REVIEW

Diagnostic Approach and Management of Inpatient Hyponatremia

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Hyponatremia is one of the most common electrolyte abnormalities encountered in clinical practice. The frequency of the disorder varies according to definition and clinical setting but has been reported to be present in 28% of patients upon hospital admission and in 7% of patients attending an ambulatory community clinic.[1] Increasing age, medications, various disease states, and administration of hypotonic fluids are among the known risk factors for the disorder.

The mortality rate in hyponatremic patients is approximately 3 times that of normonatremic hospitalized patients.[2–5] Outcomes are particularly poor in those patients whose serum sodium (Na^+) falls during a hospitalization. In 1 prospective study the mortality rate in patients with a normal serum Na^+ concentration was 0.2% in comparison to a mortality rate of 11.2% and 25% in patients with a serum Na^+ concentration <130 mEq/L and <120 mEq/L, respectively.[2] In a recent retrospective cohort study of 10,899 hospitalized patients, the incidence of hyponatremia (<135 mmol/L) at admission was 5.5%.[5] As compared to those with normonatremia, these patients were more likely to require intensive care and mechanical ventilation within 48 hours of hospitalization. In addition, hospital mortality, mean length of stay, and costs were significantly greater among patients with hyponatremia than those without.

The association with hyponatremia and adverse outcomes could be the direct result of hyponatremia, the comormidities that lead to the electrolyte derangement, or both. Whatever the mechanism, hyponatremia should not be viewed as an innocuous condition. Rather, clinicians should view this disorder with urgency and institute measures to prevent any further decline in the serum Na^+ concentration and initiate appropriate therapy for its correction. This review will first briefly summarize the pathogenesis of hyponatremia and then discuss various disease states encountered in the hospital setting in which hyponatremia is frequently present.

Pathogenesis of Hyponatremia

Hyponatremia is generally associated with a hypoosmolar state and is a marker for a disturbance in water balance. Stated differently, all hyponatremia is dilutional. The approach to the patient with hyponatremia is outlined in Figure 1.

## Is the Hyponatremia Representative of a Hypoosmolar State?

There are 3 causes of hyponatremia in which it is not associated with a hypoosmolar state. The first of these is pseudohyponatremia which involves an abnormal measurement of the serum Na^+. This occurs in patients with hyperglobulinemia or hypertriglyceridemia in whom plasma water relative to plasma solids is decreased in blood, leading to less Na^+ in a given volume of blood. In general, this problem is becoming less prevalent as many laboratories are using Na^+ electrodes without diluting the blood such that the Na^+ measurement becomes independent of plasma water and nonaqueous contents.

A second cause of hyponatremia in the absence of a hypoosmolar state involves true hyponatremia but with elevations in the concentration of another osmole. Clinical examples include hyperglycemia as seen in uncontrolled diabetes or rarely hypertonic infusion of mannitol used in the treatment of cerebral edema. The accumulation of these effective osmoles creates an osmotic force causing water to move from the intracellular to the extracellular space thus diluting the serum Na^+. For every 100 mg/dL rise in glucose or mannitol, the serum Na^+ will quickly fall by 1.6 mEq/L. This increase in tonicity also stimulates thirst and arginine vasopressin (AVP) secretion, both of which contribute to further water retention. As a result the plasma osmolality and serum Na^+ concentration will continue to fall. Once the plasma osmolality normalizes the serum Na^+ will have decreased by 2.8 mEq/L for every 100 mg/dL rise in glucose.

The third cause of hyponatremia in the absence of a hypoosmolar state is the addition of an isosmotic (or near isosmotic) non-Na^+ containing fluid to the extracellular space. This situation typically occurs during a transurethral resection of the prostate or during laprascopic surgery when large amounts of a nonconducting flushing solution containing glycine or sorbitol are absorbed systemically.

Is the Kidney's Ability to Dilute the Urine Intact?

