

Treatment of hyponatremia induced by the syndrome of inappropriate antidiuretic hormone secretion: a multidisciplinary algorithm

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ABSTRACT

Introduction: The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most frequent cause of hyponatremia in a hospital setting. However, detailed protocols and algorithms for its management are lacking. Our objective was to develop 2 consensus algorithms for the therapy of hyponatremia due to SIADH in hospitalized patients. **Material and methods:** A multidisciplinary group made up of 2 endocrinologists, 2 nephrologists, 2 internists, and one hospital pharmacist held meetings over the period of a year. The group worked under the auspices of the European Hyponatremia Network and the corresponding Spanish medical societies. Therapeutic proposals were based on widely-accepted recommendations, expert opinion and consensus guidelines, as well as on the authors' personal experience.

Results: Two algorithms were developed. Algorithm 1 addresses acute correction of hyponatremia posing as a medical emergency, and is applicable to both severe euvoletic and hypovolemic hyponatremia. The mainstay of this algorithm is the iv use of 3% hypertonic saline solution. Specific infusion rates are proposed, as are steps to avoid or reverse overcorrection of serum sodium levels. Algorithm 2 is directed to the therapy of SIADH-induced mild or moderate, non-acute hyponatremia. It addresses when and how to use fluid restriction, solute, furosemide, and tolvaptan to achieve eunatremia in patients with SIADH. **Conclusions:** Two complementary strategies were elaborated to treat SIADH-induced hyponatremia in an attempt to increase awareness of its importance, simplify its therapy, and improve prognosis.

Keywords: Hyponatremia. SIADH. Antidiuretic hormone.

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Tratamiento de la hiponatremia secundaria al síndrome de secreción inadecuada de la hormona antidiurética: algoritmo multidisciplinar

RESUMEN

Introducción: El síndrome de secreción inadecuada de la hormona antidiurética (SIADH) es la causa más frecuente de hiponatremia en el paciente hospitalizado. Sin embargo, faltan protocolos y algoritmos concretos que faciliten su abordaje terapéutico. Nuestro objetivo fue el desarrollo de dos algoritmos de tratamiento de la hiponatremia secundaria al SIADH en el paciente ingresado. **Material y método:** Un grupo multidisciplinar español compuesto por 2 especialistas en Endocrinología, 1 en Farmacia Hospitalaria, 2 en Medicina Interna y 2 en Nefrología se reunieron durante un año, bajo la tutela del grupo español del European Hyponatremia Network, y de las respectivas sociedades científicas españolas. Las pautas terapéuticas propuestas fueron basadas en recomendaciones ampliamente aceptadas, la práctica de expertos, guías de consenso, así como en la experiencia clínica de los autores. **Resultados:** Se elaboraron dos algoritmos de tratamiento. El Algoritmo 1 se dirige al tratamiento de la hiponatremia aguda como urgencia médica de abordaje inmediato, y es de aplicación al tratamiento de la hiponatremia grave tanto de tipo euvoémico como hipovolémico. Se basa en el uso de sueros salinos hipertónicos al 3 % i.v., con pautas de infusión y monitorización. Se expone cómo evitar la hipercorrección de la natremia y cómo corregirla en su caso. El Algoritmo 2 aborda el tratamiento de la hiponatremia no aguda leve o moderada asociada al SIADH. Expone cómo y cuándo usar la restricción hídrica, solutos, furosemida y tolvaptán, para alcanzar eunatremia en el paciente con SIADH. **Conclusiones:** Se han elaborado dos estrategias complementarias para el tratamiento de la hiponatremia inducida por SIADH, en un intento de fomentar la toma de conciencia acerca de esa patología, simplificar su abordaje y su tratamiento y, así, mejorar su pronóstico.

Palabras clave: Hiponatremia. SIADH. Hormona antidiurética.

