' below.)

An acute onset of AVP deficiency often results in hypernatremia if the diagnosis is delayed. Acute AVP deficiency occurs most commonly following transsphenoidal or transcranial surgery for pituitary tumor, traumatic brain injury, and subarachnoid hemorrhage [42].

In patients with known AVP deficiency who are admitted to the hospital, omission of desmopressin is common because clinical staff often fail to recognize its critical importance; this omission has resulted in tragic and fatal consequences [43,44]. Between 2009 and 2015, 471 adverse incidents were reported to the National Health Service of England involving desmopressin treatment [44]. Prescription of the incorrect dose and dose omission were the most common errors. Four of these dose omissions resulted in death due to severe hypernatremia. A web-based survey found that 24 percent of 1034 patients with AVP deficiency reported problems accessing desmopressin during routine or emergency hospitalizations, most commonly due to nonavailability; 71 of 535 patients hospitalized for any medical reason reported symptoms of dehydration when they failed to receive desmopressin while fasting without intravenous fluid replacement [44].

In patients with severe illness, desmopressin should be given parenterally [43]. Prescription of home doses of oral desmopressin may predispose to hypernatremia in patients who are vomiting or receiving nothing by mouth; similarly, intranasal desmopressin may be ineffective

because of nasal mucosal inflammation or congestion or because of improper administration to patients unable to cooperate because of illness [42,45].

Unreplaced water losses in patients with complete AVP deficiency or resistance can produce a rapid onset of hypernatremia and may result in osmotic demyelination, similar to the injury caused by a rapid elevation in serum sodium in patients with chronic hyponatremia [46]. A rapid onset of hypernatremia is particularly injurious when desmopressin is withheld from patients with AVP deficiency admitted for hyponatremia [47], a common complication of outpatient desmopressin therapy [42,43,45]. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia".)

Osmotic diuresis — An osmotic diuresis due to nonreabsorbed, nonelectrolyte solutes such as glucose, mannitol, or urea increases the output of urine that has a sodium plus potassium concentration well below serum [14,15]. The loss of such fluid would be expected to raise the serum sodium concentration. However, the changes in plasma osmolality and serum sodium concentration associated with osmotic diuresis are complex.

As an example, patients with diabetic ketoacidosis or nonketotic hyperglycemia present with a high serum osmolality due to both hyperglycemia and the osmotic diuresis. However, the serum sodium concentration is variable, reflecting the balance between the hyperglycemia-induced increase in serum tonicity, which promotes water movement out of the cells that will lower the serum sodium, and the glucosuria-induced osmotic diuresis, which will tend to raise the serum sodium. (See "Diabetic ketoacidosis and hyperosmolar hyperglycemic state in adults: Clinical features, evaluation, and diagnosis", section on 'Serum sodium'.)

Similar considerations apply to mannitol therapy. The initial rise in serum mannitol will lower the serum sodium due to osmotic water movement out of the cells. However, in the absence of impaired kidney function, mannitol is rapidly excreted in the urine and the associated osmotic diuresis will raise the serum sodium due both to the removal of mannitol from the plasma, which will allow water to move back into the cells, and to the osmotic diuresis, which will cause water loss in excess of sodium plus potassium. (See "Complications of mannitol therapy", section on 'Complications'.)

Unlike hyperglycemia and mannitol therapy, patients who have an osmotic diuresis due to urea (which most commonly occurs during the resolution of azotemia) can produce hypernatremia but not hyponatremia. Because urea is an ineffective osmole, water does not move out of cells, and therefore the elevated serum urea concentrations do not lower the serum sodium. As urea is excreted in the urine, the loss of water in the urine will raise the serum sodium concentration.