The presence of hypotonic hyponatremia implies that water intake exceeds the ability of the kidney to excrete water. In unusual circumstances, this can occur when the kidneys ability to excrete free water is intact. However, because a normal kidney can excrete 18 L of water per day, the presence of hyponatremia with normal renal water excretion implies the patient is drinking >20 L water/day. This

Serum osmolality
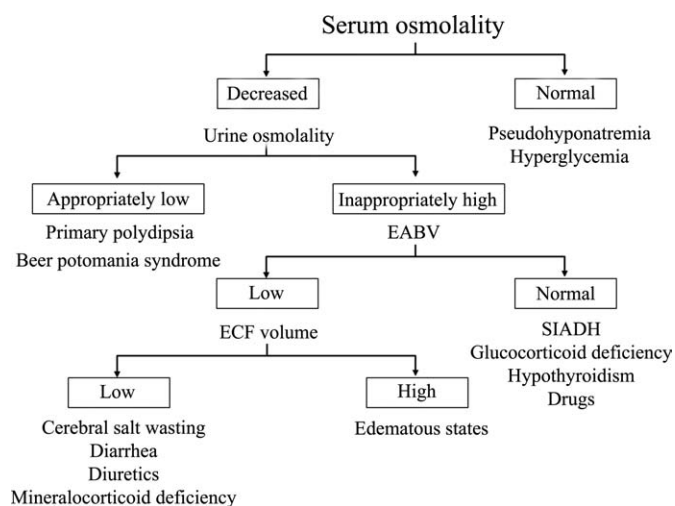
FIGURE 1. Approach to the hyponatremic patient (EABV, effective arterial blood volume, SIADH, syndrome of inappropriate antidiuretic hormone secretion).

condition is referred to as primary polydipsia. These patients should have a urine osmolality <100 mOsm/L. While primary polydipsia is a common condition which leads to polyuria and polydipsia, it is uncommon as a sole cause of hyponatremia.

Hyponatremia in association with a maximally dilute urine can also result from more moderate fluid intake combined with extremely limited solute intake, a condition often referred to as "beer potomania" syndrome. In normal subjects, daily solute excretion is usually in the range of 800 mOsm to 1000 mOsm per day. Since the limit of urinary dilution is approximately 50 mOsm/L, then maximum urine output can be calculated to be approximately 16 L to 20 L per day (1000 mOsm/L/50 mOsm/L = 20). Individuals who drink beer or who are ingesting a fad diet have very limited protein intake so that daily solute excretion may be as low as 200 mOsm per day. In this setting, water intake >4 L/day (200 mOsm/50 mOsm/L = 4 L) will exceed renal water excretion and cause hyponatremia. Urine osmolality will be maximally dilute in such a patient.

In the absence of primary polydipsia, hyponatremia is associated with decreased renal water excretion and a urine that is inappropriately concentrated. It is important to note that in the presence of hyponatremia urine should be maximally dilute and a urine osmolality higher than this (>100 mOsm/L) is inappropriate. An inappropriately concentrated urine implies a defect in renal water excretion.

Excretion of water by the kidney is dependent on three factors. First, there must be adequate delivery of filtrate to the tip of the loop of Henle. Second, solute absorption in the ascending limb and the distal nephron must be normal so that the tubular fluid will be diluted. Lastly, AVP levels must be low in the plasma. Of these 3 requirements for water excretion, the one which is probably most important in the genesis of hyponatremia is the failure to maximally suppress AVP levels. In many conditions, decreased delivery of filtrate to the tip of the loop of Henle also contributes.

What is the Volume Status of the Patient?

In patients with hypotonic hyponatremia with an inappropriately concentrated urine, one needs to define whether effective arterial volume is decreased. Most causes of hyponatremia result from a decrease in effective arterial volume which leads to both baroreceptor-mediated stimulation of AVP secretion and decreased distal delivery of filtrate to the tip of the loop of Henle. If effective arterial volume is low, extracellular fluid (ECF) volume can be low in the volume-depleted patient (hypovolemic hyponatremia) or can be high in the edematous patient (hypervolemic hyponatremia). If effective arterial volume is normal, one is dealing with the euvolemic causes of hyponatremia (isovolemic hyponatremia).

