

**Review Article**

What an Internist Need to Know About Hyponatremia?

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In the ICU, the prevalence of hyponatremia (< 135 mEq/l) is around 15%, and 4.5% have a SNa lower than 125 mEq/l [1]. Outside the hospital for patients aged more than 65 y.o. the prevalence is 4.3% (for SNa < 135 mEq/l) and 0.14% have a SNa lower than 126 mEq/l [2,3]. In virtually all common conditions, the presence of hyponatremia is associated with increased morbidity and mortality, regardless the levels of hyponatremia (for a review, see Ref. [3]).

Keywords: Hypertonic Saline; Urea Therapy; Uric Acid; Urine Osmolality; ODS

Non Hypotonic Hyponatremia

When the measured osmolality is normal, or exceeds the calculated one ($2 \times \text{Na mmol/l} + \text{glucose mmol/l}$ (or mg/dl/18) + urea mmol/l (or mg/dl/6) by more than 10 mOsm/kg H_2O , it implies the presence of an osmolal gap. This occurs either when there is a decrease in the water content of the serum, or when there is addition of a solute other than urea or glucose in the serum [4]. About 93% of the normal serum is represented by water. Sodium is diluted only in the aqueous phase where its mean concentration is 154 mEq/l ($154 \times 0.93 = 142$ mEq/l). Thus a major increase in triglyceride or protein will artefactually decrease the serum sodium concentration. However, these macromolecules do not influence the serum osmolality. When hyperproteinemia is caused by accumulation of cationic γ globulins (e.g. immunoglobulin G myeloma) another mechanisms explain the reduction of the serum sodium value, the cations of γ globulin partly substituting for sodium in balancing serum anions. Since serum osmolality remains unchanged, the increase in serum chloride must equal the reduction in serum sodium. This hyponatremia is limited to the plasmatic space where paraproteins are present in appreciable quantities [5]. Administration of a large volume of gamma-globulins (2 g/kg over 2-5 days) is a widely known factor for pseudohyponatremia (mean decrease in SNa, ~ 3 mmol/l [6]).

Generally, the tonicity is more important for the organism than is the osmolality. Tonicity is the concentration of solutes which have the capacity to exert an osmotic force across membrane and thereby initiate a movement of water into or out of cells depending on the gradient. Thus, since urea and some other low molecular weight substances such as ethanol, methanol or ethylene glycol rapidly penetrate cells, they exert no effective osmotic force across most body membranes. Hence, hyponatremia associated for example with severe azotemia represents a true hypotonic state in regards to the cells and this despite a normal or high osmolality (depending on the level of uremia). Water movement across semipermeable membranes rapidly dissipates any pathologic attempt to create a transcellular concentration gradient. So that determination of extracellular osmolality allow to known intracellular osmolality. Measurement of serum osmolality is indicated when pseudohyponatremia is suspected because of lactescent serum, multiple myeloma or in "translocational hyponatremia". Translocational hyponatremia is observed when the patient has accumulation in the extracellular fluid of a solute which does not penetrate the cell (glucose, mannitol, sorbitol, glycerol, maltose, glycine, radiocontrast agents) and which draws water from the intracellular compartment. It has been shown that a correction factor of a 2.4 mEq/l decreases in sodium concentration per 100 mg/dl increase in glucose concentration is a better overall estimate of this association than the usual correction factor of 1.6 [5].

Translocation hyponatremia is typically observed during the early phase of the "post-TURP syndrome". Transurethral resection of the prostate (TURP) and endoscopic uterine surgery necessitate large volumes of non-conductive fluid to irrigate the operative field. Glycine (200 mOsm/l, 1.5%) is the most common irrigant used, other solutes including sorbitol and mannitol. A large volume of fluid (3 to 5 l) is sometimes absorbed. This can result in the development of absorptive hyponatremia and by a spectrum of clinical manifestation named the "post-TURP syndrome". The clinical manifestations including headache, mental depression, visual manifestations, blindness, seizure, cardiorespiratory depression

and death, could be partially attributed to a direct toxicity of the absorbed glycine and its metabolites (ammonia, serine, glutamine). Experimental data shows that in the early phase (2 hr) of glycine infusion (1.5%), plasma osmolality remain normal with only minimal brain edema. Hyponatremia is “translocational” at this time. True dilutional hyponatremia could however also occur later, with brain edema as a consequence of progressive intracellular shift and metabolism of glycine. In practice, the effect of glycine infusion on osmolality and water distribution is difficult to predict and optimal treatment remains uncertain. Osmolal gap must be evaluated. In the presence of severe symptoms and hypoosmolal hyponatremia, hypertonic saline is the more appropriate approach. When severe hyponatremia is associated with an almost normal osmolality (large osmolal gap), then, hemodialysis could be used to promptly remove the excess of glycine and to correct the electrolytes disturbances [6]. The introduction of a new bipolar resectoscope that is able to function with an isotonic saline irrigant may prevent this syndrome but may have also other complication (like volume overload ...) [7].

