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Chapter 2

ENDOCRINE TESTING FOR THE SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH)

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see also Section NEUROENDOCRINOLOGY, ***CHAPTER 2 -***
NORMAL AND ABNORMAL PHYSIOLOGY OF THE HYPOTHALAMUS-POSTERIOR PITUITARY (INCLUDING DI AND SIADH) by Stephen G Ball and Peter H Bayliss

ABSTRACT

The diagnosis of Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) relies on an adequate assessment of a hyponatremic state (that is a serum sodium level <136 mmol/l) and on the exclusion of other causative conditions leading to an adequate secretion of antidiuretic hormone (ADH). The understanding of mechanisms involved in pathological ADH secretion is essential for diagnosis and therapy. Although some forms are due to dysregulation in central nervous system regulations, other forms are dependent on diseases in peripheral organs and structures including ADH-producing/secreting neuroendocrine tumors, while others are induced by medical compounds. ADH regulation is closely linked to other systems such as the sympathetic tone, baroreflex regulation. Patients with hyponatremia should be carefully clinically (neurological symptoms) assessed and be classified according to volume status, also with respect for the need of intensive care monitoring. In parallel, laboratory findings of blood and urine must be analyzed appropriately. It is important to demonstrate true hyponatremia, which is paralleled by a decrease in serum osmolality. Mandatory laboratory diagnostic steps comprise the determination of blood and urine electrolytes and serum and urine osmolality, analysis of thyroid, adrenocortical, and kidney function as well as uric acid. Different test results such as a high fractional uric acid excretion may hint to an existing SIADH. Assessment of urine osmolality and urine sodium / potassium concentrations in view of kidney disorders, diuretic use and intravasal volume level allow for further discrimination and may be indicative for a specific underlying disease, covering SIADH. Brain volume changes (“hydrocephalus ex vacuo”) may depend on age rendering the elderly more tolerant to acute or chronic serum sodium changes. The course of an incident hyponatremia, if documented, may affect therapy. A serum sodium drop within less than 48 hours is considered as acute hyponatremia. A rapid bolus of 100 to 150 ml of

intravenous 3% hypertonic saline is appropriate to avoid catastrophic outcomes in severe cases of acute symptomatic hyponatremia.

Key words:
Hyponatremia, antidiuretic hormone, SIADH, water, polydipsia, demyelination, hypertonic saline

INTRODUCTION

"Antidiuretic hormone" or "arginine vasopressin" (AVP) is physiologically released into the blood stream upon increases of plasma osmolality. AVP, a nine-amino-acid peptide, originates in the supraophthalmic nucleus (SON) of the hypothalamus and is directly regulated by plasma osmolality detected via a splice variant of the capsaicin receptor, the transient receptor potential vanilloid type-1 (Trpv1) receptor [1]. AVP is axonally transported to the posterior pituitary and released into the blood upon respective stimulation. AVP regulation is, however, more complex than a mere response to changes of plasma osmolality. In fact, an intravasal hypovolemia enhances AVP release upon increases of plasma osmolality. Conversely, hypervolemia attenuates AVP release for given increases of plasma osmolality.

In patients with "Syndrome of Inappropriate Antidiuretic Hormone Secretion" or SIADH, the cornerstone of diagnosis is hyponatremia (Na<136 mmol/l) [2] in a state of euvolemia, i.e. absence of either over- or dehydration. SIADH-related hyponatremia is caused by excess water reabsorption due to inappropriately high levels of AVP. Specifically, AVP binds to stimulatory G-protein-coupled vasopressin V_2-receptors of the basolateral membrane of collecting-duct cells, thereby increasing the intracellular cAMP level, which, in turn, activates Aquaporin-2 channels of the brush-border membrane or urine side of the collecting-duct prinicipal cells. AVP action comprises a reduced free-water clearance resulting in a more concentrated urine and total-body water (TBW) expansion. AVP-mediated TBW expansion mediates sympathoinhibition (**Figure 1**).