Hypothalamic lesions affecting thirst or osmoreceptor function — Hypernatremia can occur in the absence of increased water losses if there is primary hypothalamic disease impairing thirst (hypodipsia) [24,25]. A defect in thirst with or without concomitant AVP deficiency can be seen in children with either congenital or acquired hypothalamic structural lesions [25,48]. As an example, infants with holoprosencephaly (dysplasia of the brain midline structures) may show no signs of thirst even when their serum osmolality exceeds 330 mosmol/kg [49,50]. In such patients, forced water intake is usually sufficient to maintain a normal serum sodium concentration, although AVP deficiency, if present, must also be treated. (See "Arginine vasopressin deficiency (central diabetes insipidus): Treatment".)

Adipsic diabetes insipidus — When AVP secretion and thirst are both impaired, affected patients are vulnerable to recurrent episodes of hypernatremia. Once called essential hypernatremia, this disorder is now called adipsic diabetes insipidus or AVP deficiency with deficient thirst. Causes of adipsic diabetes insipidus include a variety of congenital and acquired central nervous system lesions, with the most common being septo-optic dysplasia, germinoma, rupture or clipping aneurysms of the anterior communicating artery of the circle of Willis, craniopharyngioma, and central nervous system sarcoidosis [38,51,52]. Measurement of subjective thirst using a visual analogue scale is a simple and useful diagnostic adjunct to the investigation of polyuric states; absent osmoregulated thirst during water deprivation or hypertonic saline infusion is the gold standard for the diagnosis of adipsic hypernatremia [42].

Adipsic diabetes insipidus was once thought to result from an upward resetting of the osmostat, such that a higher osmolality was recognized as normal. This hypothesis was based upon the observation that giving these patients water reduced AVP release. However, subsequent studies showed that the water-induced suppression of AVP was due to mild volume expansion rather than a fall in serum osmolality [24,53,54]. True upward resetting of the osmostat has been described only in patients with primary mineralocorticoid excess (such as primary aldosteronism). It is presumed that the suppressive effect of chronic mild volume expansion on AVP release is responsible for the resetting; the serum sodium concentration in these patients is usually between 143 and 147 mEq/L [55,56]. (See "Pathophysiology and clinical features of primary aldosteronism", section on 'Mild hypernatremia'.)

Patients with adipsic diabetes insipidus typically have moderate to severe hypernatremia with the serum sodium in one review ranging from 155 to 190 mEq/L in most patients [38]. Most of these patients are asymptomatic because the hypernatremia is chronic. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Hypernatremia'.)

In all patients with adipsic diabetes insipidus, a careful neurologic and radiologic evaluation should be performed, looking for a possible treatable disease (such as a benign tumor) that

might restore osmoreceptor function.

Adipsic diabetes insipidus accompanied by autoantibodies to the Na(x) channel, a sodium-sensing receptor in the hypothalamus, has been described in young patients with hypernatremia, no thirst, and low vasopressin response to hypertonicity [57,58]. In contrast to classical cases of adipsic diabetes insipidus, in which structural abnormalities of the hypothalamic area are easily seen with magnetic resonance imaging, no such lesions are identified in these cases. Na(x) channels, which respond to changes in the plasma sodium concentration, are preferentially expressed in the glial cells of sensory circumventricular organs (subfornical organ and organum vasculosum lamina terminalis), and have been shown to control sodium craving and drinking behavior in animal models [59].

Treatment of adipsic diabetes insipidus — The optimal therapy of patients with adipsic diabetes insipidus is uncertain. Urinary water losses can be controlled with desmopressin, as in patients with AVP deficiency who have intact thirst. However, with no sense of thirst as a guide, both hyponatremia from too much fluid intake and hypernatremia from too little fluid intake are common. The goal of therapy is to maintain a serum sodium concentration between 130 and 150 mEq/L.

Many patients can be taught to regulate their water intake using a sliding scale based upon body weight [60]. If the patient has complete AVP deficiency, we have given desmopressin as often as three times daily to minimize urine losses and therefore limit variability. The body weight at which the serum sodium concentration is normal is determined periodically and the daily water prescription required to maintain a constant body weight and a serum sodium concentration within the target range is determined by trial and error. Deviations from the established ideal weight are then used to modify the water prescription for that day, decreasing or increasing water intake by 500 mL for every 0.5 kg deviation in body weight. A deviation of more than 3 percent of body weight in either direction is an indication to check the serum sodium concentration.

