

Hyponatremia

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LEARNING OBJECTIVES

1. Compare and contrast the pathophysiological mechanisms of hyponatremia.
2. Explain adaptations that occur as a result of reduced extracellular fluid tonicity.
3. Describe the pathophysiological outcome of low intracellular osmolyte concentration.
4. List considerations for correction of hyponatremia

ABSTRACT

Hyponatremia is biochemically defined by a blood sodium concentration ($[Na^+]$) below the normal reference range for the laboratory performing the test (typically <135 mmol/L). The clinical relevance of a below normal blood $[Na^+]$ is largely determined by the severity of the clinical signs and symptoms associated with cellular swelling. Severe hyponatremia may induce seizures, coma and cardiopulmonary arrest. However, mild to moderate hyponatremia may present with more non-descript symptoms such as lethargy, restlessness, disorientation, headache, nausea and vomiting, muscle cramps, and depressed neural reflexes. Low $[Na^+]$ can be caused by: 1) fluid overload (hypervolemia); 2) abnormal fluid retention (euvoolemia); or 3) volume depletion (hypovolemia) or some likely combination. Morbidity and mortality from hyponatremia has been documented in infants fed dilute formula, children forced to drink excessive amounts of fluid as punishment, athletes who drink excessively during exercise, compulsive water drinkers (psychogenic polydipsia), and hospitalized patients receiving excessive amounts of intravenous fluids. Poor clinical outcomes and delayed recovery have been documented in patients with hyponatremia, compared to those who maintain normonatremia. Thus, the secret stories of *hyponatremia* often whisper tales of harm (overzealous fluid ingestion or administration) with the intention of good (prevent dehydration) except in the severely deranged (child abuse) or demented

(schizophrenic psychogenic polydipsia).

ABBREVIATIONS: $[Na^+]$ – sodium concentration, ADH - anti-diuretic hormone, AVP – arginine vasopressin, EAF - exercise associated hyponatremia, ECF – extracellular fluid, RAAS - renin-angiotensin-aldosterone system, SIADH - syndrome of anti-diuretic hormone secretion

INDEX TERMS: Water intoxication, over-hydration, sodium imbalance, SIADH, arginine vasopressin

Clin Lab Sci 2016;29(3):168-175

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Definition and Diagnosis

Hyponatremia (hypo = low; natremia = sodium in the blood) is a biochemical diagnosis in which the sodium content (in millimoles) in relationship to a liter of plasma water is below the range of normal for the laboratory performing the test. For most laboratories, hyponatremia represents any blood $[Na^+]$ below 135 mmol/L. Both the magnitude and rapidity of blood $[Na^+]$ decline influence the severity of clinical signs, symptoms and prognostic outcomes from hyponatremia. Generally speaking, the lower the blood $[Na^+]$ value, the more dire the clinical outcomes. For example, in one cohort study involving 196 hospitalized patients, a plasma sodium concentration below 130 mmol/L was associated with an 11.20% fatality rate, whereas a plasma sodium concentration above 130

mmol/L was associated with a 0.19% fatality rate. Furthermore, the mortality rate in patients with a plasma sodium concentration less than 120 mmol/L was 25.0% whereas the mortality rate in patients with a minimal plasma sodium concentration above 120 mmol/L was 9.3%.¹ A patient with a blood $[Na^+]$ level as low as 99 mmol/L has been known to survive.² The rate of serum sodium concentration decline is equally important, as a 7-10% reduction in the serum sodium concentration over 24 hours, such as in exercise associated hyponatremia (EAH), has been shown to cause severe signs and symptoms of cerebral edema, and even death, at what would typically be considered more moderate (123 mmol/L) blood sodium levels.³⁻⁵

From a temporal standpoint, hyponatremia can be further defined as acute if hyponatremia develops within (< 48 hours) hours or chronic if hyponatremia develops over a period of days (> 48 hours).⁶ The clinical significance of an acute versus chronic hyponatremia is the ability of brain cells to adapt to more gradual (chronic) changes in reduced extracellular fluid (ECF) tonicity by the extrusion of organic osmolytes (glutamate, taurine, myo-inositol, glutamine, and creatine) into the ECF space.⁷ These organic osmolytes help protect the brain from swelling, which may lead to brain-stem herniation after an 8% increase in volume.^{7,8} However, this chronically decreased intracellular osmolyte concentration can predispose the adapted brain to osmotic demyelination. Therefore, the rate of serum $[Na^+]$ correction for individuals with chronic hyponatremia must be slower than for those with acute hyponatremia to avoid demyelination syndromes.⁹