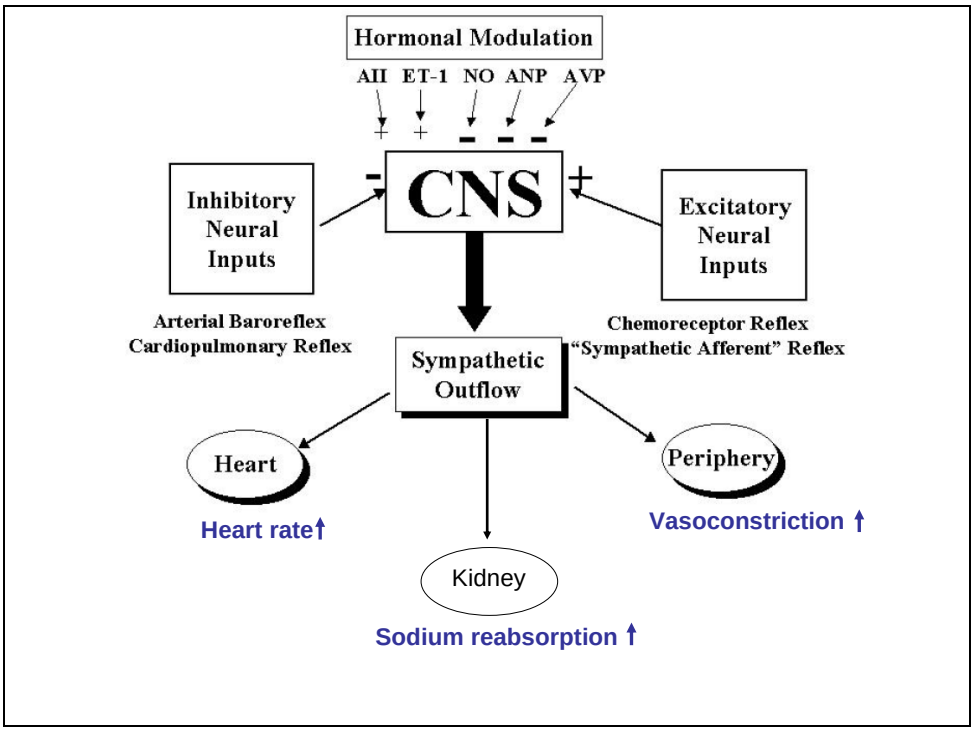

Figure 1: Role of AVP in regulation of sympathetic tone. AVP translates into sympathoinhibition (Figure amended from [3]).

In addition, AVP-induced TBW expansion translates into plasma-solute dilution leading to hyponatremia. Thereby, plasma osmolality (OSM) is decreased given the fact that sodium strongly determines OSM according to the following equation:

OSM (calculated) = 2 x Na (mmol/l) + Glucose (mmol/l) + Urea (mmol/l)

Besides AVP actions on OSM, AVP also enhances endothelial-cell synthesis and the release of von-Willebrand Factor, thereby affecting **hemostasis** [4]. This AVP effect on hemostasis is therapeutically used in bleeding disorders involving Factor VIII or von-Willebrand factor deficiency [5, 6].
SIADH may be viewed as a primary central-nervous system dysregulation of OSM and/or thirst. The etiology still is incompletely understood. Alternatively, SIADH may relate to baroreceptor unloading due to clinically inapparent hypovolemia or, hypothetically, to carotid-artery atherosclerosis affecting baroreflex regulation [7]. This alternative route of increased AVP release may ultimately translate into the clinical picture of SIADH. Generally, less wall distension of the carotid arterial walls and/or the aortic arch may lead to a decrease of arterial baroreceptor-related afferent autonomic nerve traffic to the rostral ventrolateral medulla and nucleus tractus solitarii (NTS) translating into less sympathoinhibition (sympathoexcitation) and to an increased release of AVP [8] (**Figure 2**).