INTRODUCTION

The Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) is characterized by the presence of hypotonic hyponatremia in a context of inadequately diluted urine given the hypoosmolality in plasma, in the absence of a low effective circulating volume. (either with hypovolemia or hypervolemia). For its diagnosis, the following conditions must be excluded: hypotension, renal failure, adrenal insufficiency, severe hypothyroidism, as well as non-osmotic physiologic stimuli of arginine vasopressin (AVP) secretion. In SIADH, a lowering of plasma osmolality (P_{osm}) does not inhibit AVP secretion as expected, and free water is inappropriately reabsorbed at the level of the collecting duct of the nephron, thus inducing further hemodilution and hyponatremia, concomitantly with an inappropriately elevated urine osmolality (U_{osm})^{1,2}. In the less frequent Syndrome of Inappropriate Antidiuresis (SIAD), ADH secretion is inhibited, but an activating mutation of collecting duct V2 receptors imitates excessive ADH-induced water reabsorption³⁻⁵.

Major advances have taken place over the last few years in our understanding of the negative consequences of hyponatremia. Mild, chronic hyponatremia is not asymptomatic. On the contrary, it is accompanied by mental symptoms, impaired gait, falls⁶, fractures⁷⁻⁹, and possibly osteoporosis¹⁰, as well as increased mortality^{9, 11-14}. Severe hyponatremia *per se* can be life-threatening, inducing profound cerebral edema and potentially brain herniation and death. Even once hyponatremia is corrected, complete neurologic recovery can take weeks, and some patients will have permanent neurologic sequelae as a consequence of profound hyponatremia¹⁵. Yet overly rapid correction of serum sodium can induce osmotic demyelination syndrome (ODS). Adequate and prompt correction of hyponatremia is thus imperative, avoiding and/or dealing immediately with overcorrection, while assuring that eunatremia is ultimately achieved.

Close to 30% of hospitalized patients are hyponatremic at some time during their hospital stay^{13,16,17}, yet hyponatremia is often overlooked and undertreated, even in its most severe forms. A correct diagnosis of the cause of hyponatremia is *per se* associated with reduced in-hospital mortality, as indicated by a lower death rate in patients with hyponatremia in whom plasma and/or urine Osmolality have been determined¹⁸. And specific treatment directed towards correcting hyponatremia is accompanied by a lower death rate.¹⁹

SIADH is considered to be the most frequent cause of hyponatremia in a hospital setting²⁰. However, detailed protocols and algorithms for its management are lacking. A new class of therapeutic agents, the vaptans, is currently available for the treatment of SIADH in the adult. They

block the AVP-responsive V2 collecting duct receptors that ultimately induce apical expression of aquaporin 2 channels through which water is reabsorbed following AVP stimulus²¹. Tolvaptan is the only drug of its class authorized by the European Medicines Agency, and is a selective V2-receptor blocker. Its addition to the therapeutic arsenal of 3% hypertonic saline solution, furosemide, solute, and fluid restriction further warrants a specific guide to the treatment of SIADH-induced hyponatremia.

Our objective was to develop two consensus algorithms for the therapy of hyponatremia due to SIADH in hospitalized patients. These algorithms address acute correction of hyponatremia posing as a medical emergency (Algorithm 1) and correction of mild or moderate, non-acute hyponatremia requiring less aggressive measures (Algorithm 2).

MATERIALS AND METHODS

The algorithms were developed by a multidisciplinary group made up of 2 Endocrinologists, 2 Nephrologists, 2 Internists, and 1 Hospital Pharmacist. Over the period of a year, the group held meetings and worked on-line, organized under the auspices of the European Hyponatremia Network and the corresponding Spanish Medical Societies.

Given the dearth of evidence in many aspects of the management of hyponatremia, we have based the algorithms we present on widely-accepted recommendations, expert opinion and consensus guidelines²², as well as on the authors' personal experience. Application of the protocol should be flexible, and adapted to the specific needs of each patient, as is always the case in clinical medicine.

EXPLANATION OF THE ALGORITHMS AND THEIR USE

The severity of the patient's neurologic symptoms will be the most important element to be considered when choosing which algorithm to apply initially²², together with other factors presented in tables 1 and 2. Aggressive and prompt correction (Algorithm 1) is particularly important in subjects with acute and/or severe symptomatic hyponatremia indicative of substantial cerebral edema, in patients with hypoxemia²³⁻²⁸, in children and in women of child-bearing age²⁷.

