Disorders of Water Balance: Hyponatremia
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I. Objectives
By the end of the lecture, students should have an understanding of the following concepts:
A. The role of osmotically mediated secretion and release of ADH in maintaining constancy of plasma sodium concentration and plasma osmolality.
B. Non-osmotic release of ADH interferes with excretion of water and is the main cause of water retention and dilution of body fluids.
C. The plasma sodium concentration is a ratio between total sodium and total water in the extracellular fluid compartment. A decrease in sodium concentration from normal values is usually caused by impaired excretion of water such that there is proportionately more water than sodium in extracellular fluid.
D. Hyponatremia is usually associated with hypoosmolality of the extracellular and intracellular fluid volumes.
E. Hyponatremia with hypoosmolality is always accompanied by swelling of cells, but extracellular fluid volume may be increased, decreased, or clinically normal.
F. The pathophysiology of hyponatremia associated with increased, decreased, or clinically normal extracellular fluid volume and the clinical and laboratory manifestations of these three conditions.
G. The pathophysiology of hyponatremia with hyperglycemia.

II. Lecture Outline
A. Regulation of water excretion: antidiuretic hormone, thirst, renal concentration, and dilution of urine.
B. Osmotic and non-osmotic release of ADH.
C. Hyponatremia: general concepts.
D. Hyponatremia with an increase in extracellular fluid volume.
E. Hyponatremia with a decrease in extracellular fluid volume.
F. Hyponatremia with a clinically normal extracellular fluid volume.
G. Hyponatremia associated with hyperglycemia.
H. Pseudohyponatremia.
I. Hyponatremia: Differential Diagnosis
Regulation of Water Excretion: Antidiuretic Hormone, Thirst, Concentration and Dilution of Urine

Under conditions of normal health, the solute concentration (osmolality) of extracellular and intracellular fluid is maintained remarkably constant. In a given population, the plasma osmolality varies between 280 and 295 mOsm/kg H2O. In any given person, the average osmality varies by no more than two to three percent, despite water intake that may vary from a half a liter to several liters a day. Since the major determinant of extracellular fluid osmolality is sodium and its accompanying anions, it follows that plasma sodium concentration is also very constant. This constancy is achieved by a mechanism that promotes water intake and retention, or water excretion, to keep it in balance with sodium content. This precise regulation of water balance is mediated by a feedback mechanism between the hypothalamus and the kidney. The features of this feedback mechanism are shown in figure 1.

**Figure 1.**

A small loss of water, for example from insensible losses through the skin and the respiratory tract, that produces a small increase in plasma osmolality of perhaps 1% or 2%, is detected by osmoreceptors near the hypothalamus. This stimulus causes secretion of antidiuretic hormone (ADH) from the hypothalamus and release of the hormone from the posterior pituitary gland (osmotic secretion and release of ADH). This results in increased tubular reabsorption of water in cortical and medullary collecting ducts, hence excretion of only a small volume of concentrated urine and conservation of water. Furthermore, an increase in plasma osmolality greater than 2% to 3% stimulates other osmoreceptors near the hypothalamus that produce thirst and promote water drinking. The combination of increased water intake and renal conservation of water causes water retention and lowers the plasma osmolality back to normal. Intake of water is essential to correct the deficit since the kidney can conserve but not generate water. Since extracellular and intracellular fluid are in osmotic equilibrium, it follows that intracellular osmolality also returns to normal.

As shown in the bottom part of figure 1, an intake of water that produces dilution of body fluids with a small decrease in plasma osmolality of perhaps 1% to 2% inhibits release of ADH. This leads to decreased reabsorption of water in the collecting ducts, resulting in the excretion of a large volume of dilute urine, enough to excrete the volume of water ingested. Thus the plasma osmolality is increased back to the set point. Dilution of body fluids is only a weak inhibitor of thirst, and the capacity of the kidney to excrete water is so great that the correction of the surplus of water is accomplished by excreting the excess water even when water intake continues. This is in contrast to the correction of a water deficit that requires increased water intake.