The clinical determination of effective arterial volume is usually straightforward. On physical examination the best index of effective arterial volume is the presence or absence of an orthostatic change in pulse and blood pressure. Urinary electrolytes are also extremely useful in the assessment of effective arterial volume. Patients with a low effective arterial volume will tend to have a low urinary Na^+ and Cl^- concentration and low fractional excretions of Na^+ and Cl^- in the urine. Patients with euvolemic hyponatremia will be in balance and will excrete Na^+ and Cl^- at rates that reflect dietary intake of Na^+ and Cl^-. Generally urinary Na^+ and Cl^- is >20 mEq/L and fractional excretions of these electrolytes are >1%.

Plasma composition can also be used to assess effective arterial volume. The blood urea nitrogen (BUN) is particularly sensitive to effective arterial volume. In patients with a normal serum creatinine concentration, a high BUN suggests a low effective arterial volume and a low BUN suggests a high effective arterial volume. The plasma uric acid can also be used as a sensitive index of effective arterial volume. In comparing patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and other causes of hyponatremia, patients with low effective arterial volume tend to have an elevated serum uric acid. The serum urate is low in patients with SIADH. This is due to the fact that these patients are volume expanded although it is clinically difficult to detect the degree of volume expansion.

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

In patients who are determined to be clinically euvolemic, a concentrated urine and high AVP levels are inappropriate. The most common cause of this condition is SIADH. This syndrome is generally associated with diseases of the central nervous system, pulmonary diseases, and neoplasms. These conditions lead to secretion of AVP which is inappropriate both from the standpoint of plasma osmolality and effective arterial volume. A number of other etiologies cause a condition of hypoosmolality associated with euvolemia and can mimic the syndrome of inappropriate AVP secretion. These include isolated glucocorticoid deficiency (normal

mineralocorticoid activity), hypothyroidism, pain, nausea, acute psychosis, and a variety of drugs.

Clinical Conditions Associated With Hyponatremia in the Hospital Setting

Post-Operative Hyponatremia

The postoperative patient is particularly prone to developing hyponatremia. AVP levels are increased for several days following surgical procedures due to baroreceptor and nonbaroreceptor-mediated mechanisms. These patients typically have subtle or overt decreases in effective arterial blood volume due to prolonged preoperative fasting combined with intraoperative and postoperative blood loss and third spacing of fluid. In addition to these factors which unload baroreceptors, postoperative pain, stress, anxiety, nausea, and administration of morphine can further stimulate the release of AVP. In some instances nonsteroidal antiinflmmatory drugs are given which have the effect of augmenting the hydroosmotic actions of AVP.[6] In this setting of compromised ability to excrete a water load, administration of hypotonic fluid can precipitate acute iatrogenic hyponatremia.

Postoperative hyponatremia has been a major problem in pediatric populations due to the widespread practice of using hypotonic fluids for maintenance therapy. This approach is based on guidelines developed 50 years ago which were based on calculations linking energy expenditures to water and electrolyte losses.[7] More recently, several groups have argued that isotonic rather than hypotonic fluids should be the routine maintenance fluid in such patients.[8,9] The pediatric community has been slow to embrace this approach out of the concern that excessive administration of Na^+ would increase the risk of hypernatremia. A systematic meta-analysis of studies comparing isotonic and hypotonic fluids in hospitalized children found the odds of developing hyponatremia following hypotonic solutions was 17.2 times greater than with isotonic fluids.[10] The concern that isotonic maintenance fluids carry a risk of hypernatremia was not supported in the review. Some studies actually reported a decrease in serum Na^+ concentration, presumably due to the "desalination" phenomenon in which hypertonic urine is excreted in volume expanded subjects with persistent vasopressin secretion.

Endocrine Disorders

Glucocorticoid Deficiency

Patients with glucocorticoid deficiency develop hyponatremia. It is important to separate this condition from that of mineralocorticoid deficiency and combined mineralocorticoid-glucocorticoid deficiency. In patients with mineralocorticoid deficiency, ECF volume and effective arterial volume are low. This leads to baroreceptor stimulation of AVP secretion and to decreased distal delivery of filtrate to the diluting segments of the nephron. In isolated glucocorticoid deficiency, the patients are euvolemic. In these patients, for any given level of low plasma osmolality, vasopressin levels are inappropriately elevated. The administration of hydrocortisone restores the relationship between vasopressin and plasma osmolality to normal.