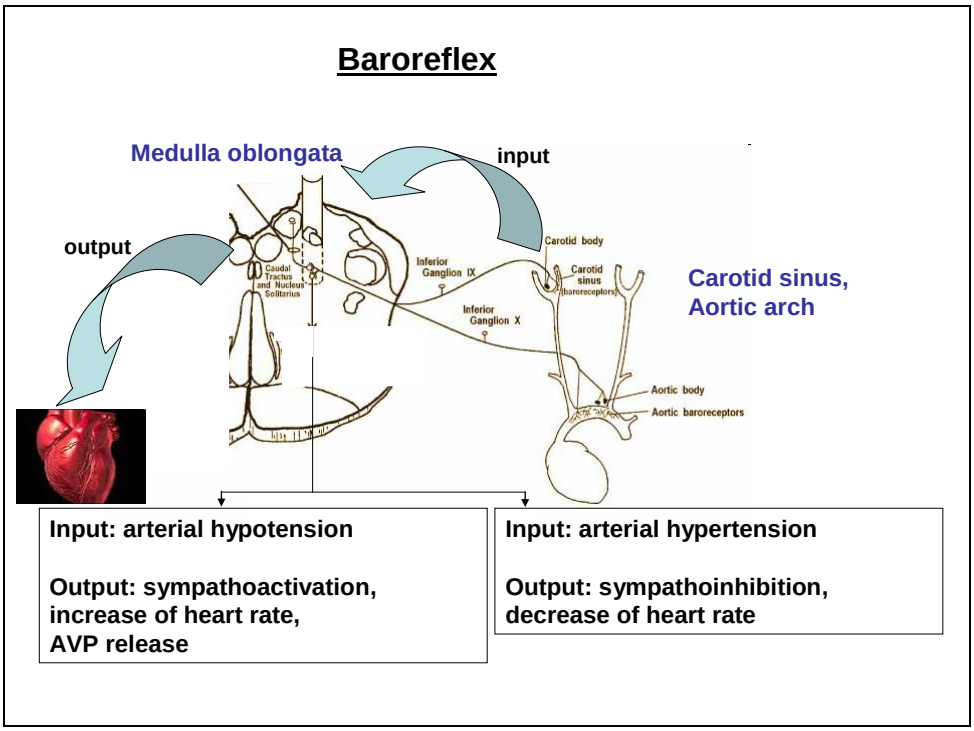

Figure 2: Baroreflex regulation and SIADH: arterial hypotension lower baroreflex-mediated afferent nerve traffic to the nucleus tractus solitarii leading to an elevated efferent sympathetic nerve activity and increased AVP release.

Lastly, hypovolemia-related cardiopulmonary (CP) reflex deactivation mediated by less wall distension of the right atrial wall and pulmonary veins may increase plasma AVP leading to SIADH [9, 10]. Conversely, CP reflex activation mediated by more right-atrial wall distension e.g. after body immersion in water is able to decrease plasma AVP [11].
The term “primary SIADH” is used for all above-mentioned causes involving a known or suspected dysregulation of OSM and/or circulating-blood volume. The term “secondary SIADH” is attributed to pituitary-independent causes of AVP increases, e.g. in hormone-active neoplasms such as small-cell lung cancer. In addition, a drug-induced type of SIADH is detailed here.

CLINICAL PRESENTATION OF SIADH

Both moderate and especially severe hyponatremia (Na < 125 mmol/l) found in newly admitted hospital patients is linked with a significantly elevated in-hospital mortality of 28% compared to 9% in-hospital mortality in normonatremic, matched control patients [12]. Mortality, in fact, increases when serum Na levels are below 137 mmol/L [13]. While (neurological) symptoms of hyponatremia such as gait disturbances, cognitive dysfunction and dizziness may lead to falls leading to subsequent injuries requiring medical care, either preceding symptom may be subtle and difficult to diagnose. Therefore, hyponatremia often is overseen or not given full attention. Furthermore, if hyponatremia is diagnosed, it is regularly classified to be asymptomatic. Diagnostic differentiation remains absent or incomplete. Thus, underlying reasons often remain obscure [14]. However, **cognitive and/or geriatric functional tests** regularly reveal a significant impairment in states of hyponatremia.

Clearly, symptoms of hyponatremia depend on the time elapsed since the start of hyponatremia development. Hyponatremia developing in less than 48 hours may already

present with **severe** symptoms which are mainly caused by cerebral edema and a high intracranial pressure. These include epileptic convulsions, a pronounced somnolence or coma, vomiting and/or a compromised respiratory regulation. Symptoms like headache or modest nausea generally reflect a rather **moderate** severity.

In patients with an acute hyponatremia, a brief patient history and a physical examination should be performed (Table 1). In cases of a rather slowly developing or chronic hyponatremia, intracellular regulations such as decreased uptake of taurin aim to adapt to the decreased extracellular osmolality. Therefore, those patients may show very subtle or even no clinical alterations. Taurin is an endogenous amino acid that mediates cellular adaptation to hyperosmotic stress [15].

Table 1: Anamnestic factors and conditions responsible for the occurrence of an acute hyponatremic state (<48h).

Medical interventions: General post-operative phase Resection of the prostate
Exercise (e.g. long distance run) with increased and rapid fluid (water) intake
Extended sauna visit
Polydipsia (transient)
Severe pain attacks (including concomitant pharmacotherapy)
Initiation of new drugs e.g. thiazides, terlipressin, psychiatric medication

For the diagnosis of SIADH, in a first diagnostic step, hyponatremia needs to be ascertained. False laboratory “measurements” of serum Na+ comprise primarily a hyperglycemic state. According to Hillier et al [16] an estimation of the true sodium concentration in serum can be drawn from the formula:

Corrected (Na+) = Measured (Na+) + 2.4 x (glucose (mg/dl) - 100 mg/dl)/100mg/dl

For example, a serum glucose level of 400 mg/dl with a measured serum sodium of 120 mmol/l corresponds to a true sodium value of 127 mmol/l [16].