The key element in this feedback mechanism is that osmotic release of ADH is prompt and very sensitive (responsive to very small changes in plasma osmolality), permitting rapid responses to small increases or decreases in plasma osmolality. Furthermore, the half-life of ADH is short; once the desired retention of water is achieved and release of the hormone is curtailed, its effect ceases.
To summarize, very small changes in plasma osmolality affect ADH secretion and release in such a way as to promptly return the osmolality back to its normal value. Disruption of this feedback mechanism causes disturbances in water balance. At one end of the spectrum, deficiency of ADH, or an impaired response of the kidney to its effects, impairs water conservation; if this is not compensated for by increased water intake a water deficit and hypernatremia will occur. At the other end of the spectrum, impairment of the ability to dilute the urine and excrete large volumes of urine, i.e. when ADH cannot be suppressed, can lead to retention of water, dilution of body fluids and hyponatremia.

**Osmotic and Non-Osmotic Release of Antidiuretic Hormone**

<table>
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<tr>
<th>TYPE</th>
<th>SIGNAL</th>
<th>RECEPTOR</th>
<th>SENSITIVITY</th>
<th>PHYSIOLOGIC RESPONSE</th>
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<tr>
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<td>↑ pOsm</td>
<td>Osmoreceptor</td>
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<tr>
<td>Non-osmotic</td>
<td>↓ ECFV</td>
<td>Baroreceptors</td>
<td>Low</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-osmotic</td>
<td>↓ blood pressure</td>
<td>Baroreceptors</td>
<td>Low</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-osmotic</td>
<td>Drugs, vomiting, stress, SIADH</td>
<td>Direct neural?</td>
<td>N/A</td>
<td>No</td>
</tr>
</tbody>
</table>

pOsm = plasma osmolality; ↓ decrease; ↑ increase; ECFV = extracellular fluid volume; N/A = not applicable; SIADH = syndrome of inappropriate ADH secretion

Sensitivity: high = small change in signal required to trigger release
low = large change in signal required to trigger release

Physiologic response: part of a feedback mechanism

Table 1 summarizes the stimuli that release ADH. These can be divided into osmotic and non-osmotic stimuli. The osmotic release of the hormone is described above. The signal for release is an increase in plasma osmolality, the receptor is an osmoreceptor, the mechanism is very sensitive since a very small change in plasma osmolality causes the release; the response is a physiological one, geared toward restoring the plasma osmolality to normal. Two non-osmotic stimuli for ADH release are a fall in systemic blood pressure, and a decrease in the extracellular fluid volume, both detected by baroreceptors located in the neck and chest. The response to both stimuli is considered a physiological one. They are part of a feedback mechanism, the purpose of which is to promote water retention to restore the blood pressure and blood volume required to perfuse vital organs, albeit at the expense of producing hypoosmolality of body fluids since these stimuli override the expected osmotic inhibition of ADH release.

The mechanism involved in the feedback response to these non-osmotic stimuli is less sensitive than that regulating the osmotic stimuli, since a large decrease in blood pressure or volume is required to elicit ADH release and overcome the osmotic inhibition of ADH release. There are also a variety of non-osmotic stimuli, such as drugs, vomiting, pain and stress that promote transient release of ADH. Such stimuli do not serve a physiologic role and probably act directly at the hypothalamus to increase the secretion of ADH. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is characterized by autonomous secretion of ADH. This occurs, for example by tumor cells, or stimulation of ADH secretion by central nervous system disease, or by hypoxia in various lung diseases, thus impairing the capacity of the kidney to maximally dilute the urine and to excrete water. The term “inappropriate” applies because, in contrast to the volume and pressure stimuli, there is no physiologic advantage to the release of the hormone in this syndrome. Most defects in the capacity to excrete water are caused by non-osmotic release of ADH. When such non-osmotic release of the hormone occurs, and water intake exceeds
the capacity of the kidney to excrete urine, water is retained causing dilution of body fluids and hyponatremia.