Daily measurements of the serum sodium may be necessary, particularly in young children and adults with cognitive impairment who cannot regulate their own water intake to achieve the goal body weight. Point-of-care devices capable of measuring the serum sodium on finger stick specimens can be used.

There is some evidence that chlorpropamide, which increases the renal effect of AVP, can also improve impaired thirst in patients with AVP deficiency [61,62]. (See "Arginine vasopressin deficiency (central diabetes insipidus): Treatment", section on 'Other drugs'.)

Water loss into cells — Transient hypernatremia (in which the serum sodium concentration can rise by as much as 10 to 15 mEq/L within a few minutes) can be induced by severe exercise or electroshock-induced seizures, an effect that is mediated by a transient increase in cell osmolality [63-65]. Breakdown of large complex organic molecules into numerous small components is thought to be at least in part responsible for the increase in cell osmolality [65].

The serum sodium concentration returns to normal within 5 to 15 minutes after the cessation of exertion or seizure activity.

Sodium overload — Acute and often marked hypernatremia (in which the serum sodium concentration can exceed 200 mEq/L) can be induced by the administration of hypertonic sodium solutions. Examples include accidental or nonaccidental salt poisoning in infants and young children, the infusion of hypertonic sodium bicarbonate to treat metabolic acidosis, administration of hypertonic saline to patients with traumatic head injury, hypertonic saline irrigation of hydatid cysts, systemic absorption of intrauterine hypertonic saline administered to induce abortion, and massive salt ingestion as can occur with a highly concentrated saline emetic or gargle [66-74].

Salt poisoning — Salt poisoning is an infrequent problem that primarily occurs in infants and young children but has been reported in adults [75]. The following scenarios have been described in different studies:

- Surreptitious intentional salt poisoning is one of the more common forms of child abuse [66]. A teaspoon of salt contains 100 mEq of Na, which can increase the serum sodium concentration in a 10 kg child by 17 mEq/L.
- The accidental substitution of salt for sugar in infant formulas resulted in an epidemic of severe hypernatremia in a hospital nursery [76].
- In parts of Turkey, the custom of "salting" of newborns by grandparents, who scrub the baby's entire body with table salt for an hour, can lead to systemic absorption of salt through the traumatized skin, possibly causing severe hypernatremia [77].

Salt poisoning causes a rapid onset of hypernatremia, often resulting in cerebral hemorrhage and irreversible neurologic injury. Osmotic demyelination can occur, similar to the injury caused by a rapid elevation in serum sodium in patients with chronic hyponatremia [78]. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia".)

Salt poisoning has a number of distinguishing features from unreplaced water loss which, as noted above, is the most common cause of hypernatremia [74] (see 'Unreplaced water losses'

above):

- Salt poisoning is initially associated with weight gain, due to the stimulation of both thirst, which increases fluid intake, and AVP release, which diminishes water loss. On the other hand, unreplaced water losses severe enough to produce hypernatremia are associated with weight loss. However, there are two potential limitations to the use of changes in body weight. First, this distinction requires accurate knowledge of the child's baseline weight, which may not be available. Second, weight gain with salt poisoning requires access to water. If the child does not drink, there may actually be a reduction in body weight due to the osmotic diuresis induced by excretion of the excess sodium.

- Sodium excretion is appropriately increased with salt poisoning and is appropriately reduced with hypovolemia due to unreplaced water losses. The urine sodium concentration may be misleading since a highly concentrated urine due to hypernatremia-induced stimulation of AVP release can raise an appropriately low urine sodium concentration to a value that might be consistent with euvolemia.

- The fractional excretion of sodium (FENa) may be more accurate than the urine sodium concentration since it is not affected by the urine volume. It has been suggested that, in infants and young children with hypernatremia and normal kidney function, a FENa greater than 2 percent is strongly suggestive of salt poisoning and values between 1 and 2 percent are consistent with the diagnosis [74].