Hypotonic Hyponatremia

Hypotonic hyponatremia always results from an excess of water relative to the exchangeable sodium and potassium pool, as a consequence of a decrease in electrolyte free water excretion [4]. Division of total body solutes by total body water allows determination of the osmolality of all body fluids and therefore: $\text{osmolality} = 2 (\text{Na E} + \text{K E}) / \text{total body water}$. Na E and KE represent, respectively, the total exchangeable body sodium and potassium. Any decrease in this ratio implies the presence of hyponatremia. Total body water (TBW) indicates sex differences and decreases with aging. For example, a male under 40 years has a TBW of about 60% of body weight (BW) and over 60 years about 50% of BW. In females TBW is about 50% (< 40 years) to 40% (> 70 years). Hence acute variation in TBW in females calls for greater modification in serum sodium concentration than in males (Figure 2). Because Na^+ is restricted to the Extracellular Fluid (ECF) volume, where it represents the most important solute, the control of sodium balance regulates the ECF volume, while the water balance determines the concentration of solute in all body fluid compartments. In general the decrease in free water excretion in an hyponatremic patient is due to the effect of ADH secretion which

is considered as appropriate if it is secondary to volume stimuli (hypovolemic or hypervolemic patients) or inappropriate (euvolemic patients: SIADH) if it occurs in the absence of osmotic or volume stimuli (see Figure 1 and Table 1) [4].

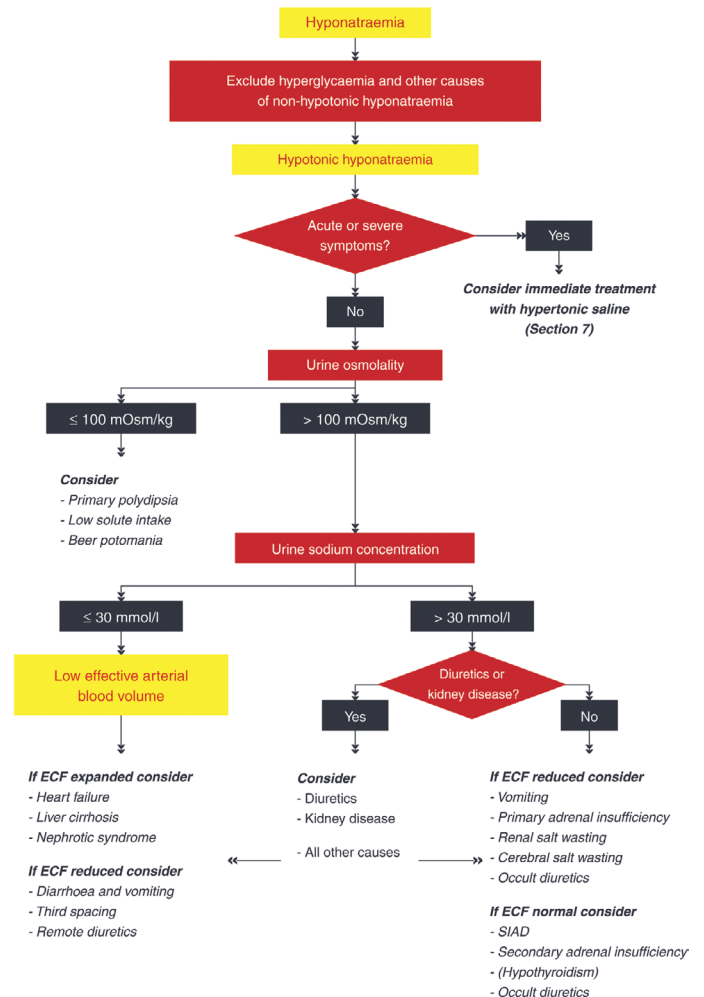


Figure 1: Algorithm for the differential diagnosis of hyponatremia (from European Guidelines 2014).

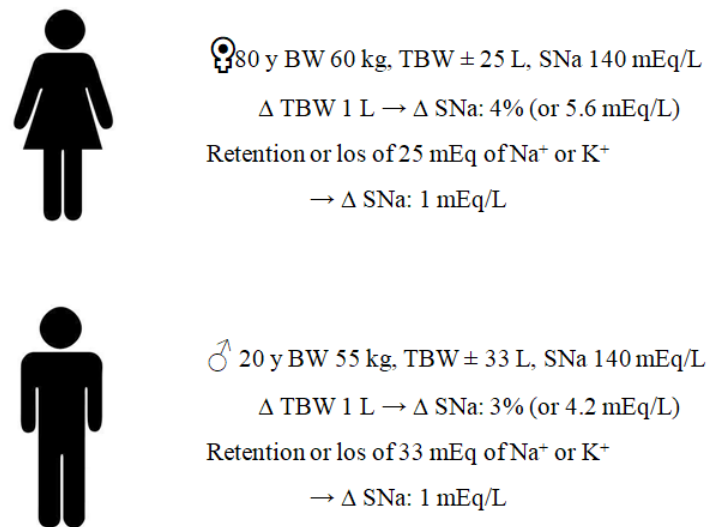


Figure 2: Effect of acute variation in total body water (TBW) and exchangeable Na and K on variation of SNa.

	Hypervolemic (\uparrow ECV; \downarrow EABV)	Hypovolemic (\downarrow ECV; \downarrow EABV)	Euvolemic (\uparrow ECV; \uparrow EABV)
History	Chronic heart failure, cirrhosis, nephrosis	Extrarenal losses (e.g. gastrointestinal, sweating, burns, third space...) Renal losses (e.g. Addison, diuretics, bicarbonaturia, salt-losing nephropathy, CSW, hypoadosteronism/mineralocorticoid resistance)	Drugs (e.g. carbamazepine, SSRI, ...) Neurological diseases (e.g. encephalitis, strokes, ...) Pulmonary diseases (e.g. tuberculosis, pneumonia, ...) Cancer (e.g. oat cell carcinoma, ...) Endocrine (e.g. hypothyroidism, pituitary hypocorticism)
Blood pressure	Low	Low	Normal
Edema	+	-	-
Plasma			
ADH	\uparrow	\uparrow	\uparrow (\downarrow) ^b
Na	\downarrow	\downarrow	\downarrow
Urea	NL- \uparrow	NL- \uparrow	NL- \downarrow
Uric acid	NL- \uparrow	NL- \uparrow	NL- \downarrow (mostly < 4 mg/dl)
Anion gap	NL- \uparrow	NL- \uparrow	NL- \downarrow ^d
Urine			
Osmolality	\uparrow	\uparrow	\uparrow
Na (mEq/l)	< 30	< 30 ^c	> 30 ^e
Clearances ratios (%)	< 0.5	< 0.5	> 0.5 ^e
FE.Na	< 18%	< 18%	< 18% ^f
FE.K ^g	\downarrow -NL (< 50)	\downarrow -NL (< 50)	NL- \uparrow
FE.urea	\downarrow -NL (< 12%)	\downarrow -NL (< 12%) ^h	> 12
FE.uric acid			
Test infusion		Plasma Na increases usually Salt retention (Δ FE.Na t24hr-t0 < 0.5%), water diuresis	Plasma Na decreases only if Uosm > 530 mOsm/kg/H ₂ O Rapid Salt excretion (Δ FE.Na t24hr-t0 > 0.5%)
2 l NaCl 0.9%/24hrs			