**Hyponatremia: General Concepts**

The plasma sodium concentration is a ratio between total sodium content and total water in the extracellular fluid. Hyponatremia, a decrease in plasma sodium concentration (less than 135 mEq/L), almost always indicates that there is proportionately more water than sodium in the extracellular fluid caused by an impairment in excretion of ingested water. Under normal conditions the kidney has the capacity to excrete large volumes of dilute urine. However, non-osmotic release of ADH disrupts the usual osmotic inhibition of ADH and interferes with the kidney’s ability to excrete water in a timely fashion. Retention of water with development of plasma hypoosmolality and hyponatremia occurs when intake of water exceeds the impaired capacity of the kidney to excrete water. Since intracellular fluid (ICF) always has the same osmolality as extracellular fluid (ECF), it follows that the osmolality of intracellular fluid is also decreased in subjects with hyponatremia. The fall in intracellular fluid osmolality results from osmotic movement of water from the extracellular to the intracellular fluid compartment.

Subjects with hyponatremia always have swollen cells to a varying degree. Swelling of brain cells accounts for the neurologic symptoms and the high mortality of patients who develop hyponatremia over a short period of time. After several days, cell swelling is lessened by elimination of solute by the cells. While the cells are always swollen in hyponatremic patients, the total body sodium, hence the volume of extracellular fluid, may be normal, increased or decreased, depending on whether the problem is pure water retention, retention of more water than sodium, or loss of sodium in excess of water compared to the proportion normally present in plasma, respectively. We describe below the pathophysiology of hyponatremia associated with an increased, decreased or normal extracellular fluid volume.

**Hyponatremia with an Increase in Extracellular Fluid Volume**

This condition occurs in patients with syndromes that cause sodium retention by the kidneys, such as congestive heart failure, cirrhosis of the liver and less frequently in kidney diseases accompanied by large losses of protein in the urine (nephrotic syndrome). The pathophysiology of the sodium retention varies in each of these syndromes, but all patients present with swelling (edema), indicating that extracellular fluid volume is increased. Usually water is retained with sodium in the same proportion as present in normal plasma, but in the more severe forms of the syndromes, water is retained in excess of sodium leading not only to edema, but also to hyponatremia. The excessive retention of water is usually caused by non-osmotic release of ADH.

**Figure 2.**
nephron segments sodium and water are reabsorbed independently, the latter through the action of ADH.

In most patients with heart failure this results in an expanded extracellular volume, detected as edema, but the plasma sodium concentration is normal because salt and water have been reabsorbed in isoosmotic proportions. However, in patients with severe and worsening heart failure the decrease in “effective circulating volume” is greater and this causes non-osmotic release of ADH, in addition to more sodium reabsorption. Furthermore, patients with severe heart failure have increased thirst, mediated in part by angiotensin II. The combination of a certain water intake and excessive release of ADH causes water retention beyond the isoosmotic water reabsorption associated with sodium retention, hence dilution of body fluids, hyponatremia, and swollen cells. The increased sodium reabsorption leads to greater expansion of the ECF volume and worsening edema. The presence of hyponatremia in patients with heart failure is a marker of the severity of the heart failure and is an indicator of a poor clinical prognosis. The treatment for the hyponatremia is water restriction; the treatment for the heart failure involves salt restriction, pharmacological agents and in some selected patients, surgical correction of precipitating factors, or heart transplantation.

**Hyponatremia with a Decrease in Extracellular Fluid Volume**

Patients who present with this type of hyponatremia have a decrease in total body sodium, hence a decrease in extracellular fluid volume. Total body water is also usually decreased, although proportionately less so than sodium; thus, salt has been lost in excess of water and the proportion of water to sodium in plasma is increased resulting in hyponatremia. The decrease in ECF volume is usually manifested by dry mucous membranes, decreased skin turgor, weight loss, changes in pulse and blood pressure. The pathophysiology of this disorder is reviewed in figure 3.

![Figure 3.](image)

In this example, the salt and water losses are presumed caused by diarrhea or sweating. Since the fluid losses are hypotonic compared to plasma, initially proportionately more water than sodium is lost, hence a decrease in ECF volume and hypernatremia will occur. The hyperosmolality of plasma causes osmotic release of ADH. Dehydration produces thirst, and if the subject drinks sufficient water, ADH-mediated retention of water will lower the osmolality back to normal. At this juncture, the subject will have a normal plasma sodium concentration, although the ECF volume will still be decreased reflecting the decrease in total body sodium and the corresponding now isosmotic decrease in water.