  By contrast, in patients with relatively normal kidney function, a FENa less than 0.1 to 0.2 percent is suggestive of hypernatremia caused by water loss [79]. A similar finding would be expected with a late presentation of salt poisoning, after the administered salt has been excreted and hypovolemia has been induced by the osmotic diuresis, or if the patient has concomitant salt poisoning and hypovolemia.

  One problem with the use of the FENa is that the values that define volume depletion vary with the filtered sodium load, which is determined by the glomerular filtration rate. The FENa that defines hypovolemia progressively rises toward 1 percent in patients with increasingly impaired kidney function. These issues are discussed in detail elsewhere. (See "Fractional excretion of sodium, urea, and other molecules in acute kidney injury".)

Treatment of salt poisoning — The duration of hypernatremia is typically less than 24 hours by the time patients with salt poisoning are seen by a clinician. At this time, the cerebral adaptation to hypernatremia is incomplete, minimizing any risk of neurologic injury from overly rapid correction of the hypernatremia, as can occur in chronic hypernatremia. Thus, the initial therapy is directed at rapid reduction in the serum sodium concentration to reduce the

neurologic risk of prolonged severe hypernatremia. (See "Manifestations of hyponatremia and hypernatremia in adults", section on 'Hypernatremia'.)

Rapid correction of hypernatremia can be accomplished in two ways:

- Rapid infusion of 2.5 percent dextrose in water – The initial rate at which this fluid should be administered can be calculated from the estimated water deficit plus estimated ongoing fluid losses (mostly insensible losses). This issue is discussed in detail elsewhere. (See "Treatment of hypernatremia in adults", section on 'Estimating the water deficit' and "Treatment of hypernatremia in adults", section on 'Designing the fluid repletion regimen'.)

  A 2.5 percent solution is preferred to the usual 5 percent solution to minimize the risk of hyperglycemia, even in patients without diabetes mellitus, due to the high glucose load with large volumes of dextrose in water. (See "Maintenance and replacement fluid therapy in adults", section on 'Dextrose-induced hyperglycemia'.)

- Acute dialysis – Patients with acute salt poisoning occasionally develop acute kidney injury and oliguria [69]. In such patients, dialysis should be used to rapidly reduce the serum sodium while avoiding fluid overload [80].

There are no reports of complications related to overly rapid correction of acute salt poisoning, but aggressive therapy may be lifesaving. As an example, one severely hypernatremic patient who presented with coma and seizures two hours after ingesting a quart of soy sauce survived after receiving 6 liters of free water over 30 minutes [73].

The prognosis of acute salt poisoning is poor regardless of the treatment chosen, most likely because treatment is initiated after irreversible neurologic injury has already occurred. In a review of 30 cases of acute salt poisoning, overall mortality was greater than 50 percent [69]. The survival rate was better in young children and with lesser degrees of hypernatremia. Neither the rate of correction of the serum sodium nor the type of therapy (hypotonic fluids versus dialysis) predicted survival.

Iatrogenic sodium loading — The administration of isotonic saline to match hypotonic fluid losses causes hypernatremia by net salt gain, equivalent to the effect of administering hypertonic saline. This scenario can occur during the treatment of various common disorders, including the following:

- Uncontrolled diabetes, in which an osmotic diuresis from nonreabsorbed glucose is replaced with isotonic solutions.

- Recovery from severe azotemia, in which a urea (osmotic) diuresis is replaced with isotonic saline.
- Nasogastric suction, in which patients often receive isotonic saline to replace fluid losses that have sodium plus potassium concentrations well below that of plasma. (See 'Application to hypernatremia' above.)
- Edematous, critically ill patients who have received large volumes of saline and then receive loop diuretic therapy, which impairs renal concentrating ability resulting in inappropriately high water losses [81,82].