^aADH, antidiuretic hormone; ECV, extracellular volume; EABV, effective arterial blood volume; FE.Na, fractional excretion of sodium; FE.K, fraction excretion of potassium; FE.urea, fractional excretion of urea; FE.uric acid, fractional excretion of uric acid; NL, normal; SSRI, selective serotonin reuptake inhibitor. ^bADH is low in nephrogenic syndrome of inappropriate antidiuresis (nephrogenic syndrome of inappropriate antidiuresis or syndrome of inappropriate secretion of antidiuretic hormone type D). ^cUnless salt depletion is of renal origin. ^dIn hyponatremia related to hypopituitarism TCO₂ is frequently lower than 22 mmol/l [8]. ^eIf salt intake is normal. ^fFE.K could be high in symptomatic hyponatremia (> 18%) [9] or with diuretic intake and in RSW [8]. ^gUrate clearance can be increased in hyponatremia related to cerebral or renal salt wasting syndrome [10], or liver cirrhosis [11,12].

Table 1: Clinical and biological data generally allowing differentiation between appropriate and inappropriate ADH secretion in patients with hyposmolality^a.

Hypervolemic Hyponatremia

We will not systematically discuss the various disease states associated with each category (see Table 1). Differentiating the hypervolemic (heart failure, cirrhosis, nephrosis) from the euvolemic or hypovolemic patient is usually simple because of the presence of edema and/or ascites in the former. In the “hypervolemic” patients, despite large increase in the ECF volume, the “effective arterial blood volume” (EABV) appears to be reduced and the kidneys respond in a manner virtually similar to the response associated with sodium depletion. There is an increase in ADH secretion due to the “hypovolemic stimulus” (the major factor) and a decreased delivery of isotonic salt-containing fluid from the proximal to the distal nephron, both contributing to a decrease in electrolyte-free water excretion. Urinary sodium concentrations are low ($UNa < 20$ mmol/l), and serum urea or uric acid concentrations are normal or increased except in cirrhosis where both could sometimes be low [13]. Vagal neuropathy could also play a role in high ADH levels in cirrhotic patients [14]. Treatment is mainly centering to improving organ function, to withdrawal if possible any medication which are known to induce hyponatremia (antidepressive medications, etc.) and to follow water restriction (< 1 l/day). Vaptans are not recommended by the European guidelines (see later).

Hypovolemic Hyponatremia

It is sometimes difficult to differentiate the hypovolemic from the euvolemic patient on clinical grounds. In two studies [15,16] about 50% of the patients suffering from salt-depletion were not detected clinically or by history. Usually, when the solute loss is of extra renal origin (gastrointestinal, excessive sweating) it is hypotonic and should lead to hypernatremia; however patients often compensate for this loss with hypotonic solution or pure water, thus eventually leading to hyponatremia. If a patient loses 2 litres of half-isotonic saline, this necessitates 4 liters of pure water to normalize ECV, but this will induce mild hyponatremia (if we suppose a TBW of 40 l in a patient, the loss of 2 l half- isotonic saline will give a slight increase in the osmolality of $(40 \times 290) - 300 = 11,300/38 = 297.4$ mOsm/kg H_2O , and the intake and retention of 4 l water will decrease the osmolality $(297.4 \times 38)/42 = 269$ mOsm/kg H_2O . But usually retention is not sufficient to normalize ECV (body weight will increase by correcting solute deficit) [17].

Depending on the degree of water retention we can understand that clinical detection of extracellular fluid volume depletion could be difficult and that prerenal azotemia may be lacking. The best treatment, if loss of extracellular electrolytes is responsible for the hyponatremia, is isotonic saline infusion (2-3 l/day, or more if severe) which, by repletion of the sodium pool and the volume expansion it induces will decrease the secondary ADH secretion and allow the kidneys to eliminate electrolyte-free water. However, if necessary, some biochemical parameters could help distinguish hypovolemic from euvolemic hyponatremic patient (SIADH) (see Table 1). The most useful and inexpensive’s one is the determination of sodium concentration in a spot urine sample, which is below 30 mEq/l in