If this deficit is uncorrected and the subject continues to lose salt and water, there will be a further decrease in ECF volume and even if there is no osmotic stimulus for ADH release, there will be a volume stimulus (non-osmotic stimulus) for ADH release. This continued loss of ECF volume will further stimulate thirst and if the subject drinks enough water (and only under these circumstances), excess water will be retained and the subject will develop dilution of body fluids, hyponatremia, and swollen cells without suppression of ADH. In most instances, the volume of retained water is not enough to compensate for the sodium losses and the patient will have clinical evidence of decreased ECF volume.
The treatment of the hyponatremia in this situation is replacement of sodium losses. The infusion of a solution of isotonic sodium chloride expands the ECF volume, which inhibits ADH release and reverses the other abnormalities that impair urinary dilution. The kidney is then able to excrete an appropriate volume of dilute urine, and sodium and water can be retained in the right proportion, thus restoring both the volume and osmolality of body fluids to normal.

**Hyponatremia with a Clinically Normal Extracellular Fluid Volume**

The most common form of hyponatremia seen in adults is characterized by a clinical examination that shows no edema or evidence of a decrease in ECF volume. In most instances this type of hyponatremia is caused by primary water retention, i.e. not triggered by either sodium retention or sodium loss. The pathogenesis involves a restriction in the capacity to excrete water in a timely fashion because of interference with the dilution of urine (inability to dilute the urine below 100 mOsm/kg H₂O), combined with intake of fluid that exceeds the capacity of the kidneys to excrete water. If the diluting defect is severe, the intake of water need not be excessive to develop hyponatremia. The reason these patients do not develop an obvious increase in ECF volume (edema) is that most of the retained water moves into the intracellular compartment. Also, as described below, the slight expansion of the ECF volume that may occur is partially compensated by a transient loss of salt and water by the kidneys. The most common cause for the impairment of urinary dilution is non-osmotic, nonphysiologic release of ADH, called the syndrome of inappropriate ADH secretion (SIADH), some of the causes of which are indicated in Table 2.

| TABLE 2. COMMON CAUSES OF SYNDROME OF INAPPROPRIATE ANTIURETIC HORMONE (SIADH) SECRETION |
|--------------------------|-----------------|-----------------|-------------------|
| **Cause**                | **Example**     | **Mechanism**   | **Comment**       |
| Tumors                   | Oat cell carcinoma of the lung | Ectopic production of ADH by tumor cells | This is the tumor most commonly associated with SIADH. |
| Disorders of the central nervous system | Head trauma; encephalitis | Promote hypothalamic secretion of ADH | |
| Lung diseases            | Pneumonia; abscess | Synthesis by cells of hormone that resembles ADH. In some instances, hypoxemia may trigger release from neurohypophysis. | |
| Drugs                    | Chlorpropamide (oral hypoglycemic drug) | Drugs release ADH; they may enhance or simulate its effects in the nephron. | Some do not classify drug-caused hyponatremia as SIADH. |
The most common causes of SIADH are malignancy, pulmonary disease, and diseases of the central nervous system. There are other factors that may cause a primary impairment of urinary dilution. These include drugs that simulate the effects of ADH, endocrine deficiencies that either trigger release of ADH or impair the amount of free water that can be formed, and severe renal failure, which limits the amount of free water that can be generated for excretion.

Figure 4 illustrates the pathophysiology of the hyponatremia seen with SIADH. The disorder starts with non-osmotic, nonphysiologic release of ADH, for example from tumor cells. If the affected person drinks enough water (and only if this condition is met), retention of water will occur with consequent dilution of ECF volume, development of hyponatremia and movement of water into the ICF compartment until osmotic equilibrium between both compartments occurs. This results in swelling of cells. Although most of the retained water goes into the larger of the two fluid compartments, the ICF volume, some of the water remains in the ECF volume.