Hypervolemic hypernatremia is managed by reversing the process that created the disturbance. Loop diuretics are administered to induce hypotonic urinary losses, and 5 percent dextrose in water (D5W) is administered to match these losses [83]. The net effect is salt loss with positive free water gain.

Thiazide diuretics are theoretically attractive because their mechanism of action promotes sodium loss with electrolyte-free water retention. However, a small, placebo-controlled trial of 50 critically ill patients showed that hydrochlorothiazide in a dose of 25 mg per day was not effective, possibly because of the high prevalence of acute kidney injury (13 of 25 thiazide-treated patients) [84].

Prevention of hypernatremia in the intensive care may be achieved by adjusting the tonicity of infused fluids to the urine [81,82], using less normal saline to dilute drugs and keep catheters open [85], and restricting high-protein enteral nutrition [86].

EVALUATION OF HYPERNATREMIA

The cause of the hypernatremia is usually evident from the history. In adults, it is most often due to water losses in older patients whose losses are not replaced because of impaired mental status (table 1). On the other hand, a hypothalamic lesion affecting the thirst center should be strongly suspected in an alert patient with access to water who has a serum sodium concentration above 150 mEq/L. (See 'Hypothalamic lesions affecting thirst or osmoreceptor function' above.)

Diagnostic approach — If the etiology of hypernatremia is unclear, the diagnosis can usually be established by measurement of the urine osmolality and, if the urine osmolality is less than 600 mosmol/kg, observing the change in urine osmolality after administration of exogenous arginine vasopressin (AVP, also called antidiuretic hormone) [87].

A rise in the serum sodium concentration is associated with a rise in the plasma osmolality, which is a potent stimulus to both AVP release and thirst (figure 2). A plasma osmolality above 295 mosmol/kg (which represents a serum sodium concentration above 145 to 147 mEq/L) generally leads to sufficient AVP secretion to maximally stimulate urinary concentration.

Thus, if both hypothalamic and kidney function are intact, the urine osmolality in the presence of hypernatremia should be above 600 mosmol/kg and, if given, exogenous AVP should **not** produce a further rise in the urine osmolality. These basic principles permit the following approach to identifying the cause of hypernatremia:

- **Urine osmolality is low or intermediate** – If the urine osmolality is less than the plasma osmolality (usually less than 300 mosmol/kg), then the patient has either AVP deficiency or AVP resistance. These disorders can be distinguished by the administration of exogenous AVP followed by monitoring of the urine osmolality and volume every 30 minutes over the next two hours [87]. (See "Evaluation of patients with polyuria" and "Arginine vasopressin deficiency (central diabetes insipidus): Etiology, clinical manifestations, and postdiagnostic evaluation" and "Arginine vasopressin resistance (nephrogenic diabetes insipidus): Etiology, clinical manifestations, and postdiagnostic evaluation".)

  If the urine osmolality is intermediate (between 300 to 600 mosmol/kg), the hypernatremia may be due to an osmotic diuresis or to an AVP disorder. In such patients, the presence of an osmotic diuresis can be confirmed by measuring total solute excretion (equal to the product of the urine osmolality and the daily urine volume). The normal value on a regular diet is 600 to 900 mosmol per day (consisting primarily of sodium, potassium, ammonium salts, and urea). A value well above 1000 mosmol per day suggests at least a contribution from increased solute excretion. Patients with an osmotic diuresis and hypernatremia will not respond to exogenous AVP, since the endogenous effect is already maximal. If an osmotic diuresis is not present, an evaluation to rule out an AVP disorder should be performed. (See "Evaluation of patients with polyuria" and "Evaluation of patients with polyuria", section on 'Solute (osmotic) diuresis'.)