When applying either algorithm, medication that can potentially cause hyponatremia must be discontinued when feasible. Pain and nausea are potent stimuli of AVP secretion and must be adequately treated. If the underlying cause of SIADH-induced hyponatremia is not evident, a Chest x-ray, brain, cervical and thoracic CT, and abdominal

Table 1. Definitions**The Syndrome of Inappropriate Antidiuretic Hormone Secretion**

Euvolemic Hyponatremia :

- Rule out a low effective circulating volume (normal OP, normal CVP, absence of orthostatic hypotension, ascites, and edema)
- Rule out diuretic therapy
- Rule out adrenal and renal failure, severe hypothyroidism
- Rule out physiologic stimuli of ADH secretion (post-surgery, pain, etc.)

and:

- $S_{Na} < 135$ mmol/L
- $P_{osm} < 275$ mOsm/Kg
- $U_{osm} > 100$ mOsm/Kg
- $U_{Na} > 40$ mmol/L when sodium intake is adequate

OP: ocular pressure; CVP: central venous pressure; S_{Na} : serum sodium concentration; P_{osm} : plasma osmolality; U_{osm} : urine osmolality; U_{Na} : urine sodium concentration.

ultrasound must be considered. If ordered, these diagnostic tests should follow initial emergency correction of S_{Na} and improvement of patient's symptoms if hyponatremia is severe.

Application of Algorithm 1

In the setting of acute and/or severe hyponatremia with symptoms indicative of profound cerebral edema, the initial aim of this algorithm is reduction of said edema, while avoiding overcorrection of serum sodium. It is applicable to severe euvolemic or hypovolemic hyponatremia *per se*, regardless of the cause, and thus prior to diagnosis of its origin. The algorithm specifies initial treatment of cerebral edema with 3% hypertonic saline iv, monitoring of the subsequent rise in serum sodium concentration (S_{Na}), and avoidance or treatment of overcorrection of hyponatremia.

Hypertonic saline solution**1. 3% Hypertonic saline is the mainstay of treatment.**

The mainstay of therapy is the use of 3% hypertonic saline solution (HSS) administered iv²⁹, to assure the movement of water from the intracellular to the intravascular compartment following an osmotic gradient, thereby reducing neuronal edema. A central

venous line is unnecessary and can only delay treatment. 3% saline, if unavailable, can be prepared by adding 60 ml of 20% saline to 500 ml of 0.9% isotonic saline. The resulting solution must be shaken before administration. Immediately prior to initiating treatment, blood must be drawn for determination of S_{Na} , serum potassium (SK), urea, creatinine and plasma osmolality (P_{osm}). Urine for the determination of Na (U_{Na}), K (U_K) and U_{osm} must be obtained as soon as possible, without delaying initiation of hypertonic saline administration. Hypoxemia must be ruled out and corrected if detected, since it worsens prognosis²³⁻²⁸.

Infusion rate. We propose an initial iv infusion rate of 3% HSS at 0.5 ml/Kg/hour or 1-2 ml/Kg/hour depending on the severity of the neurologic symptoms^{30,31}. Patients in coma, or presenting with seizures, stupor or respiratory distress, should be started on an initial infusion rate of 2 ml/Kg/hour. In these patients, an alternative can be the administration of an iv bolus of 100 ml of 3% HSS, that can be readministered up to 2 more times at 10-minute intervals, and stopped once the acute symptoms have subsided^{22,32}. We do not advise the use of formulas to estimate the quantity and rate of infusion, since these calculations often lead to overcorrection³²⁻³⁴ and can needlessly complicate therapy.

As previously mentioned, treatment must be particularly aggressive in children and in women of child-bearing age²⁷, given that their risk of severe hyponatremic encephalopathy is higher, potentially leading to subsequent brain herniation and death, or permanent neurologic sequelae. This is also the case for patients with acute hyponatremia. Patients who have recently ingested large quantities of liquid (acute water intoxication) are at special risk, since their neurologic symptoms and serum sodium will often worsen as they continue absorbing water from the gastrointestinal tract³⁵. We note that in these patients, sodium levels in arterial blood are often several mmol/L lower than in peripheral venous blood, and thus the latter can underestimate the true degree of hyponatremia³⁶.