most saline responsive hyponatremic patient and higher than 30 mEq/l in saline non-responders (SIADH). In fact, it is not unusual in hypovolemia for UNa to reach values as high as 50-60 mEq/l [18], particularly in older people who may have slower adaptative mechanisms for retention of sodium when effective volaemia is decreasing. The determination of the fractional sodium excretion in these patients shows values lower than 0.5% and gives less overlap than in patients with SIADH ($FENA > 0.5\%$) [16,19]. Tubular handling of the electrolytes, urea and uric acid are highly influenced by the “effective vascular volume”. Tubular reabsorption of a substance can be evaluated by measurement of the fractional excretion of that filtered substance (FE). This is easily obtained by measuring the concentration of creatinine, by measurement of the substance in a spot urine collection, and by the same measurement made concomitantly in the serum ($FE.X$ (in %) = $Ux/Px.Pc/Uc \times 100$). In patients with salt depletion, urea and uric acid clearance decrease proportionally more than the creatinine clearance, so that their respective fractional excretion is reduced ($FE.urea < 55\%$ and $FE.uric\ acid < 12\%$). This decrease in urea and uric acid clearance reflects an increased tubular reabsorption secondary to the decreased effective volaemia. It is not rare for patients with depletion hyponatremia to present low serum urea or uric acid concentrations reflecting low synthesis. The measurement of the fractional urea and uric acid excretion will be low in these patients. A diagnostic test of an infusion of normal saline solution might sometimes be considered. If the patient has SIADH, natriuresis will be substantially increased and serum sodium will not be corrected or may further decrease except if urine osmolality is lower than 530 mOsm/kg in which case the serum sodium will increase [20].

Salt depletion could be of renal origin: in Addison’s disease, combined mineralo-corticoid deficiency (which causes renal sodium wasting and hyperkalaemia) and glucocorticoid deficiency (which enhances AVP secretion) contribute to high AVP concentration. In hyponatraemia-related to “Cerebral Salt Wasting” (CSW) syndrome, natriuresis is believed to precede water retention (natriuresis follows water retention in classical SIADH). This syndrome has been reported with different brain diseases and particularly with subarachnoid hemorrhage (SAH) in which up to one third of patients develop hyponatraemia. It has been shown that despite large volumes of isotonic saline infusion hyponatremia developed in 32% of patients with SAH in association with non-suppressed plasma AVP levels [21]; the high AVP concentration was therefore not secondary to volume depletion. It seems likely that SAH represents a mixed disorder in which some patients have both exaggerated natriuresis and uricosuria, related to secretion of natriuretic factors and inappropriate AVP secretion [21].

Thiazides are a major contributing factor in patients admitted to the hospital for severe hyponatremia (this will not be develop her). In some of these patients, polydipsia may play a major role in the development of hyponatremia. Patients “could typically” present hyponatremia, hypokalemia and metabolic alkalosis. The presence of a high $FE.K^+$ ($> 15\%$) is highly “suggestive” of diuretic “induced”

hyponatremia (sometimes taken surreptitiously).

A high FE_K is also frequently reported in symptomatic hyponatremia whatever the origin (reflecting cell adaptation to hypotonicity) [9]. In hyponatremia related to diuretic intake (mainly thiazide), one group appears volume depleted and another group seems volume “expanded” as in SIADH.

It has been recently shown that even in patients with a SIADH like profile hyponatremia result mainly from severe solute depletion and not water retention [17]. Measurement of urine Na concentration could be highly variable (depending if diuretic is still acting or not). In these patients, full recovery of diluting ability may be delayed for 1 to 2 weeks.

In a series of 110 elderly hyponatremic patients isotonic saline infusion was useful in about 2/3 of the patients (represented by patients with saline depletion, diuretics patients, polydipsic patients, salt losing patients and some salt depleted SIADH patients) [18].

Treatment is by solute repletion, usually isotonic saline (around 2 l/day) and if hyponatremia is severe (< 115-120 mmol/l), to avoid an increase in SNa of more than 8 mmol/l the first day and no more than 8 mmol/ during every 24hr thereafter (see later).

Euvolemic Hyponatremia (Normal or Mild Increase in Tbw)

Psychogenic polydipsia and beer potomania

If the daily solute excretion is for example 700 mOsm and the patient can dilute his urine to about 50 to 100 mOsm/kg H₂O, he should be able to eliminate 7 to 14 liters of urine daily, or 291 to 583 ml/hour. In fact these patients could sometimes drink very large volume of water in a few hours, and overcome the quantitative diluting ability of their kidney. Many of these patients have some degree of impairment of diluting ability of various origins (nicotine, psychotropic drugs, nausea associated with massive water intake, psychosis itself, enhanced sensitivity to ADH, reset osmostat). These patients present frequently acute symptomatic hyponatremia (see later). In beer potomania, patients frequently stop eating, the only caloric intakes being represented by beer which contains very little protein and electrolytes. Low solute intake will increase the risk of hyponatremia (“tea and toast hyponatremia”) [4]. These patients (usually presenting a FE_{Osm} < 1%) [21] if they don’t want to restrict their water intake are easily treated with a small increase in their daily osmole intake (like 15 g urea, representing 250 mmol) [21].

Exercise induced hyponatremia

It occurs in association with overwhelming physical efforts (e.g. marathon races) or sometimes with less intense physical activity (at least four hours) [22]. Clinical presentation includes symptoms of acute hyponatremia and should be suspected in the event of collapse during exercise. It can be associated with non-cardiogenic pulmonary edema [23]. The incidence of this disorder is unclear, 27% in a series of participant to a race who

needed medical care developing hyponatremia (SNa < 130 mEq/l, lowest value 114 mEq/l). The etiology of this hyponatremia is still unclear. The role of excessive sodium losses in the sweat is probably marginal. Hyponatremia is mainly dilutional through combination of excessive water ingestion during exercise and defect in free water clearance. Nausea, stress, and exercise itself add up to stimulation of ADH secretion. These patients should be treated immediately with a bolus infusion of 100 ml of 3% NaCl to acutely reduce brain edema with up to 2 additional 100 ml of 3% NaCl bolus infusions that should be given at 10 minutes intervals if there is no clinical improvement. Each bolus will increase SNa by about 2 mmol/l. It has been shown a similar efficacy of oral hypertonic saline (even better as it was not associated with a plasma volume expansion like with the intravenous route [24].