- **Urine osmolality is high** – A urine osmolality >700 mosmol/kg indicates adequate AVP levels, and the patient does not have AVP deficiency [42]. If the urine osmolality is above 600 mosmol/kg in a dehydrated patient, hypernatremia is most likely due to extrarenal water losses, but a partial AVP disorder is still possible. Repeat measurements of urine and plasma osmolality should be obtained as the patient is treated with hypotonic fluids. If the urine becomes dilute while the plasma osmolality is still higher than normal, then the diagnosis is partial AVP deficiency or resistance [88]. If the urine osmolality remains above 600 mosmol/kg, then both the secretion of and response to endogenous AVP are intact. In

this setting, unreplaced gastrointestinal, renal, or insensible losses are present or, rarely, sodium overload or a primary defect in thirst may be responsible for the hypernatremia [87]. Measurement of the urine sodium concentration may help to distinguish among these disorders:

- The urine sodium should be less than 25 mEq/L when water loss and volume depletion are the primary problems, as with vomiting or diarrhea. However, values somewhat higher than 25 mEq/L do not necessarily exclude hypovolemia, since there may also be a high rate of water reabsorption; in this setting, the rate of sodium excretion is low but the urine sodium concentration is higher than expected due to a low urine volume. Calculation of the fractional excretion of sodium (FENa), using either standard units (calculator 1) or SI units (calculator 2), may be helpful since it eliminates the effect of urine volume. However, the FENa value used to define hypovolemia is much lower than the 1 percent cutoff used in acute kidney injury. In patients with a normal glomerular filtration rate, for example, the FENa cutoff may be less than 0.1 percent because of the high filtered sodium load. (See "Etiology, clinical manifestations, and diagnosis of volume depletion in adults", section on 'Urine sodium concentration' and "Fractional excretion of sodium, urea, and other molecules in acute kidney injury".)

- The urine sodium is typically well above 100 mEq/L following the ingestion of salt or infusion of a hypertonic sodium solution [67].

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: Fluid and electrolyte disorders in adults".)

SUMMARY AND RECOMMENDATIONS

- **Pathogenesis** – Hypernatremia is a relatively common problem particularly among young children, older adults, and critically ill who depend upon others to control their water intake. (See 'Introduction' above.)

  Hypernatremia occurs when osmotically active electrolytes (sodium and potassium) are retained without water, when water is lost without these electrolytes, or a combination of these two. (See 'Determinants of the plasma sodium concentration' above.)

Salt intake and water loss seldom result in hypernatremia because the ensuing rise in plasma osmolality stimulates the release of both arginine vasopressin (AVP, also called antidiuretic hormone) and thirst, thereby minimizing further water loss and increasing water intake. (See 'The importance of thirst' above.)

- **Etiology**

  - **Loss of body fluids** – Loss of body fluids with a sodium plus potassium concentration lower than the serum sodium will increase the serum sodium concentration if these losses are unreplaced. Common examples of hypotonic losses include:

    - Upper gastrointestinal fluid (see 'Gastrointestinal losses' above)
    - Diarrhea caused by osmotic cathartics like lactulose or infections (see 'Gastrointestinal losses' above)
    - Urinary losses due to an AVP disorder (formerly called diabetes insipidus), glycosuria, urea, and osmotic or loop diuretics (see 'Osmotic diuresis' above)

  - **Hypothalamic disease** – Hypernatremia can occur in the absence of increased water losses if there is primary hypothalamic disease impairing thirst (hypodipsia), sometimes associated with concurrent AVP deficiency (also called adipsic diabetes insipidus). In such patients, forced water intake is usually sufficient to maintain a normal serum sodium concentration, although in patients with adipsic diabetes insipidus, desmopressin must also be given. (See 'Hypothalamic lesions affecting thirst or osmoreceptor function' above and 'Treatment of adipsic diabetes insipidus' above.)

  - **Translocation of water into cells** – Transient hypernatremia can develop after seizures or intense exercise. The ensuing increase in intracellular osmolality via break down of glycogen into smaller more osmotically active molecules leads to internal shift of water into cells. (See 'Water loss into cells' above.)

  - **Salt intake**

    - Acute and often marked hypernatremia can be induced by massive salt ingestion or administration of hypertonic sodium-containing solutions. In such patients, initial therapy is directed at rapid reduction in the serum sodium concentration to reduce the neurologic risk of prolonged severe hypernatremia. (See 'Salt poisoning' above.)