The slight expansion of the ECF volume signals the kidney to excrete sodium (the usual stimulus for sodium retention or excretion is diminution or expansion of the ECF volume, respectively, as mediated by various baroreceptors). The short-lived and small excretion of sodium brings the ECF volume toward normal and contributes, probably in small measure, to the hyponatremia. The patient then reaches a steady state wherein water excretion equals water ingestion; even with the same amount of ADH secretion and volume of water intake, no further dilution of body fluids occurs, i.e., the collecting duct becomes relatively resistant to the effects of the hormone. However an increase in water intake to a higher level would again trigger water retention with the same consequences described above. One should keep in mind that, even in the new steady state, there will be slight expansion of the ECF volume (not clinically detectable). Therefore, subjects with SIADH tend to rapidly excrete ingested or infused sodium, which explains the high sodium concentration measured in their urine if intake of sodium is adequate.

One should suspect SIADH in subjects who have the following characteristics: (1) Hyponatremia accompanied by hypoosmolality in plasma. (2) A normal ECF volume as judged by good skin turgor and no edema. (3) Absence of other known causes of hyponatremia with clinically normal ECF volume (indicated above). (4) Urinary sodium excretion that is normal if the subject consumes a normal amount of sodium. (5) A urine osmolality that is not as dilute as it should be, considering the presence of hypoosmolality of plasma. A plasma osmolality below approximately 270 mOsm/kg H₂O should be accompanied by a urinary osmolality of less than 100 mOsm/kg H₂O.

The treatment of SIADH involves correction of the causal disorder, if possible. Hyponatremia can usually be managed with restriction of water intake enough to ensure that the combined losses of water from skin and respiratory tract (insensible water loss) and urine exceed intake, such that a negative water balance is achieved. When the plasma sodium concentration returns to normal, the water restriction is only that required to ensure that plasma sodium remains normal. More rapid correction of the hyponatremia is required when a very low (120 mEq/L or less) plasma sodium concentration is present and the patient has neurologic symptoms of any type. The rapid correction involves promoting prompt renal excretion of water by infusing a concentrated solution of sodium chloride, which is then excreted in a larger volume of water than that at which it was infused. Other treatment approaches can be used for the treatment of the hyponatremia occurring with incurable and/or long-lasting SIADH.
Hyponatremia Associated with Hyperglycemia

Figure 5

While most subjects with hyponatremia have concomitant hypoosmolality of plasma caused by retention of ingested water in the presence of a defect in the dilution and excretion of urine, there is one condition in which the hyponatremia is not caused by retention of ingested water. This condition is caused by water movement from the intracellular to the extracellular fluid compartment, with hyperosmolality rather than hypoosmolality of body fluids and with shrunken rather than swollen cells. The presence in extracellular fluid of a large concentration of a solute that cannot penetrate the cells causes hyperosmolality of ECF and determines the movement of water out of cells.

The most common example is that of severe hyperglycemia in uncontrolled diabetes mellitus. The mechanisms involved are reviewed in figure 5. Insulin deficiency impedes the entry of glucose into cells and creates an osmotic gradient with movement of water out of cells (cell shrinkage) causing dilution of sodium and other solutes, including glucose, in the ECF. The persistently high concentration of glucose in the uncorrected condition accounts for the high osmolality of body fluids. Hyperglycemia, in turn, leads to glycosuria with increased urine volume and loss of sodium, potassium and other solutes (osmotic diuresis). These patients therefore have a decrease in ECF volume with a deficit of water usually in excess of sodium and would have had hypernatremia rather than hyponatremia had there not been an osmotic gradient for water movement out of cells. Treatment of the condition involves giving insulin to lower glucose concentration in plasma, and correcting the deficit of water and solutes, generally with the administration of intravenous fluids. In this manner the osmolality of body fluids and the ECF and ICF volumes are returned to normal.