The syndrome of inappropriate secretion of ADH (SIADH)

It represents the most frequent cause of hyponatremia [4]. Initially hyponatremia results mainly from water retention, but urinary solute loss also plays an important role. Excess natriuresis follows water retention and mainly exceeds the intake if volume expansion is relatively acute. After a few days, the Na balance is re-established and a decline in the hydro-osmotic effect of ADH is observed (vasopressin escape). In SIADH there is no edema as fluid retention rarely exceeds 4 liters part of which is localized intracellularly. To diagnose SIADH, the following criteria are needed:

- 1) hypoosmolality,
- 2) inappropriately concentrated urine (> 100 mOsm/kg H₂O, although usually hypertonic to serum),
- 3) natriuresis > 30 mEq/l (dependent on sodium intake),
- 4) reversal of renal sodium wasting and correction of hyponatremia after water restriction, and
- 5) normal renal, adrenal and thyroid function and non signs of volume depletion (for example: lack of diuretic intake).

In fact urine osmolality does not help in the differential diagnosis of SIADH, as urine osmolality is also elevated in hypervolemic or hypovolemic hyponatremia, but the high urine osmolality in these conditions is mainly due to high urea concentration which allows electrolyte free water excretion. Because the regulation mechanisms of sodium excretion are intact in the SIADH, extreme dietary sodium restriction can lead to urine that is nearly sodium free, while a large sodium load is typically followed by a rapid increase in sodium excretion. SIADH has been reported by ectopic production of ADH by tumors (typically with small cell carcinoma) or by disordered secretion by the neurohypophysis. SIADH is observed in malignancies, pulmonary diseases and central nervous system disorders. Many drugs are known to induce SIADH [4]. Glucocorticoid deficiency related to hypopituitarism and hypothyroidic state may be associated with a hyponatremia similar to SIADH.

Biological markers of SIADH and therapeutic implication

Making the difference between SIADH or salt depletion is crucial for a well-adapted treatment (decreasing water excess or repletion of the Na pool). In the SIADH serum uric acid concentration is lower than expected for dilution. Many factors affect urate clearance [25,26] but the main one is the EABV. The EABV is considered to be increased which induces a high uric acid clearance, and a high uric acid fractional excretion (generally > 12%) (there is a decrease in proximal tubule sodium and urate reabsorption while uric acid is not reabsorbed distally like it is for sodium). Serum uric acid concentration is generally lower than 4 mg/dl in 84% of the patients [18]. Hypouricemia in SIADH also results from a decrease in urea tubular reabsorption; however it is less frequently observed than hypouricemia particularly in the elderly. This is explained partly by the lower FE_{urea} in the elderly and also to lower urea clearance in patients with high salt excretions [4]. When patients with hyponatremia present all the biological markers of SIADH except that bicarbonate is mildly decreased, adrenocorticotropin deficiency should be suspected. The low bicarbonate level (mean value of TCO₂ 20 mmol/l) is related to respiratory alkalosis and low aldosterone levels [8]. When studying the relationship between ADH and plasma osmolality variation obtained by saline hypertonic infusion in patients with SIADH, 5 subtypes have been described (this will not be discussed here) [27].

In some patients, a test infusion of isotonic saline is helpful to determine the precise cause of the hyponatremia. This procedure is especially useful for the differential diagnosis between SD patients and patients with SIADH when FENa and FE_{urea} values are close to the proposed differential values (although with caution to avoid a too rapid increase of SNa). It also is useful to unmask SD patients with SIADH, presenting an initial biochemical profile undistinguishable from SD patients [18]. Such SD patients with SIADH can in fact only be recognized after saline administration. In SD, plasma sodium (SNa) usually increases with only a mild increase of FENa (< 0.5% after 2 liters of isotonic saline over 24h); however, in SIADH, salt excretion rapidly occurs after saline infusion without high modification in SNa. A rapid increase in FENa (> 0.5% after 2 liters of isotonic saline over 24h) without correction of SNa correlates with inappropriate ADH secretion. Although an increase of SNa of 5 mEq/l has been proposed as indicative for depletion hyponatremia, we observed that 29% of SD patients did not increase their SNa with 5 mEq/l and that 30% of patients with true SIADH responded surprisingly well to isotonic saline with an increase of SNa of at least 5 mEq/l [18,19]. The correct interpretation of this test should take into account variation in both SNa and FENa. Patients with SIADH and a fixed urine osmolality of approximately 300 mOsm/kg (of which only third are represented by Na + K) will increase SNa by 5 mmol/l if infused with 2 liters of isotonic saline over 24 hours [4]. They can be differentiated, however, from patients with depletion hyponatremia by their high urinary salt excretion

because salt-depleted hyponatremic patients conserve salt as long as hyponatremia persists. However, it remains true that SIADH patients with urine osmolality higher than 530 mOsm/kg H₂O will, as expected, decrease their SNa after isotonic infusion [4,19]. It must be noted that in SIADH when hyponatremia is stable, the urine concentration of (Una + Uk) can varied hourly while urine osmolality stay stable. In SIADH the U(Na + K) is negatively correlated with urea [28,29]. This explain why in SIADH the urine osmolality give more information concerning the predictive value of isotonic saline infusion than the U(Na + K) value [28,29]. For SIAD different treatments have been proposed if water restriction does not normalize SNa.