HSS can induce substantial water diuresis, favoring overcorrection. Thus diuresis must be closely monitored to detect frank polyuria (urine output of approximately 2 ml/Kg/hour) and the need to initiate corrective measures directed towards relowering of S_{Na} . These patients are also candidates to receive 1 mcg of sc or iv desmopressin directly upon detection of polyuria, thus preventing an excessive rise in serum sodium^{32,37}.

Specific treatment goals of hypertonic saline infusion.

In the treatment of patients with chronic hyponatremia (of a duration of 48 or more hours), the maximum recommended rise in S_{Na} is currently 10 mmol/L in 24

Table 2. Classification of hyponatremia according to severity of clinical symptoms

	Severe	Moderate	Mild
Symptoms	<ul style="list-style-type: none"> - Stupor - Coma - Convulsions - Respiratory Distress 	<ul style="list-style-type: none"> - Nausea - Vomiting - Disorientation - Somnolence - Confusion 	<ul style="list-style-type: none"> - Headache - Attention deficit - Memory impairment - Gait impairment - Cognitive impairment
	Moderate/severe symptoms, usually: [S _{Na}] < 120 mmol/L		Mild/moderate symptoms, usually : [S _{Na}] ≥ 120 mmol/L
	See Algorithm 1: Acute therapy (medical emergency)		See Algorithm 2: Non-acute therapy
Outline^a	<p>Therapeutic objective: Eunatremia (S_{Na} ≥ 135 mmol/L)</p> <ul style="list-style-type: none"> - Factors that favor the use of Algorithm 1: <ul style="list-style-type: none"> Women of child-bearing age Children Brain tumors/hemorrhage Hypoxemia (pO_{2a} < 70mmHg) S_{Na} < 120 mmol/L Usually ≤ 48 hours duration - Factors that favor the use of Algorithm 2: <ul style="list-style-type: none"> Malnutrition Hypokalemia Frail elderly S_{Na} ≥ 120 mmol/L Usually > 48 hours duration 		
	Laboratory evaluation: plasma and urine electrolytes and osmolality		
	General therapy. Correct hypoxemia		

^a Consider the magnitude and speed of the reduction of S_{Na}

S_{Na}: serum sodium concentration; pO_{2a}: partial pressure of oxygen in arterial blood.

