



## Review Article

## Ten common pitfalls in the evaluation of patients with hyponatremia

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## ABSTRACT

Hyponatremia is the most common electrolyte disorder in hospitalized patients associated with increased morbidity and mortality. On the other hand, inappropriate treatment of hyponatremia (under- or mainly overtreatment) may also lead to devastating consequences. The appropriate diagnosis of the causative factor is of paramount importance for the proper management and avoidance of treatment pitfalls. Herein, we describe the most common pitfalls in the evaluation of the hyponatremic patient, such as failure to exclude pseudohyponatremia or hypertonic hyponatremia (related to glucose, mannitol or glycine), to properly assess urine sodium concentration and other laboratory findings, to diagnose other causes of hyponatremia (cerebral salt wasting, reset osmostat, nephrogenic syndrome of inappropriate antidiuresis, prolonged strenuous exercise, drugs) as well as inability to measure urine osmolality or delineate the diagnosis and cause of the syndrome of inappropriate antidiuretic hormone secretion. Clinicians should be aware of these common clinical practice pitfalls, which could endanger patients with hyponatremia.

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Hyponatremia is the most common electrolyte disorder in hospitalized patients, with an incidence ranging from 10 to 30% [1–3]. Acute (<48 h) and chronic hyponatremia are both associated with increased morbidity and mortality [4,5]. On the other hand, inappropriate treatment of hyponatremia could also have devastating consequences, including the osmotic demyelination syndrome that leads to major neurologic disabilities or even death [4–6]. The appropriate diagnosis of the causative factor is of paramount importance for the proper management and avoidance of treatment pitfalls, which can lead to under or mainly overtreatment of hyponatremia.

Herein, we describe the ten most common pitfalls in the evaluation of the hyponatremic patient (Table 1).

### 1. Failure to exclude pseudohyponatremia

Patients with pseudohyponatremia exhibit non-hypotonic hyponatremia with normal values of plasma osmolality (Posm 275–290 mOsm/kg), measured with an osmometer. However, since an osmometer is not invariably available, the suspicion of pseudohyponatremia should be raised upon a case of hyponatremia in an entirely asymptomatic patient. Pseudohyponatremia is observed in

patients with hyperproteinemia (as seen in multiple myeloma and other monoclonal gammopathies or with intravenous immunoglobulin administration) and severe hypertriglyceridemia [7–9]. Severe hypercholesterolemia, mainly due to primary biliary cirrhosis, is also a cause of pseudohyponatremia [10]. Serum levels of total proteins and lipid parameters (total cholesterol and triglycerides) should be always measured in patients with low serum sodium levels. It is worth mentioning that pseudohyponatremia is observed when indirect potentiometry with diluted samples is used to determine serum sodium levels. The analysis of electrolyte concentrations with indirect ion-selective electrodes is preceded by a dilution step of the sample. Thus, the dilution step and the subsequent calculation of concentration lead to a falsely low sodium concentration, when water concentration has been altered by increased lipid or protein levels [11]. In patients with suspected pseudohyponatremia, measurement of sodium levels with a direct potentiometer (using one of the most modern blood gas analyzers), which does not include a dilution step, could reveal the true serum sodium concentration [9,12].

### 2. Failure to exclude hypertonic hyponatremia

Hypertonic hyponatremia (normal/increased Posm >280 mOsm/kg) is related to the presence of an osmotically active substance in the circulation [9]. In this case, free water is osmotically moved from intracellular environment to intravascular space leading to decreased serum sodium levels. The diagnosis of hypertonic hyponatremia can be easily achieved when an osmometer is available. In the absence of an osmometer,

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**Table 1**  
Common pitfalls in the evaluation of hyponatremic patients.

Pitfall	Associated conditions that could be missed and/or clues to diagnosis
Failure to exclude pseudohyponatremia	Hyperproteinemia (multiple myeloma, other monoclonal gammopathies, intravenous immunoglobulin administration), severe hypertriglyceridemia and hypercholesterolemia
Failure to exclude hypertonic hyponatremia (measurement of Posm)	Elevated levels of glucose, administration of mannitol, glycine, hyperosmolar radiocontrast media administration
Inability to measure and properly evaluate the urine osmolality (Uosm)	Primary polydipsia (Uosm <100 mOsm/kg), beer-potomania syndrome, tea and toast diet
Failure of assessment of urine sodium concentration in a random urine specimen	Low effective arterial blood volume (urine sodium <30 mEq/l), SIADH (>30 mEq/l)
Failure to properly evaluate other laboratory findings in hyponatremic patients	Serum uric acid levels: <4 mg/dl → SIADH, >5 mg/dl → hypovolemia. FEUA: <4% → hypovolemia, 4–11% → reset osmostat or primary polydipsia, >11% → SIADH Urea levels (<10 mg/dl) with increased FEurea (>55%) → SIADH Hypothyroidism, adrenal insufficiency, pituitary insufficiency Drug-associated hyponatremia, malignancy, temporal arteritis, Waldenström macroglobulinemia
Diagnosis of SIADH without exclusion of other causes of hyponatremia	Serum urea levels: increased in CSW. Central venous pressure: low in CSW.
Inability to delineate the cause of SIADH	Administration of NaCl 0.9%: increase in serum sodium in CSW. FEUA: >11% in CSW after restoration of normonatremia
Failure to diagnose the underlying cause of hyponatremia in patients with neurological diseases: Differential diagnosis between SIADH and cerebral salt wasting (CSW)	Reset osmostat syndrome, nephrogenic syndrome of inappropriate antidiuresis, strenuous exercise
Failure to recognize other causes of hyponatremia not usually considered in the evaluation of hyponatremic patients	Thiazides, selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors (SNRIs), carbamazepine, oxcarbamazepine, ecstasy
Failure to realize the supreme role of a growing list of medications associated with decreased sodium levels	
SIADH = syndrome of inappropriate antidiuretic hormone secretion; FE = fractional excretion	