Likewise, pseudohyponatremia may occur in patients with paraproteinemia, e.g. multiple-myeloma patients [17].

Another pitfall with serum sodium is the mode of its determination: the regular way involves ion-selective electrodes, no flame-photometric determination. The latter method may yield occasionally "diluted" Na^+ levels. Measured, not calculated serum osmolality may help discriminate true from pseudohyponatremia: true hyponatremia associates with a decreased serum osmolality.

True-hyponatremic patients are regularly identified at hospital admission, e.g. in the emergency room. However, a large number of hospitalized patients have or develop either **mild** (Na 131 – 136 mmol/l), **moderate** (Na 126 – 130 mmol/l) or **severe** (Na <125 mmol/l) hyponatremia after admission during the hospital stay. Although all hyponatremic patients will present with a chronic hyponatremia, however, some patients present with a proven acute hyponatremia. Since acute hyponatremia means an incomplete adjustment of the difference in osmolality between plasma (extracellular space) and intracellular cell space of tissues and organs such as the brain, a 48-hours threshold to discern acute from chronic hyponatremia appears reasonable. However, in everyday practice, this discrimination might not be feasible due to a lack of documentation of serum sodium levels in newly hospitalized patients.

DIAGNOSIS OF SIADH

As an important step to approach the hyponatremic patient, volume status must be determined. Accordingly, a state of overhydration characterized by the presence of peripheral edema needs to be ruled out. Hyponatremia accompanied by **peripheral edema**, anasarca, jugular vein distension in absence of a significant tricuspid-valve regurgitation, dyspnea, and/or signs of a lung fluid or pulmonary edema on the chest radiograph are not consistent with the diagnosis of SIADH. Here, underlying diseases such as **chronic heart failure** should be diagnosed and addressed. Likewise, hyponatremia in a state of hypovolemia needs to be excluded. In exsiccosis, e.g. due to diuretics, both water and solutes may be lost. Hypovolemia triggers sympathoactivation via CP and baroreflex leading to an appropriate ADH release.

In patients presenting with hyponatremia in a state of euvolemia, i.e. absence of overhydration or exsiccosis, the diagnosis of SIADH should be corroborated, after excluding conditions such as chronic heart failure. A known and medically treated chronic heart failure condition may present as a hypervolemic, euvolemic or – when vigorously treated – hypovolemic state. Both, chronic heart failure and liver cirrhosis are characterized by arterial underfilling and, hence, activation of both the renin-angiotensin-aldosterone system and antidiuretic hormone leading to both sodium chloride retention and water retention. The net effect may be hyponatremia, if AVP stimulation dominates. Thus, urine-sodium measurements in 24-hours urine collection may prove the presence of a sodium-sparing disorder, thereby rendering SIADH unlikely.