The diagnosis of hyponatremia is based on the numerical value for blood $[Na^+]$, and also broadly categorized by symptomatology along a clinical continuum. Asymptomatic hyponatremia is a biochemical diagnosis without obvious signs or symptoms, although it has been argued that symptomatology is often subtle and if left untreated, can lead to other problems like falls due to postural instability.¹⁰ Symptomatic hyponatremia can be further subdivided as either mild (without signs and symptoms of cerebral edema) or severe (with signs and symptoms of encephalopathy).⁵ Mild hyponatremia has diffuse, non-descript, symptoms shared by many other clinical conditions such as lethargy and disorientation.⁷ Severe

hyponatremia presents significant neurological signs and symptoms such as with encephalopathy, non-cardiogenic pulmonary edema, vomiting, severe headache, altered mental status, delirium, obtundation, seizure and coma and is an emergent, life-threatening, condition. Of note, the symptoms of hyponatremia are quite similar to those associated with hypernatremia; therefore, an accurate diagnosis must be confirmed by a blood test before treatment is initiated.

Pathophysiology

In an over-simplification of what is truly a highly complex and overlapping spectrum of pathophysiological possibilities, there are three main mechanisms that mathematically describe how hyponatremia develops: 1) too much water is forced into the body (overhydration/hypervolemia) which dilutes sodium levels; 2) water is abnormally retained by the body (fluid retention/euvolemia) which dilutes sodium levels; and/or 3) sodium is being lost from the body with inadequate replacement (volume depletion/hypovolemia). Figures 1 and 2 summarize the three different volemic classifications detailed below.

1. Overhydration (hypervolemia): When more fluid is ingested or administered than can be excreted (entrance routes include: oral ingestion, intravenous,¹¹ transcervical,¹² transurethral,¹³ or transrectal¹⁴) fluid overload hyponatremia may develop. Sometimes referred to as “water intoxication,”¹⁵ fluids consumed beyond the physiological dictates of thirst may dilute a fairly consistent or increased number of sodium ions. Urinary excretion of excess body water is the main defense mechanism protecting against fluid overload, with maximal kidney excretion rates somewhere between 778 to 1043 mL per hour when the anti-diuretic hormone (ADH), arginine vasopressin (AVP), is maximally suppressed.^{16,17} During exercise, maximum sweat rates in elite athletes working in moderately hot environments (25 °C and above) exceed 2 L/hr.^{13,18} Edematous disease states such as liver cirrhosis and congestive heart failure may also precipitate fluid overload hyponatremia from more complex pathophysiological processes that are beyond the scope of this short review.¹⁹

2. Fluid retention (euvolemia): As stated above, maximal kidney excretion rates generally range between 778 to 1043 mL per hour when ADH/AVP is

maximally suppressed.^{16,17} As such, it is plausible that individuals such as those with diabetes insipidus (i.e. those who do not secrete or resistant to the actions of ADH at the kidney) or psychogenic polydipsia can still maintain normal natremia status²⁰ as the kidney excretes up to 15-20 L of fluid per day.²¹ However, there are many different “nonosmotic” stimuli to ADH/AVP that serve to conserve body water in anticipation of losses, such as nausea/vomiting,²² endurance exercise,²³ or plasma volume losses.^{23,24} Other “nonosmotic” stimuli which trigger fluid retention by stimulating ADH/AVP secretion from the posterior pituitary gland include heat, pain, and medications (such as anti-depressants and anti-psychotics).²⁵⁻²⁷ Therefore, when ADH/AVP is stimulated by these “nonosmotic” factors, abnormal water retention (even with modest fluid intakes) can trigger dilutional hyponatremia. This variant of hyponatremia is clinically referred to as the syndrome of anti-diuretic hormone secretion (SIADH).²⁸