Pseudohyponatremia

Pseudohyponatremia or “false hyponatremia” results from a technical problem with analysis that causes an underestimate of the plasma sodium concentration, so that the subject appears to have a low plasma concentration when it is, in fact, normal and the plasma osmolality is normal. Thus, these subjects do not have a defect in water excretion, and cell volume is normal. They have a metabolic problem characterized by marked elevation in plasma of large molecules, such as lipids and/or proteins. In these situations, the concentration of sodium in plasma water, and therefore the osmolality, is normal, but the concentration of sodium per liter of plasma, as measured by flame-photometry, is artifactually decreased. This occurs because the method overestimates the volume of water in the sample of plasma; in fact a substantial portion of the sample is composed of the elevated concentration of the macromolecules. The measurement of plasma osmolality is not influenced by the macromolecules and is normal in this condition. The treatment of pseudohyponatremia is obviously directed at the metabolic problem, since there is no surfeit of water. The use of ion-specific electrodes for measurement of plasma sodium concentration has diminished, but not completely eliminated this type of error. To better explain this error in measurement, we have used the imaginary situation depicted in figure 6.
Assume that a fish tank has 5 fish in 5 liters of water. Further assume that you introduce 1 kg of pebbles into the tank, thus displacing 1 liter of water and the fish that was swimming in that liter of water. There are now 4 fish in 4 liters of water and the concentration of fish is still 1 fish per liter. However, if the calculation assumes that the pebbles are water, then we will think that there are 4 fish in 5 liters of water and the concentration will be falsely assumed to be 0.8 fish per liter. A situation of a pseudo decrease in fish concentration!!

Flame-photometry assumes that all of a certain volume used for analysis is fluid and cannot detect the solid component.

Finally, one should mention that the lipids and proteins contribute little if at all to the total osmolality because of their high molecular weight.
### Hyponatremia: Differential Diagnosis

<table>
<thead>
<tr>
<th>Conditions Associated with Hyponatremia</th>
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<tbody>
<tr>
<td><strong>Posm</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Normal ECFV</td>
</tr>
<tr>
<td>↓ ECFV</td>
</tr>
<tr>
<td>↑ ECFV</td>
</tr>
<tr>
<td>Spurious or false</td>
</tr>
<tr>
<td>↑ ECF solute</td>
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Posm: Plasma osmolality; Uosm: Urine osmolality; UNa: Urine sodium concentration; SIADH: Syndrome of inappropriate ADH secretion; ECFV: Extracellular fluid volume; CHF: congestive heart failure

*Unless the kidney is the source of salt losses

**Inappropriate considering the hypoosmolality of body fluids, but water retention serves the function of partially correcting severe ECF volume depletion.

***If sodium intake is plentiful.

Table 3 shows an approach to the differential diagnosis of hyponatremia. A first step in the differential diagnosis is to separate patients who have hyponatremia associated with plasma hypoosmolality from those who have hyponatremia explained by other mechanisms. This can be done by measuring plasma osmolality. Patients with a normal plasma osmolality, with few exceptions, have pseudohyponatremia; patients with a high plasma concentration of a certain solute (such as glucose) have a higher than normal plasma osmolality. Patients who have a defect in water excretion have a lower than normal plasma osmolality. The latter patients fall into three categories: those who have obvious edema, indicating that ECF volume (and therefore total body sodium) is increased; those who have diminished ECF volume (and therefore decreased total body sodium) and those that have a clinically normal ECF volume. The differential diagnosis of these three groups of subjects with hypoosmolality of plasma is based primarily on the clinical features.

A careful history and a thorough physical examination looking for edema or signs of decreased ECF volume will usually provide a clue as to the pathogenesis of the hyponatremia. Laboratory determinations serve to confirm the clinical impression and to assess the severity of the problem. One should emphasize that all three groups of patients with hypoosmolality of plasma have a urine that is inappropriately concentrated (less than maximally dilute, since the osmolality should be less than 100 mOsm/kg H$_2$O when plasma osmolality is less than 270 mOsm/kg H$_2$O). This is to be expected since the retention of ingested water results from an impairment of urinary dilution.
The laboratory variable that may be most useful in separating these three groups of patients is the sodium concentration in urine. This is very low in patients who have a salt-retaining state and in patients who have experienced extrarenal losses of salt and water, since in both circumstances the kidney retains sodium very avidly. Patients with SIADH are in sodium balance and therefore excrete normal amounts of sodium if their intake is normal. It is obvious that the differential diagnosis of hyponatremia is of the utmost importance since the treatment of the hyponatremia is different in each of these syndromes. Finally, it should be noted that, while SIADH is the most common cause of hyponatremia with a clinically normal ECF volume, hypothyroidism and hypocortisolism may also present with an impairment of water excretion that may simulate SIADH. Therefore, these conditions must be excluded with measurement of the concentration of the respective hormones in blood before making the diagnosis of SIADH.