    - The administration of isotonic saline to match hypotonic fluid losses causes hypernatremia by net salt gain, equivalent to the effect of administering

hypertonic saline. This scenario commonly occurs during the treatment of uncontrolled diabetes, recovering azotemia, nasogastric suction, and critically ill patients who have received large amounts of saline and subsequently treated for edema using loop diuretics. (See 'Iatrogenic sodium loading' above.)

- **Evaluation** – The cause of the hypernatremia is usually evident from the history. In adults, it is most often due to water losses in older patients that are not replaced because of impaired mental status (table 1). (See 'Evaluation of hypernatremia' above.)

  If the etiology of hypernatremia is unclear, the diagnosis can usually be established by measurement of the urine osmolality and, if the urine osmolality is less than 600 mosmol/kg, observing the change in urine osmolality after administration of exogenous AVP. (See 'Diagnostic approach' above.)

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Topic 2376 Version 26.0

GRAPHICS

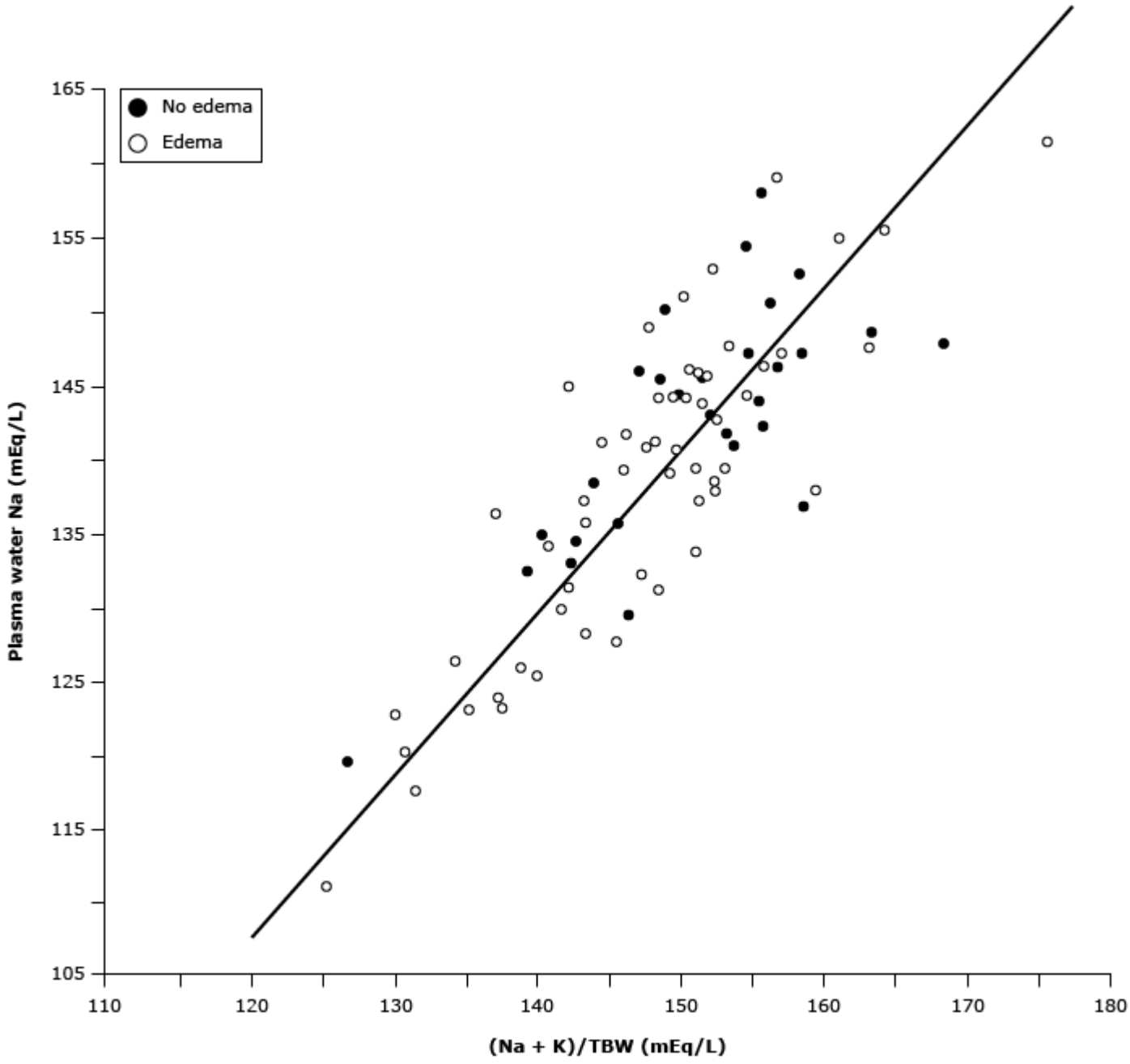