A useful algorithm to approach hyponatremia is depicted in Figure 3,

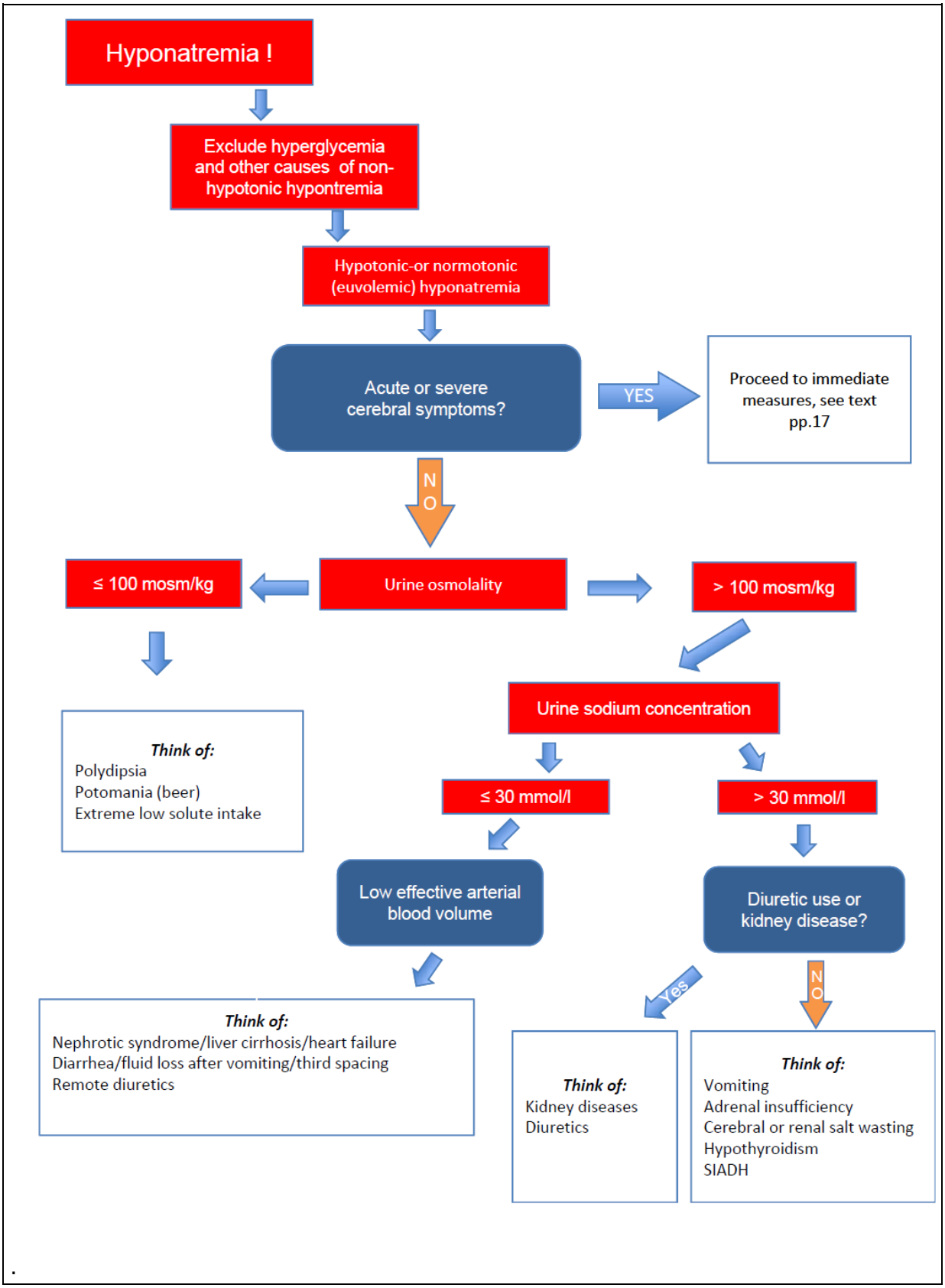

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Figure 3**: Approach to the patient with hyponatremia (adapted and modified from [18], with permission).**

In the clinical assessment, **euvolemic patients** suspected to have **primary SIADH** often show a **slight weight gain by 5 – 10 % of body weight** and/or a worsened condition of arterial hypertension, and urine output is normal or slightly reduced. In secondary, neoplasm-associated SIADH, however, an unexplained weight loss and/or state of cachexia may prompt further diagnostics including chest radiograph and thoracic computed tomography scan, if deemed necessary.
It is crucial to assess and to treat infections effectively, since they may establish or worsen a tendency to hyponatremia.
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To correctly evaluate laboratory results besides aspects of methodology, diuretics, especially thiazides, should be discontinued, and nutritional **sodium chloride intake should not exceed 5 – 6 g per day**.

Hyponatremia in euvolemia: assessment for SIADH

The diagnostic, step-wise approach for evaluating hyponatremia in euvolemic patients is detailed below:

1st step:

Here, a laboratory work-up (**Table 2**) is proposed to establish a preliminary diagnosis being consistent with SIADH.

As a diagnostic cornerstone of SIADH diagnosis, determination of fractional uric-acid excretion has recently emerged. Fenske et al. [19] could confirm earlier reports demonstrating fractional uric-acid excretion (cut-off 12 %) to rule out hyponatremic states with reduced extracellular fluid volume, e.g. due to diuretics.

$$\textbf{Fractional uric-acid excretion} = \frac{\text{uric acid (urine)} \times \text{creatinine (serum)}}{\text{uric acid (serum)} \times \text{creatinine (urine)}} \times 100 \ (\%)$$

There is sometimes debate on whether measurements of AVP in the plasma are helpful or not for diagnosis of SIADH or other hyponatremic circumstances. There are, however; multiple obstacles rendering AVP determination and interpretation difficult. Only few and adequately equipped laboratories might provide tests with good sensitivity, since AVP is very unstable when isolated from plasma and binds to other structures. A potential alternative is the more stable copeptin, also called C-terminal proarginine vasopressin, which is generated by enzymatic cleavage of the vasopressin prohormone. Some studies argue for distinct copeptin levels in relation to serum osmolality being able to discriminate SIADH subtypes, or even other forms of hyponatremia; however, this issue is subject to further clinical research [20, 21].