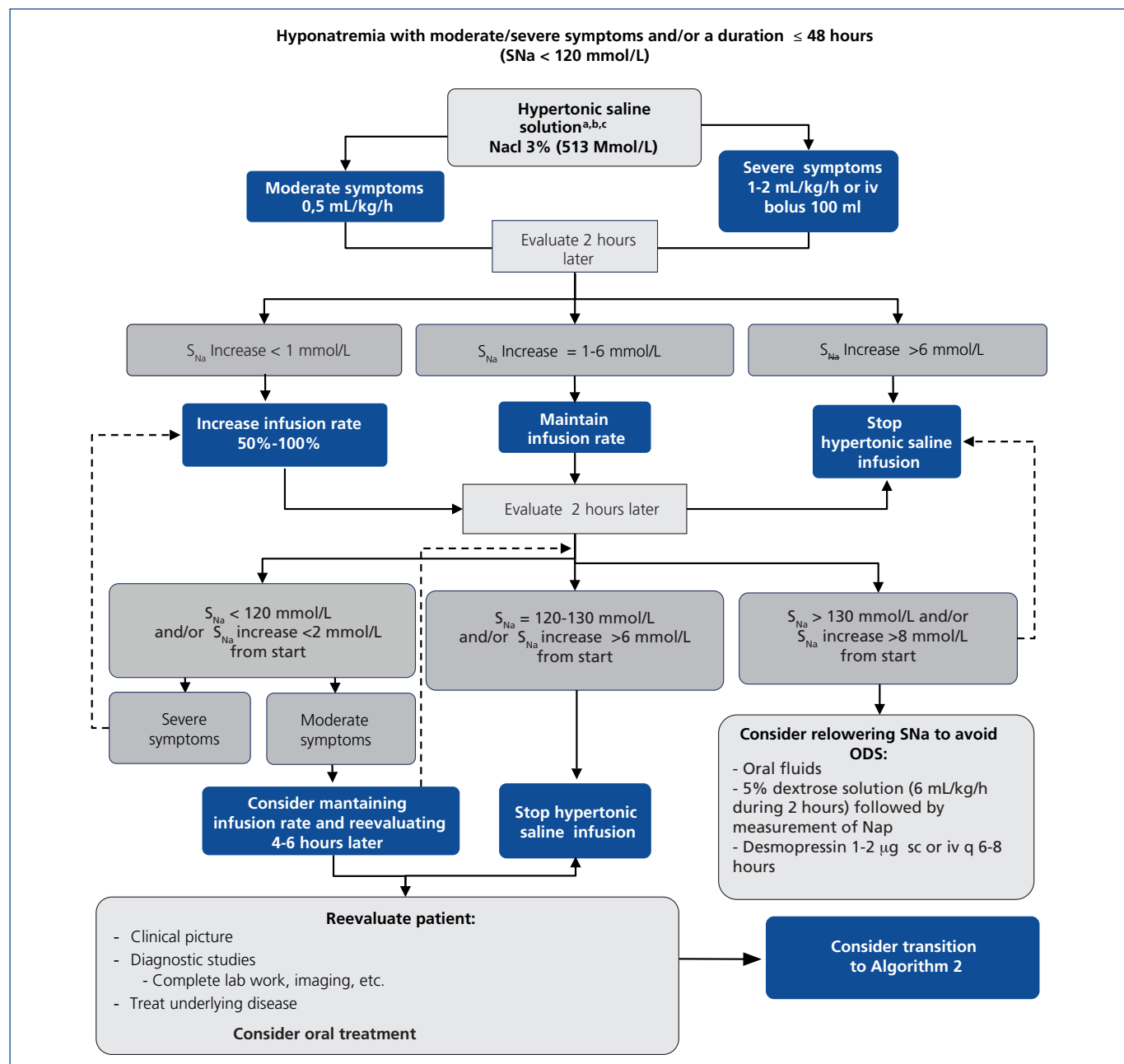
hours, and 18 mmol/L in 48 hours, to avoid the appearance of osmotic demyelination syndrome²². Furthermore, a 4-6 mmol elevation in sodium levels is accompanied by a reduction in cerebral edema of the order of 50%³⁸. A recent study found that patients presenting an initial S_{Na} below 120 mmol/L had a higher mortality rate if their S_{Na} rose less than 6 mmol/L over the first 24 hours of treatment³⁹. Thus, our aim should be to achieve an increase in serum sodium of the order of 6 to 8 mmol over a 24-hour period. Avoiding overcorrection is particularly important in patients at a high risk of developing the osmotic demyelination syndrome such as alcoholics, patients who are malnourished, and those presenting hypokalemia⁴⁰⁻⁴². In these patients maximum correction rates should therefore be from 6 to 8 mmol/L and from 14 to 16 mmol/L over 24 and 48 hours respectively. However, in patients with acute hyponatremia S_{Na} can rise more quickly, without negative consequences.

No other treatments that raise serum sodium levels should be given concomitantly with hypertonic saline, with the

exception of iv furosemide in patients with a history of heart failure. Since the combination of hypertonic saline and a loop diuretic will increase sodium levels more than the use of hypertonic saline alone, the initial objective in these patients should be a rise in S_{Na} of approximately 4-5 mmol/L with hypertonic saline infusion.

Monitoring and discontinuing hypertonic saline infusion. S_{Na} should be repeated 2 hours after initiating HSS infusion. If sodium levels have risen more than 6 mmol/L, saline infusion must be stopped, since S_{Na} can still rise after the infusion has been discontinued. If serum sodium has increased 1 to 6 mmol/L, infusion can be maintained at the same rate. If there is no increment in S_{Na}, the infusion rate should be increased by 50-100%, taking into account the clinical status of the patient. If bolus therapy has been used, sodium levels should be monitored 30 minutes after the last bolus.