3. Volume depletion (hypovolemia): It is impossible to completely deplete whole body sodium stores. However, clinically significant sodium losses can occur from protracted vomiting and/or diarrhea^{24,29} as well as during prolonged exercise in the heat, especially when under-acclimatized³⁰ or when a genetic defect is present that increases sweat sodium output, like cystic fibrosis.³¹ Sustained, under-replaced, sodium losses may cause plasma volume to shrink (i.e. less sodium in the vascular space will attract less water into the circulation) which will activate both ADH/AVP as well as the renin angiotensin-aldosterone system (RAAS).^{24,32} Angiotensin will stimulate thirst, while ADH/AVP will act to retain all fluids subsequently administered. The combination of water retention plus volume-driven (baroreceptor-mediated) thirst may facilitate the development of the volume-depletion form of hyponatremia. Of note, the typical sodium content of diarrhea (30-90 mmol/L)³³ and sweat (10-70 mmol/L)³⁴ is significantly less than blood (135-145 mmol/L). Thus, more water is actually lost than sodium with prolonged gastrointestinal or sweat sodium losses, which would actually stimulate hypernatremia in the absence of fluid replacement.

Morbidity and Mortality from Hyponatremia in Community Dwellers

Severe, life-threatening, hyponatremic encephalopathy (with seizures and coma) may occur in otherwise

healthy individuals (community dwellers) who ingest exuberant amounts of fluid that far exceeds excretion rates. Such “uncompensable” fluid intake characteristically occurs when any hypotonic fluid (including tea, diet cola, sports drinks, and beer)^{5,35-37} are ingested well-beyond the physiological dictates of thirst. Typical scenarios include: when competing homeostatic mechanisms supersede the suppression of thirst (hungry infants fed water instead of formula), individuals believe that excess water is good for health (athletes fearful of dehydration), cognitive abilities are impaired (schizophrenics), or when superfluous fluid intake is not recognized as potentially toxic (hazing, game shows, child abuse, etc.). More detailed examples are provided below.

Infants: Reports of infant morbidity and mortality from water intoxication have been reported in babies who were bottle-fed either dilute formula and/or tap water.³⁸ The families of hyponatremic infants generally cannot afford baby formula and thereby supplement feedings with tap water or watered-down baby formula to conserve food supplies. In such cases, the sensation of hunger and yearning for nutrition overpowers the suppression of thirst so that excessive amounts of dilute fluids are voluntarily consumed. This voluntary overconsumption of fluids, in response to the stronger biological drive of hunger, mirrors the standardized induction of hyponatremia in experimental animals.³⁹ In investigations of hyponatremia in murine models, rats and mice are only offered a liquid diet in combination with the anti-diuretic hormone analogue, desmopressin. These animals eat because they are hungry but cannot excrete any of the excess fluid which carried the food.⁴⁰ Therefore these lab animals, like infants, develop hyponatremia from a SIADH-like mechanism worsened by an inability to form urine due to a lack of solute from adequate nutrition.

Athletes: Exercise-associated hyponatremia (EAH) is well-described and primarily caused by overzealous fluid consumption before, during and immediately following exercise.⁵ The increase in fluid availability coupled with commonly held beliefs that exuberant fluid consumption (beyond the dictates of thirst) is necessary to prevent muscle cramps and heat illness⁴¹ while essential for peak performance,⁴² has led to preventable deaths in otherwise healthy individuals. Marathon runners, football players, hikers, a canoeist, a cyclist,

and army recruits have all died from EAH.⁵ Steps to limit fluid availability in marathon and Ironman triathlon courses coupled with instructions for athletes to drink only when thirsty have been implemented to reduce the incidence of dilutional hyponatremia in athletic populations.⁵

Compulsive water drinkers: Psychogenic polydipsia, or compulsive water drinking, is a frequent behavioral consequence of schizophrenia.⁴³ Such individuals report that continuous water consumption reduces their anxiety, and constantly seek out additional sources of fluids such as toilet bowls or flower vases^{20,44,45} to satiate this unusual compulsion to drink. It is likely that anti-psychotic medications also contribute to abnormal drinking and water retention^{27,44} although cases of morbidity and mortality from pure water intoxication have been reported.⁴⁶ Strategies focused on withholding fluids⁴⁵ or offering sodium-containing fluids⁴⁴ to psychogenic polydipsic patients have offered moderate or temporary success.