While it is possible to develop isolated glucocorticoid deficiency with adrenal disease, most adrenal diseases cause loss of mineralocorticoid and glucocorticoid function. Glucocorticoid deficiency in the absence of mineralocorticoid deficiency is usually due to pituitary disease. In fact, severe hyponatremia may be the initial clue to the presence of previously unrecognized hypopituitarism. Insufficient adrenal secretion of glucocorticoids may also be a complication following the long term use of exogenous glucocorticoids.

In addition to high AVP levels, AVP-independent mechanisms lead to increases in urinary osmolality in glucocorticoid deficiency. The nature of this AVP-independent effect is likely multifactorial. First, glucocorticoid deficiency is associated with a diminished cardiac output and an impaired systemic vascular response to hypotension. These changes will lead to a slight decline in glomerular filtration rate and increased volume absorption in the proximal tubule and thin descending limb. As a result, distal delivery of filtrate to the diluting segment will be abnormally low in glucocorticoid deficiency. Second, mineralocorticoid and glucocorticoid deficiency have both been shown to result in increased expression of aquaporin 2 water channels in the collecting duct.[11] This later effect will further limit maximal urinary dilution and contribute to net water retention.

These AVP-independent mechanisms are consistent with the clinical observation that patients with diabetes insipidus appear to improve clinically when they develop coexistent anterior pituitary insufficiency, and treatment of these patients with glucocorticoids appears to worsen the diabetes insipidus. Thus, in the patient with diabetes, insipidus-free water excretion will be extremely large. When simultaneous glucocorticoid deficiency develops, free-water excretion decreases.

Hypothyroidism

Myxedema coma is the most severe form of hypothyroidism and is commonly associated with hyponatremia.[12] In this setting, blood pressure can be low because of decreased intravascular volume and cardiovascular collapse. The hypotension can be refractory to vasopressor therapy in the absence of thyroid hormone therapy. Cardiac output and stroke volume are low. A defect in renal water excretion develops as a result of baroreceptor mediated increases in AVP along with decreased delivery of filtrate to the distal nephron. In hypothyroid rats, there is upregulation of aquaporin 2 water channels. In these animals, administration of a V_2 receptor antagonist reverses the increased water channel expression and corrects the impaired response to an acute water load.[11]

While reduced cardiac output and blood pressure associated with severe hypothyroidism can provide a stimulatory effect for AVP release through a baroreceptor mediated

mechanism, milder forms of hypothyroidism can be considered in the differential diagnosis of euvolemic hyponatremia. In this setting, impaired renal excretion of water is presumably due to increased release of AVP due to the absence of a tonic inhibitory effect of thyroid hormone in the central nervous system. The degree of hyponatremia in this setting is typically mild.

Heart Failure

Hyponatremia is a common complication of left-sided heart failure and several studies have shown that it is an independent predictor of mortality.[13,14] A similar association between reduced survival and hyponatremia is present in advanced right-sided heart failure in patients with pulmonary arterial hypertension.[15] Patients with heart failure who are hyponatremic have higher circulating levels of neurohormones (catecholamines, renin, angiotensin II, aldosterone, and AVP) than normonatremic subjects and are more likely to have prerenal azotemia. In addition to being a marker for the extent of neurohumoral activation, hyponatremia may play a more direct role in adverse outcomes through maladaptive volume regulatory responses of cardiac myocytes and by direct effects of AVP on cardiac and coronary V_{1a} receptors.

Heart failure is associated with arterial underfilling leading to arterial baroreceptor-mediated activation of the neurohumoral axis. This underfilling is due to decreased cardiac output in low-output heart failure and decreased systemic vascular resistance in high-output heart failure. Activation of the sympathetic nervous system along with the renin-angiotensin-aldosterone system leads to renal salt retention while the increase in AVP is associated with water retention and hyponatremia.