During treatment with a vaptan (V2 antagonist), there is a high urine output with a low urine osmolality and no major change in sodium excretion [30]. Treatment with 30g urea (osmotic diuresis) is associated with a mild increase in diuresis, a transient decrease in sodium excretion and no decrease in urine osmolality [31]. Treatment with furosemide induces a transient high diuresis with a high sodium excretion and a urine osmolality around 300 mOsm/kg H₂O [32,33] (see Figure 3). Patients with a normal or high solute intake (FE_{osm} > 2.5%) [21] and/or urine osmolality lower than 400mOsm/kg H₂O could usually be treated by mild water restriction (< 1.5l/24hr) [34].

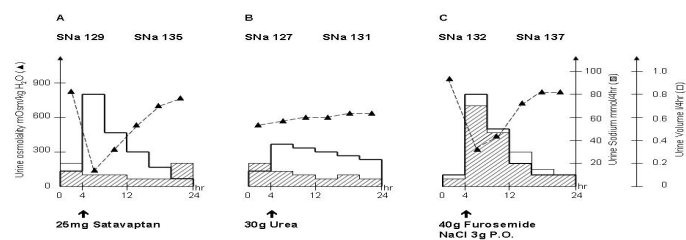


Figure 3: Evolution over 24hr of urine volume, urine osmolality, urine Na and SNa in three patients with SIADH treated with satavaptan (a V2 antagonist) (panel A), urea (panel B) or furosemide with salt supplement (panel C).

Risks Associated With Hyponatremia And Its Correction

Patients with severe hyponatremia (< 115-120 mEq/l) are exposed to major neurological complications. On the one hand, when serum sodium decreases rapidly, brain edema develops, increasing intracranial pressure because of the rigid confine of the skull. If hyponatremia is insufficiently corrected or remains untreated, uncontrolled seizures, non-cardiogenic pulmonary edema, cardiorespiratory arrest, brain herniation could develop with major risks of neuropathological sequelae or death [35,36]. On the other hand, excessive correction induces brain dehydration and could be followed by brain demyelinating lesions (central pontine and extrapontine myelinolysis or ODS) [37]. Volume regulatory mechanisms protect brain against abrupt changes in serum tonicity. Brain prevents excessive swelling by extruding electrolytes and organic osmolytes, a process almost fully achieved in 48 hr (for a review see reference

[38]). Conversely, during subsequent increase in serum sodium, reestablishment of intracerebral osmolytes occurs but their reuptake is more delayed (± 5 days) [38]. In both situations, these mechanisms may be overwhelmed, leading to brain damage. The distinction between acute (< 48 hr) and chronic hyponatremia and the presence of symptoms are crucial informations for the physician. Common symptoms include nausea, emesis and headaches. Severe neurologic manifestations develop more particularly when serum sodium fall is rapid, even after moderate decrease, as observed in the postoperative state (seizure, coma...) [35]. Hyponatremia related neuropathological sequelae are reported mainly in postsurgical period and hypoxia sometimes associated with hyponatremia encephalopathy could play as a comorbid factor [36,38]. Hyponatremic encephalopathy can present with non-cardiogenic pulmonary edema and hypoxia which has generally been fatal if serum Na is not rapidly corrected [38]. When hyponatremia develops more slowly, the brain is able to adapt to the decrease in osmolality so that chronic (> 48 hours) hyponatremia is generally better tolerated. Patients generally present more subtle symptoms (confusion, dizziness...). With extremely low serum sodium values, major neurological manifestations could be attributed to residual brain edema or to depletion in brain solutes content. Correction of the serum sodium is more hazardous in these patients, with regard to the risk of subsequent development of brain myelinolysis. Experimental data suggest that myelinolysis is the consequence of excessive brain dehydration. Indeed, hyponatremic brain dehydrates more than during normonatremia after osmotic increase, consequently to its previous depletion in osmolytes [38]. Various mechanisms are probably implicated in the demyelinating process [39]. Patients affected generally present a biphasic course, the neurological status deteriorating generally 1 to 7 days after initial improvement due to serum sodium correction. Typical signs include spastic quadriplegia, pseudo-bulbar palsy and locked-in syndrome which can lead to coma and death. Focal neurological deficit are also frequently encountered. Complete recovery is possible, but many patients have major residual disability. Diagnosis can be made by magnetic resonance imaging, generally 2 weeks to one month after the osmotic insult. To prevent this catastrophic event, the clinician must be aware of the different factors that may increase the risk of myelinolysis [38]. The major risk concerns the total daily magnitude of the serum sodium correction. Available experimental and clinical data suggest that the incidence of iatrogenic brain injuries can be greatly minimized if correction is limited to a gradient of less than 10 mmol/l/24 hr [38]. Particularly the first day the treatment should be even slower (< 8 mmol/l/24 hr) (as the daily increase in SNa is not always easy to determined, the patient could have initiate a spontaneous diuresis outside the hospital). Additionally, because of the rigidity of the skull, brain water cannot increase by more than 8-10% and there is thus theoretically no justification to prone larger correction levels of serum Na (no more than 8% of initial serum sodium). To avoid brain demyelinating lesions (ODS), the magnitude of correction should be less than 10 mmol/l/24 hr (and 18 mEq/l/48hr if no risk factors for ODS), but below this limit the rate of correction is not important [38]. Treatment is interrupted once SNa is around 130 mEq/l [40]. This means that, if necessary, an increase in 5-8 mEq/l in

one hour is possible without fear of brain damage [40,41]. The serum sodium must be also cautiously normalized in the presence of other recognized predisposing factors for myelinolysis. With concomitant hypokalemia or alcoholism, poor nutritional state, liver disease or burns, the serum sodium should be wisely corrected by less than 8 mEq/l/24 hr [38]. These patients will probably benefice the most of a rapid decrease in SNa if over treated (see later) [40,42,43].