Major causes of hypernatremia

Unreplaced water loss (which requires an impairment in either thirst or access to water)
Insensible and sweat losses
Gastrointestinal losses
Central or nephrogenic diabetes insipidus
Osmotic diuresis
Glucose in uncontrolled diabetes mellitus
Urea in high-protein tube feedings or recovery from azotemia
Mannitol
Hypothalamic lesions impairing thirst or osmoreceptor function
Primary hypodipsia
Reset osmostat in mineralocorticoid excess
Water loss into cells
Severe exercise or seizures
Sodium overload
Intake or administration of hypertonic sodium solutions
ICU-acquired positive solute balance

ICU: intensive care unit.

Graphic 69879 Version 4.0

Determinants of the plasma sodium concentration



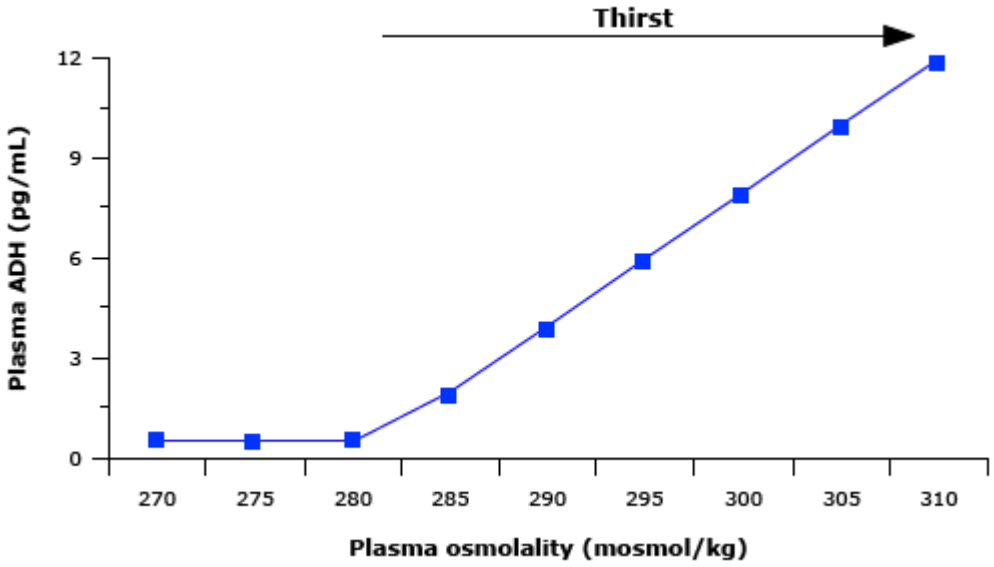
Among both normal subjects and patients with a variety of diseases, there is a very close correlation between the plasma water sodium concentration and the ratio of total body exchangeable solutes (primarily Na salts in the extracellular fluid + K salts in the cells) to the TBW. The exchangeable portion 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

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