2nd step:

Administration of 500 ml saline (NaCl 0.9 %) is regarded as an empiric, first-line therapeutic and diagnostic measure. Especially when arterial underfilling and baroreflex and/or CP reflex deactivation are thought to be relevant, i.v. saline corrects the initial disturbance leading to hyponatremia/SIADH. This relates, strictly speaking, to volume regulation and respective reflex stimulation. Isotonic saline may not resolve hyponatremia in cases of ongoing urine concentration with urine osmolality exceeding 400 mosm/kg.

In addition, a **water-load test** as described in www.endotext.org, NEUROENDOCRINOLOGY, HYPOTHALAMUS, AND PITUITARY, chapter 2, may be performed at the next morning under utmost scrutiny and precaution, in the hospital. The water-load test relates to the fact that normal subjects excrete 78-82% of the ingested water load within 4 hours due to AVP suppression. In patients with SIADH, the expected urine amount within 4 hours is reduced to 30-40%. **However, the test involves a massive water intake in a short period of time and, therefore, is not considered a safe procedure for the majority of patients for the following three reasons:**

1) In SIADH patients, a relative intravascular overhydration will be enhanced
2) An underlying cardiac co-morbidity may be adversely affected
3) The water challenge may lead to a deterioration of hyponatremia including the risk of symptoms such as epileptic convulsions

Therefore, in the majority of patients with hyponatremia suspected to have SIADH, this test can be replaced by the following 3rd and 4th diagnostic step (below). The water-load test **only adds information in hospitalized individuals free of cardiac conditions presenting with rather mild hyponatremia in whom the 4th step usually will not be performed.** Again, the physician has to weigh risks and benefits of this water challenge versus alternate diagnostic steps (step 3, step 4 below).

3rd step:

A balanced fluid-intake restriction (500 ml /d) is able to correct hyponatremia over the next 3 to 4 days with an aimed plasma-sodium increase of 0.5 mmol/l/h or less than 10 mmol/l/d. Most patient do not tolerate a very strict fluid intake reduction.

4th step:

If step 1 – step 3 did not lead to an improvement of hyponatremia, therapy with an antagonist of the vasopressin V_2-receptors, e.g. tolvaptan, for four days should be instituted [22] with an aimed plasma-sodium increase of 0.5 mmol/l/h or less than 10 mmol/l/d.

	PARAMETER	SIADH diagnosis
SERUM:	**sodium**	**<136 mmol/l**
	potassium	**normal**
	glucose	**normal**
	urea	**normal**
	uric acid	**normal**
	creatinine	**normal**
	thyroid hormones	**normal**
	cortisol	**normal (within the reference range)**
	aldosterone	**normal**
URINE:		
	osmolality	**>100 mosm/kg**
	sodium	**> 30 mmol/l**
	uric acid*	
	creatinine*	
	***Fractional uric-acid excretion [13]**	**≥ 12%**

Table 2: Laboratory work-up for SIADH

INTERPRETATION OF CLINICAL AND LABORATORY RESULTS

SIADH leads to an increase of free-water reabsorption, thereby increasing the circulating blood volume. By virtue of AVP action, both hematocrit and plasma sodium are being lowered by dilution. Likewise, a decrease of urine output can be found.
In cases of a **prolonged, subclinical hypovolemia**, baroreflex- and/or CP-reflex unloading stimulates AVP secretion leading to the clinical picture of SIADH. There, discontinuation of diuretics and/or the **empirical infusion of 500 ml saline (0.9 %)** as outlined above as step 2 may correct such a state of subclinical hypovolemia and lead to an improvement in hyponatremia driven by SIADH.
In assessing key laboratory results including plasma and urine sodium concentration and -osmolality, both the theoretical or calculated OSM should be compared to the actually measured OSM. That way, states of hyponatremia due to uremia or hyperglycemia can be ruled out. In such cases of hyponatremia, high plasma urea or high plasma glucose lead to a rise in OSM prompting a physiologic release of AVP, which, in turn, leads to a plasma-sodium dilution in order to maintain a normal OSM.
Urine sodium within normal range rules out a dietary sodium deficiency or states of increased tubular sodium reabsorption such as in chronic heart failure or liver cirrhosis.

After fulfilling the above-mentioned steps to diagnose SIADH, the following conditions should be separately considered as a possible differential diagnosis:

DIFFERENTIAL DIAGNOSIS OF HYPONATREMIA OTHER THAN SIADH

- **Sodium chloride depletion, low dietary sodium intake** regularly is accompanied by hypovolemia, low urine sodium, elevated serum uric acid and serum urea.

- **Anterior-lobe pituitary gland insufficiency** often is accompanied with signs and symptoms, and respective laboratory findings indicating hormone deficiencies such as hypothyroidism, hypocortisolism or hypogonadism. In addition, bitemporal hemianopsia and hyperprolactinemia are found in cases of anterior-lobe pituitary tumors as a cause of anterior-lobe pituitary gland insufficiency.