Cirrhosis

Hyponatremia is a common electrolyte abnormality in patients with cirrhosis and occurs with a frequency that tends to parallel the severity of liver disease.[16] Patients with a serum $Na^+ \leq 130$ mEq/L are more likely to have refractory ascites and require therapeutic paracentesis. Hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis are also more common in patients with a serum $Na^+ \leq 130$ mmol/L than in patients with a normal serum Na^+ concentration. Hyponatremia increases morbidity and mortality from hepatic transplantation and is associated with osmotic demyelination in the postoperative period because of the large increase in Na^+ concentration associated with the procedure.[17]

Hepatic cirrhosis is characterized by a decreased effective arterial blood volume and activation of neurohumoral effectors. Reduced effective circulating volume due to generalized and specifically to arterial splanchnic vasodilation leads to baroreceptor-mediated nonosmotic stimulation of AVP release and an impaired ability to excrete electrolyte-free water.[18] Reduced Na^+ delivery to the distal tubule because

of a low glomerular filtration rate and increased proximal Na^+ reabsorption adds to the susceptibility of cirrhotic patients to hyponatremia.

Hyponatremic-Hypertensive Syndrome

The development of hyponatremia in patients with severe hypertension associated with renal artery stenosis has been called the hyponatremic-hypertensive syndrome.[19,20] Patients with this syndrome present with a variety of signs and symptoms that include headache, confusion, postural dizziness, polyuria, polydipsia, and salt craving. In a retrospective review of 32 patients with this syndrome, most of the subjects were thin, elderly, women smokers who had atherosclerotic renal vascular disease.[19] Biochemical abnormalities included not only hyponatremia, but hypokalemia and increased plasma renin activity. The mean serum Na^+ concentration was 129.7 mmol/L (range 120-135).

The precise mechanism of this syndrome is not known. Given the available data, angiotensin-mediated thirst coupled with nonosmotic release of AVP provoked by angiotensin II and/or hypertensive encephalopathy are likely. Na^+ depletion due to pressure natriuresis, and K^+ depletion due to hyperaldosteronism are also likely to play a role in the pathogenesis of hyponatremia.
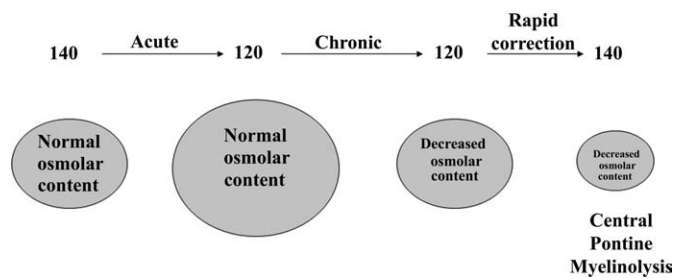
Pneumonia

An association between pneumonia and hyponatremia has been known for quite some time but has been poorly defined. Of the various etiologic agents, legionella is more commonly associated with hyponatremia as compared to other types of community acquired disease. As has been true for many disorders, hyponatremia is associated with longer hospital stays and hospital mortality, most likely reflecting the severity of the pneumonia rather than morbidity from the usually mild and asymptomatic hyponatremia.

Central Nervous System Disease

Hyponatremia is a frequent complication of central nervous system disease to include bacterial meningitis and traumatic brain injury. Potential mechanisms include the development of SIADH, cerebral salt wasting (CSW), or hypotonic fluid administration in the setting of impaired renal water excretion as in patients with low effective volume. Of these various causes, hyponatremia is frequently attributed to SIADH. As previously mentioned, this syndrome is characterized by hyponatremia in the setting of an inappropriately concentrated urine, increased urine Na^+ concentration, and evidence of normal or slightly increased intravascular volume.

However there are patients with intracranial disease who develop hyponatremia with similar characteristics but differ in that there is clinical evidence of a contracted ECF volume. This form of hyponatremia is due to excessive renal Na^+ excretion resulting from a centrally mediated process and is termed CSW. The onset of this disorder is typically seen within the first ten days following a neurosurgical

140 —Acute→ 120 —Chronic→ 120 —Rapid correction→ 140

Normal osmolar content   Normal osmolar content   Decreased osmolar content   Decreased osmolar content

Central Pontine Myelinolysis

FIGURE 2. Change in cell size with acute and chronic hyponatremia. Hyponatremia initially leads to cell swelling driven by the higher intracellular osmolality. The net result is equilibration of intracellular and extracellular osmolality at the expense of increased brain volume. Cells in general, and brain cells in particular, then respond by decreasing the number of intracellular osmoles and as intracellular osmolality decreases, cell size returns toward normal despite the presence of hyponatremia. Rapid correction of chronic hyponatremia causes acute cellular shrinkage and can lead to osmotic demyelination.

procedure or after a definable event, such as a subarachnoid hemorrhage or stroke. CSW has also been described in other intracranial disorders, such as carcinomatous or infectious meningitis and metastatic carcinoma.[21] The distinction between SIADH and CSW is of considerable clinical importance given the divergent nature of the treatments. Fluid restriction is the treatment of choice in SIADH, whereas the treatment of CSW comprises vigorous Na^+ and volume replacement.