Child abuse and misuse: Forced exercise plus drinking, as a form of punishment, has led to fatal hyponatremic encephalopathy.^{47,48} Such unfortunate deaths have led to convictions of murder, highlighting the known lethal consequences of forced water intoxication within the medical community.⁴⁹ Mortality from water intoxication has also been documented from fraternity hazing whereas a 21-year-old male was instructed to repeatedly drink from a five gallon water jug while performing calisthenics until he collapsed.⁵⁰ Additionally, a radio station was ordered to pay \$16.5 million dollars in damages to the family of a 28-year-old woman who died from dilutional hyponatremia after entering the radio contest “Hold Your Wee for a Wii”. This live radio contest featured how much water contestants could drink before having to urinate, to which this particular mother of three (who wanted to win a Wii console for her children) drank nearly two gallons of water in three hours and died a few hours later.⁵¹ Collectively, these tragedies reflect the apparent lack of mainstream knowledge regarding the potentially lethal consequences of drinking too much fluid.

Hospital-acquired hyponatremia and patient prognosis: The first reported fatality from water intoxication was reported in 1935 in a 50-year-old woman who underwent gallbladder surgery and was

administered ~9 L of tap water (post-operatively) via proctoclysis.¹⁵ Subsequent studies document the development of hyponatremia in patients admitted into the hospital for illness or surgery.^{52,53} Hyponatremia which develops after admission, is referred to as “hospital acquired”, which is different from “community acquired” hyponatremia which is diagnosed upon arrival.^{54,55} The incidence of hospital acquired hyponatremia has ranged from 30-40% of patients treated in the ICU⁵⁶ to 30% of patients postoperatively.⁵² Patients with hyponatremia demonstrate longer recovery times⁵⁵ and have poorer outcomes compared with patients being treated for similar conditions but remain normonatremic throughout their hospital stay.^{1,57} It is widely hypothesized that the hyponatremia is more reflective of the actual disease state than the cause of poorer outcomes, although correction of dysnatremia has led to significant improvements in clinical outcomes in recent studies.⁵⁸

Treatment and prevention of hyponatremia: The treatment of hyponatremia is challenging, in both healthy and diseased populations, and should be approached on a case-by-case basis according to the underlying pathophysiology (Figures 1, 2, and 3).⁵⁹ There are several important considerations that should be made when correcting hyponatremia: (1) the underlying pathophysiology, (2) severity or magnitude (3) duration of onset, and (4) clinical symptoms.²⁴ From these considerations come general rules of efficacious and safe treatment. The most efficacious treatment and preventative strategies target the underlying cause of the hyponatremia. In general, for dilutional hyponatremia (overhydration and fluid retention), fluid restriction coupled with free water excretion is indicated. For depletional hyponatremia (volume depletion), a combination of salt and water is recommended to restore plasma volume while elevating blood sodium levels. Severe hyponatremia with signs and symptoms of encephalopathy is a life-threatening emergency and must be treated immediately with intravenous administration of highly concentrated salt solutions (i.e. hypertonic solutions, such as 3% saline), which serve to reduce cerebral edema and prevent brainstem herniation (the main cause of death from hyponatremia). While, hypertonic saline triggers higher rates of correction, it also carries an increased potential for overcorrection.⁶⁰

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A correction rate which exceeds 12 mmol/L (increase in blood [Na⁺]) per day is not advised (especially if the origins of hyponatremia are unknown) and may lead to adverse consequences such as osmotic demyelination syndrome.⁶¹ As a rule of thumb, a maximal correction rate of 1-2 mmol/L/hr is recognized as safe, as long as

the total rate of correction does not surpass 25 mmol/L in the first 48 hours.²⁴ Correction rates will vary, however, depending on whether or not hyponatremia is acute or chronic and how the patient responds to treatment. Correction rates may exceed the recommended 12 mmol/L per day if the hyponatremia