- **Adrenal-gland insufficiency** including iatrogenic mineralocorticoid-receptor antagonism (spironolactone/eplerenone) regularly is accompanied by hyperkalemia and hypovolemia.

- **Thiazide diuretics** can induce hyponatremia by an AVP-dependent mechanism and by a thiazide-induced increase of water permeability in the medullary collecting duct. **Loop diuretics** can induce hyponatremia by AVP activation, if hypovolemia is reached.

- Severe **hypothyroidism** regularly is accompanied by dilutional hyponatremia due to a reduced free-water clearance.

- **Chronic kidney disease**: In salt losing nephropathy, a condition that occurs in advanced kidney failure with a GFR below 15 ml/min, hyponatremia is paralleled by

hypovolemia. This is a feature classically seen in forms of interstitial kidney disease. On the other hand, many patients with near end-stage renale failure of divers causes show increased Na excretion to balance body sodium content, but, due to (continuous) reduction in urine production, a diluted urine cannot be achieved, leading to hyponatremia.

- **Acute kidney (transplant) failure** without signs of uremia, a water-excretion dysfunction may lead to dilutional hyponatremia.

- **Hyperglycemia** or poor diabetes mellitus control may lead to a so-called translational hyponatremia due to intra- to extracellular water shift and consequent plasma sodium dilution (see above).

- **Cerebral sodium wasting** is an important differential diagnosis to SIADH occurring in cases of aneurysmal subarachnoidal hemorrhage and in other intracranial pathologies. Cerebral sodium wasting still is not completely characterized and most likely involves a putative central nervous system-derived factor and/or a sudden decrease of renal sympathetic nerve activity favoring a urinary loss of sodium chloride. Cerebral-sodium wasting - associated urinary sodium-chloride loss improves after successful neurosurgical care of the initial intracranial disease condition and may require temporary high amounts of sodium chloride replacement.

- **Overdose of antidiuretic-hormone analogs** in cases of known central diabetes insipidus. If the primary physician is unaware of the underlying medical condition, SIADH may be suspected based in laboratory results mentioned above. Patient history including medication list clarifies this case.

THERAPY OF SIADH

If left untreated, SIADH may lead to a severe, life-threatening hyponatremia with or without clinically apparent overhydration. Acute complications of SIADH include cerebral edema and epileptic convulsions. SIADH therapy clearly depends on the specific etiology.
Only if there are **severe symptoms** related hyponatremia, it is advised to administer a small amount of a hypertonic NaCl-solution for a very short period of time. In practice, this must be accomplished with closely monitored sodium concentration measurements which can be accomplished on a regular ward rather than in the intensive care unit, especially when considering the urgency. **150 ml of a 3% saline solution can be infused over 20 minutes**.
If the symptoms do not ameliorate with this management, the infusion with 100 ml of 3% hypertonic saline can be repeated every 30 minutes until the target serum Na is reached (usually 5-8 mmol increase from baseline). Above all, a 5 mmol/l increase in serum sodium concentration should not be exceeded within the first hour. These recommendations have also been summarized in recent guideline reports [18].
The management after relief of the symptoms should be focused on a careful administration of 0.9% (only) sodium chloride solution. Independently of the initial rise in serum sodium concentration by the above measures, the maximal rise within the first 10 hours should not exceed 10 mmol/l.
In some cases of overcorrection, desmopressin can be administered [13, 23].

Once therapy is initiated, repeat measurements of plasma sodium are mandatory to gauge the therapeutic success, and, most importantly, to ascertain a slow plasma-sodium normalization with a recommended maximum rate of 0.5 mmol/l/h plasma-sodium increase. Again, the delivery of higher concentrated sodium chloride solution is allowed strictly for symptomatic patients, as outlined before. A significant proportion of in-hospital mortality relating to hyponatremia likely is due to a too rapid sodium normalization in long-standing hyponatremia. The consequence of too rapid sodium normalization is the osmotic demyelination syndrome due to a rapid intra- to-extracellular water transfer and subsequent brain swelling that exceeds the percentage of cerebrospinal fluid volume capacity (usually around 8% but higher in elderly with a hydrocephalus ex vacuo).
Besides the therapeutic goal to avoid rapid changes in plasma osmolality, the underlying reason of hyponatremia in SIADH, excess total body water, should be addressed by balanced fluid-intake reduction. All therapeutic interventions discussed here target the consequences of exaggerated AVP secretion rather than sodium-chloride supplementation.