Complications of Chronic Asymptomatic Hyponatremia

Patients with chronic hyponatremia are frequently considered asymptomatic and left untreated when fluid restriction fails (WR). Hyponatremia has been associated with attention deficit gait disturbances falls [44,45] bone fractures [2] osteoporosis [46], sarcopenia [47] and an excess mortality [48]. The unstable gait and propensity to fall, observed in hyponatremia could result from nerve conduction velocity alterations [49].

Therapeutic Guidelines

The origin of the hyponatremia and its duration are sometimes difficult to determine. Patient's history is essential. Hyponatremia in outpatients is generally subacute or chronic. When associated with exercise, polydipsia or recent thiazide intake it may develop acutely, although appearing outside the hospital. Acute symptomatic hyponatremia is generally hospital acquired, occurring mainly in the postoperative period and/or after excessive infusion of intravenous fluids. Rapid normalization of the serum sodium in these cases is theoretically devoided of risks to develop brain demyelination. A limited correction is however generally sufficient to improve the neurological status. When hyponatremia is symptomatic, an initial rapid correction could be obtained by administration of hypertonic saline 3% (0.514 mEq/ml). A bolus infusion of 100 to 150 ml of NaCl 3% which may be repeated two times at 10 min interval if needed (some patients continue to reabsorb water from the gastrointestinal tract, which explain that SNa will not increase despite therapy; reported for example after ecstasy or exercise induced hyponatremia). An acute increase in SNa of 5 mmol/L is expected to decrease significantly brain oedema [38,40].

The other therapeutic option consists of administering urea [47]. Urea which diffuses slowly into the brain (4 to 10 hours to equilibrate), allows a rapid reduction in brain oedema and in intracranial pressure, before any increase in serum sodium (see Figure 4). One dose of 0.5 to 1 gr/kg BW of urea increases the osmolality by 15-30 mOsm/kg H₂O in 1-2 hours [8]. It has been shown recently that a low dose of enteral urea administration (15 g) is associated with a significant reduction of ICP (at 90 min) independent of changes in sodium levels [50]. Oral intake of 0.5 g/kg urea induces an increase in its concentration in 15 min of 5 mmol/l (and 15 after one hour). This is in fact a gradient much more rapidly obtained than a gradient obtain by hypertonic saline (100-150 ml 3%) given 2-3 times over one hour (unpublished data). In rats it has been shown that correction of severe hyponatremia by urea decreases the risk of ODS [51-52]. Whatever the method, treatment must be interrupted as soon as symptoms improve. Although an increase of 8% of serum sodium

should theoretically suffice to significantly decrease brain edema, it is wiser to interrupt the rapid correction after a total increase of 5-6 mEq/l and to continue with a more conservative regimen (normal saline, water restriction) particularly if symptomatic hyponatremia is chronic or of unknown duration, given the risks of myelinolysis. Final correction must remain < 8 -10 mEq/l/24 hours particularly in the presence of other risk factors for myelinolysis (< 8 mEq/l/24hr). Serum sodium must be monitored frequently during the initial phase of treatment (48-72 hrs). If necessary, correction must be stopped and the diuresis interrupted by dDAVP administration (Minirin 4 μ g subcutaneously or IV each 8-12 hrs) [53]. If needed acute administration of 1 l of water (orally or intravenously) will decrease SNa by 4 to 6 mmol/l if combined with dDAVP (see Figure 2). In asymptomatic hyponatremia, there is no reason for an aggressive approach and treatment can be more conservative and specific (Table 2). No treatment is actually available for myelinolysis. Nevertheless, recent experimental results showed that reinduction of hyponatremia

in rats after excessive correction of the serum sodium dramatically reduces the mortality rate and the incidence of neuropathological sequelae even in early symptomatic rats [42,43]. These encouraging results require further evaluation of rapid decrease in serum sodium through dDAVP and hypotonic fluid for overly corrected hyponatremic patients, first results show that it is easy to perform [38,54]. Future direction in therapy of hyponatremia is focused mainly on the development of the oral or parenteral nonpeptide AVP V2 receptor antagonists. Nevertheless, their uses are not devoid of risks of excessive correction and brain damage. Vaptans are actually not accepted to treat acute symptomatic hyponatremia [40]. We are currently studying a treatment combining dDAVP, urea (30 g/12 hr) and one litre of isotonic saline every 12 hr for the treatment of severe hyponatremia (≤ 120 mEq/l) (dDAVP prevents a too rapid increase in SNa, urea decreases a possible elevated intracranial pressure and has a protective effect against ODS, isotonic corrects the salt depletion) (preliminary data are particularly promising; unpublished data).