hypertonic hyponatremia should be suspected in patients with elevated levels of glucose [13]. In these cases, it is imperative to calculate the serum sodium corrected for the degree of hyperglycemia by increasing the measured serum sodium level by 1.4 to 2.4 mEq for every 100 mg/dl of blood glucose increase above normal [14]. In these cases, patient's management should proceed according to the corrected serum sodium levels [15,16]. Hypertonic hyponatremia is also observed with the administration of mannitol, glycine (for example during transurethral resection of the prostate or gynecological procedures), or even with hyperosmolar radiocontrast media administration [9,17]. A careful and thorough history can reveal the cause of hyponatremia in such cases.

### 3. Inability to measure and properly evaluate the urine osmolality (Uosm)

Uosm (measured with an osmometer) is useful for the determination of urine diluting ability, which actually reflects vasopressin (antidiuretic hormone, ADH) activity. A value below 100 mosmol/kg suggests that kidneys' ability to excrete maximally diluted urine remains intact. In this case, the cause of hyponatremia is either primary polydipsia or other underlying psychiatric disorders, such as schizophrenia, which are associated with massive water intake [18]. However, hyponatremia with decreased Uosm can also be observed in individuals who consume large amounts of fluid but small amounts of salt and protein. This results in a limited amount of solutes to be excreted and leads to decreased water excretion. This phenomenon has been reported in ill-nourished heavy drinkers (beer potomania syndrome) but also in elderly with increased water and low solute intake (for example, tea and toast diet) [19–22]. Psychiatric patients with increased water intake (partially due to drug-associated xerostomia) and impaired renal diluting ability (underlying renal disease, volume depletion, decreased solute intake or drugs affecting water homeostasis such as thiazide diuretics) may exhibit hyponatremia with relatively dilute urine but with Uosm > 100 mosmol/kg (usually between 100 and 300 mosmol/kg) [6]. It has also been reported that acute psychosis results in increased ADH secretion and water retention [23]. Finally, low urine osmolality is similarly observed after rehydration with saline solutions in patients with hyponatremia attributed to hypovolemia. In hypovolemic hyponatremia, the restoration of euovolemia rapidly reverses the defect in water excretion (hypovolemia-induced ADH increase) and may lead to brisk aquaresis and rapid correction of hyponatremia (autocorrection).

In this case frequent measurement of serum sodium concentration and appropriate limitation of the rate of correction are mandatory [6,24]. It is worth mentioning that patients with severe kidney disease exhibit decreased urine diluting ability and are prone to develop hyponatremia [25].

### 4. Failure of assessment of urine sodium concentration in a random urine specimen

The estimation of urine sodium concentration is mandatory for the etiologic diagnosis of hyponatremia. Values of less than 30 mEq/l are suggestive of low effective arterial blood volume due to either true hypovolemia or to edematous states, such as congestive heart failure or ascites [26–28]. On the contrary, a value of >30 mEq/l points toward the diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [29]. However, it should be mentioned that increased urine sodium levels are frequently observed in several clinical conditions associated with the development of hyponatremia, such as renal failure, salt losing nephropathy, primary adrenal insufficiency, thiazide administration, glucosuria and metabolic alkalosis [30]. In the case of metabolic alkalosis, a useful clue is the identification of low urine chloride concentration (<30 mEq/l), which points toward extracellular volume depletion [31]. On the other hand, low urine sodium levels can be found in patients with chronic SIADH on a low salt diet or anorexia.

### 5. Failure to properly evaluate other laboratory findings in hyponatremic patients

Other laboratory parameters that should be assessed in patients with hyponatremia include:

- Serum uric acid levels: values <4 mg/dl are commonly encountered in SIADH, while values >5 mg/dl are mainly observed in patients with hypovolemia [32]. It is worth mentioning that the determination of serum uric acid levels is also useful in patients with thiazide-associated hyponatremia, since it can be used in the differential diagnosis between the two distinct subgroups of patients with thiazide-associated hyponatremia, namely patients with extracellular volume depletion (serum uric acid >5 mg/dl) and patients with a SIADH-like picture (serum uric acid levels <4 mg/dl) [33].

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