In primary SIADH, plasma-sodium dilution can be addressed by an ongoing fluid-intake restriction of 500-800 ml/d which many patients do not tolerate well.
However, subclinical hypovolemia and ensuing baroreflex and CP reflex suppression leading to AVP stimulation should be kept in mind. Addressing arterial hypotension and/or central-venous hypotension is effective in lowering AVP in plasma. At the same time, fluid-intake restriction may appear contradictory. Even though fluid-intake restriction appears to be a proven measure in terms of attenuation of AVP consequences, it is the clinician`s judgement to test both interventions and compare the best results in terms of a slow plasma-sodium increase.

In secondary SIADH, identification of the neoplasm is the goal. A thorough tumor search including radiologic diagnostics such as whole-body computed tomography scan is warranted to further determine the underlying pathology and, if applicable, consider all options of curative therapy. Chemotherapy, surgical and/or radiation therapy of malignancies with AVP activity represent definitive therapeutic approaches. On clinical grounds, neoplasm-associated, secondary SIADH often requires V2-receptor antagonism therapy until a specific oncologic care is employed.
This might be especially true while performing cytostatic therapy cycles with increased intravenously administered fluid volumes However, to date, no survival benefit has been demonstrated in favour of V2-receptor antagonism in oncologic-care of patients with secondary, neoplasm-associated SIADH.
Besides malignancies, infections such as tuberculosis have been associated with occurrence of SIADH [24].

Drug-induced SIADH: SIADH initiating drugs and substances include psychotropic and chemotherapeutic drugs (see Table in Ref. 18) such as

- Vincristine
- Vinblastine
- Cyclophosphamide
- Carbamazepine
- Tricyclic antidepressants
- Selective Serotonine Reuptake Inhibitors (e.g. citalopram [25])
- Oxytocin

- Opiates
- Barbiturates
- Nicotine

have the potential to promote SIADH. Either they enhance ADH release, are analogues of ADH, or they amplify renal effects of ADH. However, for some drugs, the mechanism remains unclear. If applicable, a suspected drug should be discontinued under close supervision of plasma sodium levels. Once hyponatremia improves after cessation of a specific drug, drug-induced SIADH is likely. However, unless reexposition takes place, drug-induced SIADH is not proven.

In both primary and secondary SIADH or in euvolemic, hyponatremic patients with suspected SIADH without a therapeutic effect of fluid-intake restriction, the lowest recommended standard dose of a vasopressin V_2-receptor blocker, e.g. Tolvaptan, should be applied perorally. Besides the diagnostic approach outlined above as step 4, empiric V2-receptor antagonism represents a rescue therapy and is suitable to gain time needed to perform further diagnostics and therapies in (suspected) SIADH.
Low-dose Tolvaptan therapy was shown to significantly improve hyponatremia (by 3 – 4 mmol/l) within 4 days when compared to placebo [26, 27]. Alternatively, conivaptan (approved for SIADH in the United States) has a broader target than its competitors tolvaptan or mozavaptan. Conivaptan selectively targets the V1a and V2 receptors. Conivaptan can be administered intravenously in patients who are unable to take drugs orally. In addition, conivaptan has a longer bioavailability than newer vaptans including tolvaptan [28]. In a large proportion of SIADH patients, whether or not the underlying circumstances leading to SIADH are known, fluid-intake restriction controls hyponatremia attributed to SIADH. It is important to note, that with the use of higher daily tolvaptan dosages, the risk of liver injury may increase, as revealed in a recent study in which vaptans were tested to treat autosomal-polycystic kidney disease (ADPKD) [29].
In essence, V_2-receptor antagonism remains both a diagnostic and a therapeutic tool for SIADH when applied under scrutiny and for a limited period of time. To date, data on long-term use of V_2-receptor blockers have not been published, especially not for the use of a combined V1a-V2 receptor blockade. V2 antagonists that have been used for the treatment of SIADH are listed in Table 3. The fact that hyponatremia may reoccur shortly after V_2-receptor-blocker discontinuation emphasizes the need to identify the underlying cause of SIADH in order to devise a definitive therapy.

Drug	Route of administration	Receptor affinity	Literature
Tolvaptan	oral	V2	[26, 27]
(Lixivaptan)			[30]
(Mozavaptan) (only approved in Japan)			[31]
(Satavaptan)			[32]
(Conivaptan) (only approved in U.S.A.)	intravenous	V2 /V1A	[28, 33]

Table 3: V2 Receptor antagonists. In parenthesis: limited or no availability.

The issue of hyponatremia and especially SIADH with its different aspects from diagnosis to treatment has lead to much new information for clinicians in recent years. This has been paralleled by recent publications which give specific recommendations or formulate guidelines that readers may wish to review [13, 18].

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