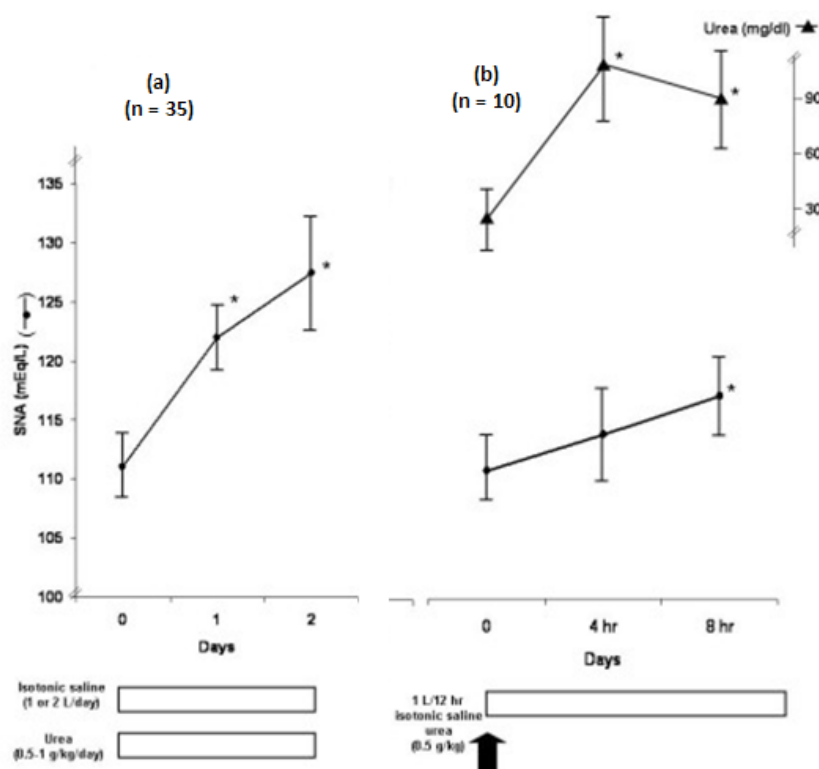


Figure 4: Evolution of SNa in 35 patients with severe hyponatremia treated by urea and isotonic saline. (a) Daily evolution of SNa (mean \pm SD) in 35 patients with severe hyponatremia (≤ 115 mEq/L) treated with isotonic saline and urea (* $P < 0.001$ compared to Day 0). (b) Evolution of SNa (mean \pm SD) each four hours in 10 patients with severe symptomatic hyponatremia treated with 1 L isotonic saline over 12 hr and urea (0.5 g/kg) ($P < 0.01$ compared to time 0) (Decaux G, et al. Crit Care 2010; 14(5): R184).

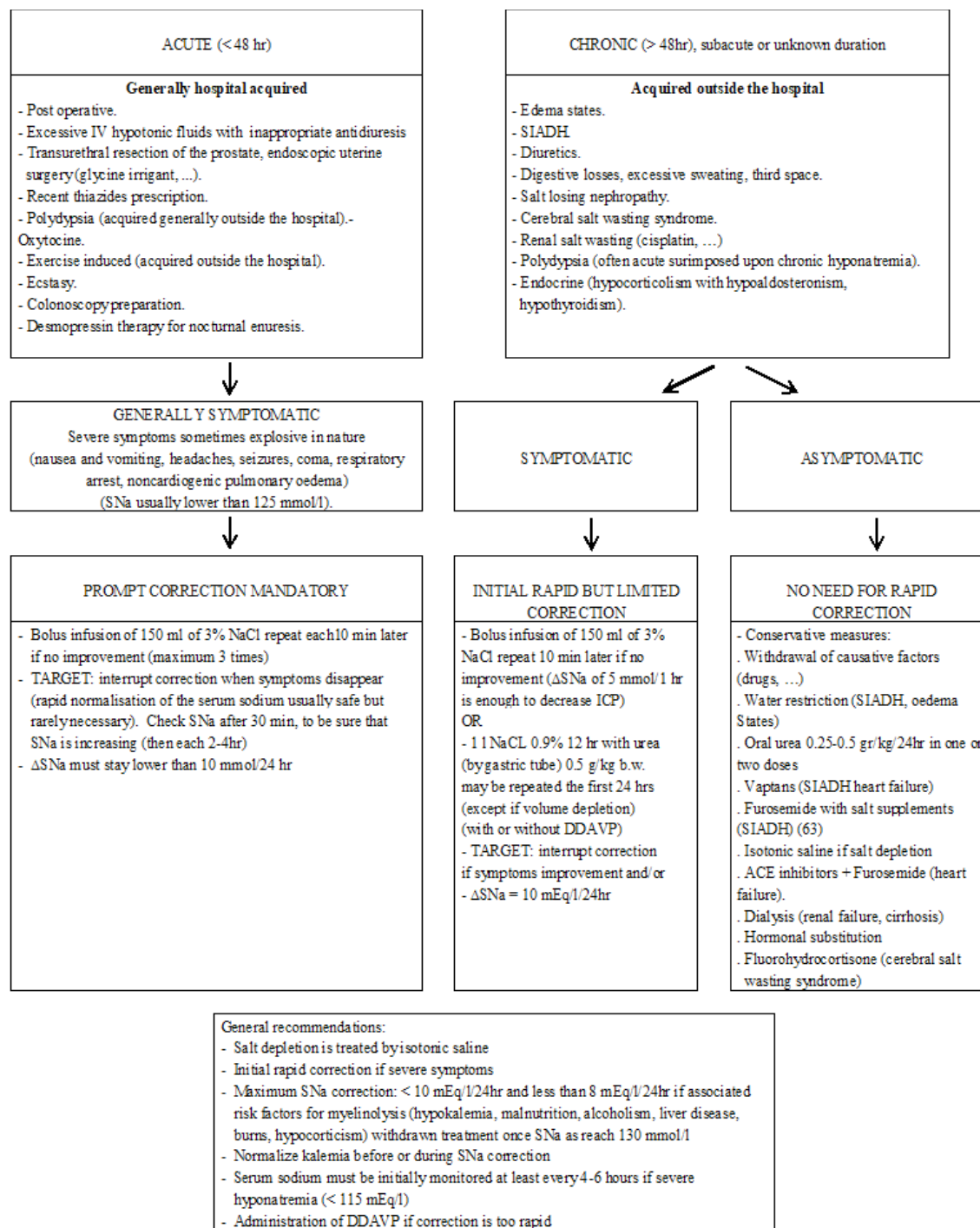


Table 2: Therapeutic guidelines for treatment of severe hyponatremia (SNa < 120 mEq/l).

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