Treatment of Hyponatremia

Symptoms of hyponatremia include nausea and malaise, which can be followed by headache, lethargy, muscle cramps, disorientation, restlessness and obtundation, and seizures. The principal danger of hyponatremia or hypernatremia relates to effects on central nervous system function due to changes in brain size (Figure 2).

Hyponatremia initially leads to cell swelling driven by the higher intracellular osmolality. The net result is equilibration of intracellular and extracellular osmolality at the expense of increased brain volume. Cells in general, and brain cells in particular, then respond by decreasing the number of intracellular osmoles and as intracellular osmolality decreases, cell size returns toward normal despite the presence of hyponatremia. If the decrease in ECF osmolality is slow, there will be no measurable cell swelling. This pathophysiologic sequence correlates well with clinical observations. If hyponatremia is slow in onset, neurologic symptoms and permanent brain damage are unusual, even if the decreases in Na^+ concentration and ECF osmolality are large. Conversely, if hyponatremia is rapid in onset, cerebral edema and significant CNS symptoms and signs can occur with lesser changes in serum Na^+ concentration.

When treating a patient with hyponatremia, the Na^+ concentration should be raised at the rate at which it fell. In a patient whose serum Na^+ concentration has decreased rapidly (<48 hours), neurologic symptoms are frequently present and there is cerebral edema. In this setting there has not been sufficient time to remove osmoles from the brain and rapid return to normal ECF osmolality merely returns brain size to normal. In general, the development of hyponatremia in the outpatient setting is more commonly chronic in duration and should be corrected slowly. By contrast, hyponatremia of short duration is more likely to be encountered in hospitalized patients receiving intravenous free water. Use of "ecstasy", exercise-induced hyponatremia, or patients with primary polydipsia can also develop acute hyponatremia and if symptomatic may similarly require rapid correction. Raising the serum Na^+ concentration by 4 mEq/L to 6 mEq/L over a several hour period is both safe and effective in preventing untoward effects of acute hyponatremia.[22] A reasonable strategy to accomplish this goal is the regimen recommended for the treatment of athletes with hyponatremia and encephalopathy.[23] These guidelines suggest an immediate bolus of 100 mL 3% NaCl (513 mEq/L). If there is no neurologic improvement two additional 100 mL 3% NaCl bolus infusions separated by 10 minute intervals can be given.

In patients with chronic hyponatremia (>48 hours duration) the serum Na^+ concentration has fallen slowly. Neurologic symptoms are generally minimal, brain size is normal, and the number of intracellular osmoles is decreased. Sudden return of ECF osmolality to normal values will lead to cell shrinkage and possibly precipitate osmotic demyelination. Experts in the field suggest this complication can be prevented by adhering to the following limits of correction: 10 mmol/L in 24 hours, 18 mmol/L in 48 hours, and 20 mmol/L in 72 hours.[22] In order to maximize patient safety, the goals of therapy should be more modest: 6 to 8 mmol/L in 24 hours, 12 to 14 mmol/L in 48 hours, and 14 to 16 mmol/L in 72 hours.

A formula designed to predict the increase in serum Na^+ concentration to be expected from the infusion of 1 L of a given infusion is given below:

$$\text{Predicted increase in Na}^+ = ([Na^+]\text{in infusate} - [Na^+]serum)/total\ body\ water + 1 \quad (1)$$

According to this calculation, the increase in serum Na^+ concentration will be for every liter administered of the chosen solution. Adding 1 to the denominator is to account for the increase in total body water resulting from the one liter infusate. A recent report found this formula tended to underestimate the increase in serum Na^+ after hypertonic saline (3% saline = 513 mEq/L).[24] In some cases the actual correction was as much as 5 times the predicted value emphasizing the need for frequent measurements of the Na^+ to guide therapy.