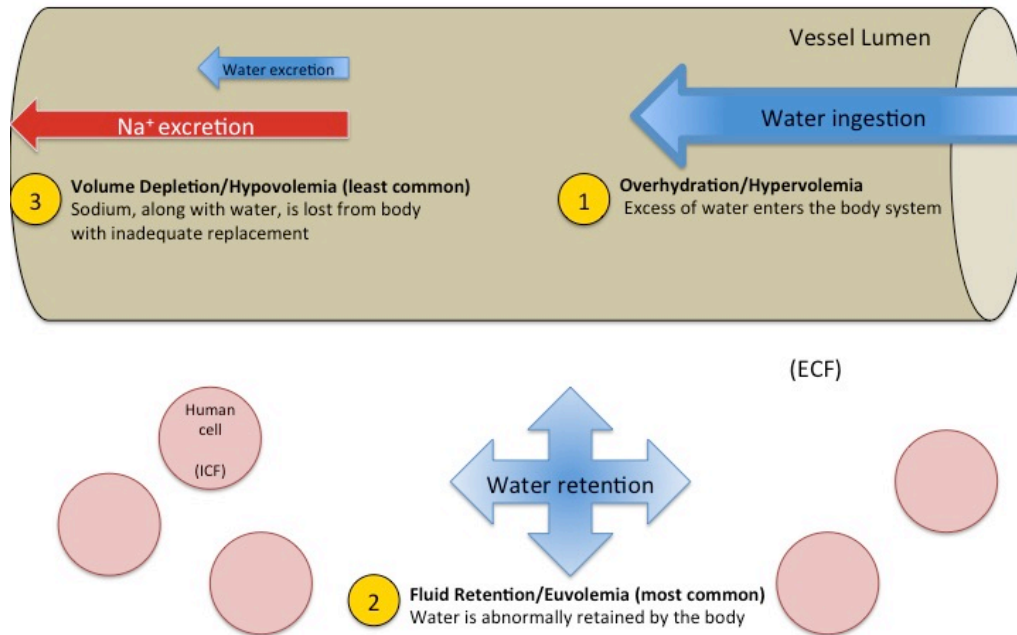


Figure 1. Schematic diagram of the pathophysiology of hyponatremia. See text for more information regarding the pathophysiology corresponding to the circled numbers.

- 1 Overhydration/Hypervolemia**
 Too much water is forced into the body via:

 - Oral ingestion
 - IV infusion
 - Peritoneal lavage
 - Colorectal enema
 - Edematous states
$$\downarrow [Na^+] = \frac{Na^+ (mmol)}{\uparrow Volume(L)}$$
- 2 Fluid Retention/Euvolemia (most common)**
 Nonosmotic (inappropriate) AVP/ADH secretion causes water to be abnormally retained by the body and can be stimulated by the following triggers:

 - Endurance exercise
 - Plasma volume losses
 - Nausea/vomiting
 - SIADH
 - Heat
 - Pain
 - Medications
$$\downarrow [Na^+] = \frac{Na^+ (mmol)}{\uparrow Volume(L)}$$
- 3 Volume Depletion/Hypovolemia (least common)**
 Sodium, along with water, is lost from body with inadequate replacement via:

 - Diarrhea or vomiting
 - Prolonged exercise in heat
 - Genetic defects
$$\downarrow [Na^+] = \frac{\downarrow Na^+ (mmol)}{Volume(L)}$$

Figure 2. Examples of the underlying etiologies of hyponatremia. See text for more information regarding the pathophysiology corresponding to the circled numbers.