There are several settings where a defect in renal water excretion can be easily reversed resulting in a brisk water diuresis and rapid rise in the serum Na^+ concentration. Such

TABLE 1. Conservative Management of Chronic Hyponatremia

Treament	Mechanism	Advantages	Limitations
Fluid restriction (0.5-1.0 L/day)	↓ water intake	Effective, inexpensive	Poor compliance
Demeclocyline (600-1200 mg/day)	Inhibits action of AVP	Widely available	Slow onset, nephrotoxic, expensive
Urea (30 gm/day)	Osmotic diuresis	Possible↓risk of osmotic demyelination	Poor palatability, avoid in chronic kidney and liver disease
Lithium (up to 900 mg/daily)	Inhibits action of AVP	Widely available	Slow onset, toxicity

Abbreviation: AVP, arginine vasopressin.

settings include restoration of ECF volume in patient with total body salt depletion, discontinuation of thiazide diuretics, and cortisol administration to a patient with adrenal insufficiency. The administration of volume causes renal water excretion to rapidly increase in beer potomania syndrome where hyponatremia develops in association with extremely low solute intake. In all of these settings desmopressin acetate (DDAVP) either with or without hypotonic fluids (5% dextrose in water) can be given to slow the rate of correction.[25]

Fluid restriction is generally a part of the therapeutic strategy in the management of chronic hyponatremia (Table 1). Fluid restriction is safe and inexpensive but somewhat variable in effectiveness in large part due to poor patient tolerability and difficulty in adhering to the prescribed regimen. Measurement of urine electrolytes can be helpful in predicting the response to fluid restriction. A prompt increase in the serum Na^+ concentration can be anticipated when the sum of the urine Na^+ and K^+ concentration is divided by the plasma Na^+ concentration and the ratio is <0.5. By contrast, a ratio >1.0 is indicative of no electrolyte-free water in the urine and predicts a poor response unless water intake is severely limited.

When treating patients with SIADH with intravenous salt solutions, one can worsen the degree of hyponatremia if the osmolality of the administered fluid is less that the urine osmolality. One liter of isotonic saline contains 150 mEq each of Na^+ and Cl^- and has an osmolality of 300 mOsm. In a patient with SIADH who has a urine osmolality of 600 mOsm, the administered NaCl will all be excreted in 500 mL of water (300 mOsm in 500 mL = 600 mOsm/L). The remaining 500 mL of administered fluid will be retained in the body and cause further dilution of the serum Na^+ concentration. By contrast, 1 L of 3% saline contains 513 mEq each of Na^+ and Cl^- and has an osmolality of 1026 mOsm. All of the NaCl in 1 L of this solution will be excreted in 1.7 L of water and therefore will cause the serum Na^+ concentration to increase as a result of the loss of 700 mL of water.

Loop diuretics can also be employed as part of the strategy to treat chronic hyponatremia. Loop diuretics directly interfere in the countercurrent concentrating mechanism by inhibiting NaCl reabsorption in the loop of Henle. The coadministration of these drugs will enhance the effect of intravenous salt solutions by lowering urine osmolality

thereby increasing the likelihood that the osmolality of the administered fluid is greater than the urine osmolality. Other measures used to treat chronic hyponatremia are given in Table 1.

AVP antagonists block the V_2 receptor located on the basolateral surface of the collecting duct thereby antagonizing the ability of AVP to cause insertion of water channels (aquaporin 2) into the apical membrane. The net effect is increased water excretion with little to no change in urinary Na^+ excretion. AVP antagonists have been shown to be more effective than placebo in increasing the serum Na^+ concentration in patients with modest asymptomatic hyponatremia.[26,27] These agents can be considered in patients with hyponatremia associated with heart failure or cirrhosis and in patients with irreversible SIADH but should not be used in patients with hypovolemic hyponatremia. The role of these drugs is discussed further in an accompanying article in this supplement, titled "New horizons in the pharmacologic approach to hyponatremia: The V_2 Receptor Antagonists."