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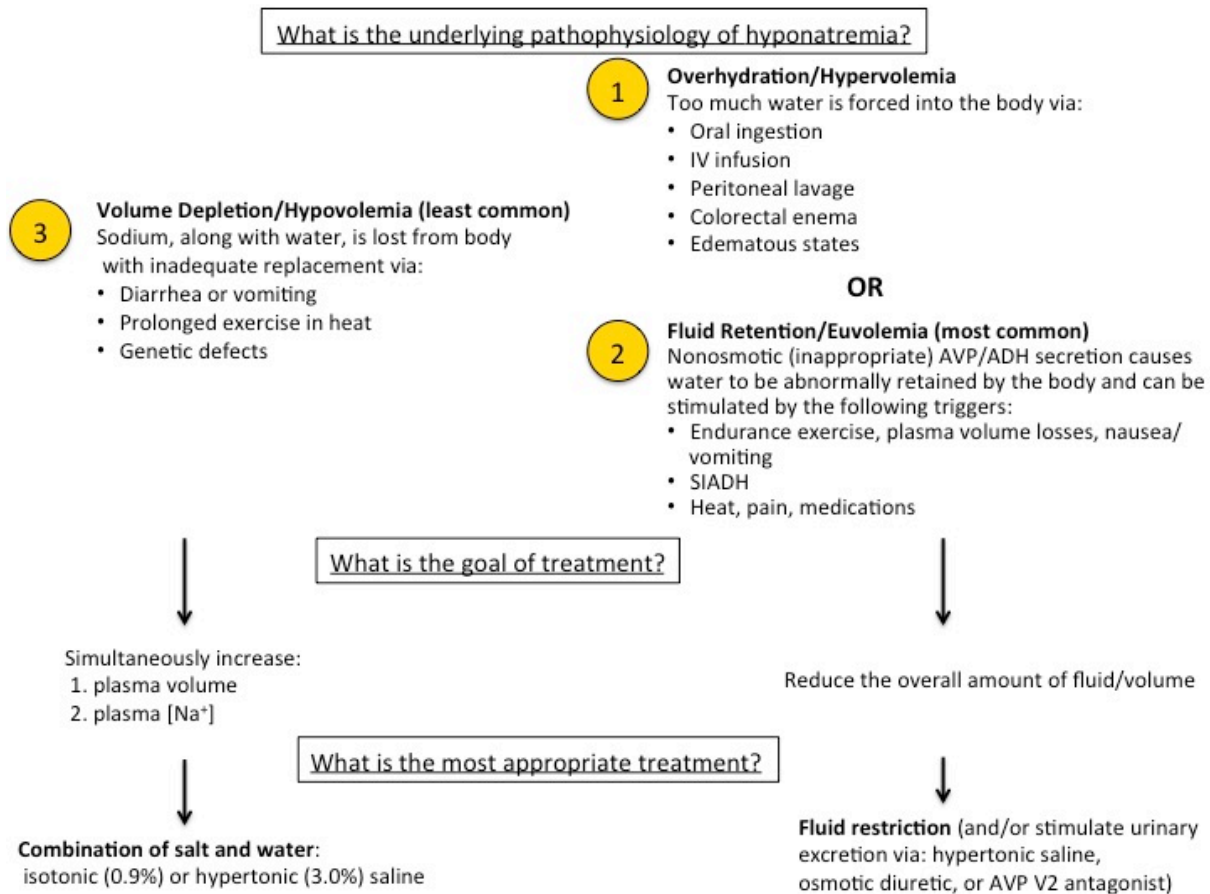


Figure 3. Treatment of hyponatremia categorized by underlying pathophysiology. See text for explanation of circled numbers.
Note: osmotic diuretics refer to urea and mannitol.

known to be of acute onset (such as in EAH). Appropriate treatment is critical, because although efficacious treatment methods are currently available, most hyponatremic patients are still hyponatremic when discharged.⁶⁰ Treatment may need to be adjusted to maintain a proper rate of correction and as such should be monitored every four hours.²⁴ Finally, acute treatment should be stopped when one of these three endpoints has been met: (1) patients symptoms resolve, (2) total magnitude of correction of 20 mmol/L has been reached, or (3) an absolute [Na⁺] of 120 mmol/L has been reached.²⁴ A generalized approach to treatment is summarized in Figure 3. A more comprehensive overview of evidenced-based treatment and prevention guidelines can be found in more detailed reviews.^{5,9,19,24,60,62}

In conclusion, it is clear that infants, athletes, psychotics, hospital patients and normal people die from hyponatremia because they ingest or are

administered (dilute) fluids in excess of excretion rates. Hyponatremia induces whole body cellular swelling, with cerebral edema and brainstem herniation the main cause of morbidity and mortality, respectively. Fluids consumed according to the dictates of thirst will prevent hyponatremia in most free-living community dwellers. Thus, these sodium stories collectively suggest that most hyponatremic deaths are avoidable and stronger warnings to “drink responsibly” (not too much and not too little!) should be re-enforced amongst the general population. As such, advice to “drink plenty of water” may do more harm than good.

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