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References
1. Hawkins R. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chem Acta*. 2003; 337: 169–172.
2. Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med*. 1985; 102(2):164–168.
3. Gill G, Huda B, Boyd A, et al. Characteristics and mortality of severe hyponatraemia-a hospital-based study. *Clin Endocrinol (Oxf)*. 2006; 65(2):246–249.
4. Waikar S, Mount D, Curhan G. Mortality after hospitalization with mild moderate and severe hyponatremia. *Am J Med*. 2009; 122: 8857–8865.
5. Zilberberg MD, Exuzides A, Spalding J, et al. Epidemiology, clinical and economic outcomes of admission hyponatremia among hospitalized patients. *Curr Med Res Opin*. 2008; 24: 1601–1608.
6. Palmer BF. Renal complications associated with use of nonsteroidal anti-inflammatory agents. *J Investig Med*. 1995; 43(6):516–533.
7. Paut O, Lacroix F. Recent developments in the perioperative fluid management for the paediatric patient. *Curr Opin Anaesthesiol*. 2006; 19: 268–277.
8. Moritz M, Ayus J. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. *Pediatrics*. 2003; 111: 227–230.

9. Hoorn EJ, Geary D, Robb M, Halperin Ml, Bohn D. Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. *Pediatrics*. 2004; 113(5):1279–1284.

10. Choong K, Kho ME, Menon K, Bohn D. Hypotonic versus isotonic saline in hospitalized children: a systematic review. *Arch Dis Child*. 2006; 91(10):828–835.

11. Schrier R. Vasopressin and Aquaporin 2 in clinical disorders of water homeostasis. *Semin Nephrol*. 2008; 28: 289–296.

12. Wartofsky L. Myxedema coma. *Edocrinol Metab Clin N Am*. 2006; 35: 687–698.

13. Gheorghiade M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J*. 2007; 28(8):920–921.

14. Schrier R, Bansal S. Pulmonary hypertension, right ventricular failure, and kidney: different from left ventricular failure. *Clin J Am Soc Nephrol*. 2008; 3: 1232–1237.

15. Forfia PR, Mathai SC, Fisher MR, et al. Hyponatremia predicts right heart failure and poor survival in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2008; 177(12):1364–1369.

16. Angeli P, Wong F, Watson H, Ginès P; CAPPS investigators. Hyponatremia in cirrhosis: results of a patient population survey. *Hepatology*. 2006; 44(6):1535–1542.

17. Yu J, Zheng SS, Liang TB, Shen Y, Wang WL, Ke QH. Possible causes of central pontine myelinolysis after liver transplantation. *World J Gastroenterol*. 2004; 10(17):2540–2543.

18. Palmer BF. Pathogenesis of ascites and renal salt retention in cirrhosis. *J Invest Med*. 1999; 47: 183–202.

19. Browne WL, Nair B. The hyponatremic hypertensive syndrome in renal artery stenosis: An infrequent cause of hyponatremia. *J Postgrad Med*. 2007; 53: 41–43.

20. Agarwal M, Lynn K, Richards M, Nicholls M. Hyponatremic-hypertensive syndrome with renal ischemia: an underrecognized disorder. *Hypertension*. 1993; 33: 1020–1024.

21. Palmer BF. Hyponatremia in patients with central nervous system disease: SIADH or CSW. *Trends Endocrinol Metab*. 2003; 14: 182–187.

22. Sterns R, Nigwekar S, Hix J. The treatment of hyponatremia. *Semin Nephrol*. 2009; 29: 282–299.

23. Hew-Butler T, Ayus J, Kipps C, et al. Statement of the second international exercise-associated hyponatremia consensus development conference, New Zealand. *Clin J Sport Med*. 2008; 18: 111–121.

24. Mohmand H, Issa D, Ahmad Z, Cappuccio J, Kouides R, Sterns R. Hypertonic saline for hyponatremia: risk of inadvertent overcorrection. *Clin J Am Soc Nephrol*. 2007; 2: 1110–1117.

25. Perianayagam A, Sterns R, Silver S, et al. DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. *Clin J Am Soc Nephrol*. 2008; 3: 331–336.

26. Zeltser D, Rosansky S, va Rensburg H, Verbalis J, Smith N. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. *Am J Nephrol* 2007; 27: 447–457.

27. Schrier R, Gross P, Gheorghiade M, et al., Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006; 355: 2099–2112.