S_{Na} should once more be monitored 2 hours later (4 hours after initiation of saline infusion). If a patient has yet to

**Algorithm 1. Acute therapy.**

^{a,b} Preparation of 3% hypertonic saline solution: Add 60 ml of 20% NaCl saline solution to a 500 mL 0.9 % isotonic saline NaCl at 0.9%, and shake well. Administer via peripheral vein; ^c Consider furosemida 20 mg iv (history of heart failure)

S_{Na} : serum sodium concentration; ODS: osmotic demyelination syndrome; SC: subcutaneous; IV: Intravenous

present an increase of 2 mmol/L, and shows insufficient clinical improvement, the rate of saline infusion should again be increased, with S_{Na} determined once more after two hours. If the patient presents only moderate or mild symptoms, the infusion rate can be maintained and S_{Na} repeated 4-6 hours later. In patients whose S_{Na} has risen over 6 mmol/L, saline infusion should be discontinued. If S_{Na} has risen over 8 mmol/L, corrective measures should be initiated (see below). If the rise in S_{Na} is between 2

and 6 mmol/L, infusion should be maintained, and S_{Na} monitored every 2 hours until it has risen by 6 mmol/L.

One of the most important recommendations we can make in the use of hypertonic saline is that the prescribing physician personally supervise cessation of the iv infusion.

Once hypertonic saline infusion has been discontinued, and until 24 hours have passed since the start of treatment,

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oral salt can be administered and fluid restriction initiated in patients with SIADH. Other measures that can potentially raise S_{Na} should be avoided, to decrease the risk of overcorrection. We include potassium chloride (KCl) in this category: mild hypokalemia should not be corrected until the following day, since KCl administration will increase serum sodium levels.

Corrective Measures to Relower Serum Sodium

Relowering of serum sodium, following an excessive rise, prevents ODS. The development of ODS has been associated with an excessive rise in serum sodium over a 24 or 48 hour period. ODS can induce death or leave permanent neurologic sequelae. It is for this very reason that the 2007 guidelines²² recommend a maximum serum sodium increment of 10 mmol/L and 18 mmol/L in 24 and 48 hours respectively. However, a rapid reinduction of hyponatremia has been shown to prevent ODS symptoms^{37,43,44} and has been successfully used to treat patients that have developed ODS⁴⁵⁻⁴⁹.

Specific Measures

If S_{Na} is overcorrected (S_{Na} rise greater than 8 mmol/L following discontinuation of HSS or S_{Na} rise greater than 10 mmol/L 24 hours after initiation of therapy), measures should be taken immediately to once again lower the S_{Na} level. These include oral liquids, 5% iv dextrose solution (4-6 ml/Kg/hour for 2 hours with subsequent reevaluation of S_{Na}) and 1-2 mcg iv or sc desmopressin every 6 hours if and as needed³⁷. When using desmopressin, we recommend a lower initial rate of dextrose infusion: 1.5 to 2 ml/Kg/hour, repeating S_{Na} 2 hours later, and increasing the dextrose infusion rate as necessary. A lowering rate of 1 mmol/L/hour has been recommended⁵⁰. The association of desmopressin to iv dextrose is particularly important in patients who will not otherwise reabsorb large quantities of water in the collecting duct, as is the case of patients with primary polydipsia, and other patients with low U_{osm} . With low AVP levels, these patients will have few patent aquaporin-2 channels, (reflected by a low U_{osm}) and desmopressin should be administered for dextrose infusion to be useful. Iv furosemide can be administered once the desired serum sodium level has been reached, to put a halt to a further reduction in S_{Na} .

Patients at high risk for overcorrection. Certain groups of patients present a higher risk of overcorrection of serum sodium than others, and must be more closely monitored. These include patients in which the cause of hyponatremia is transitory, e.g. hyponatremia-inducing medication which has just been discontinued, or physiologic stimuli of AVP secretion once the stimulus has passed³². Patients with an extremely low salt intake prior to admission also fall into this category.

Patients with adrenal failure, either primary or secondary, are a separate case. They should receive high enough hydrocortisone doses to cover their glucocorticoid and mineralocorticoid needs. S_{Na} can rise very quickly after initiation of steroid therapy, particularly if high doses of hydrocortisone are given, and especially if administered by iv bolus, as when treating an adrenal crisis. In these patients, if S_{Na} rises by 8 mmol/L before 24 hours have elapsed since the start of treatment, 1-2 mcg of iv or sc desmopressin can be administered every 6-8 hours to prevent a further increment in S_{Na} levels. In many patients, however, the infusion of lower doses of hydrocortisone will be sufficient (between 60-150 mg daily⁵¹, with or without an initial bolus of 50 mg iv) and will induce a slower rate of correction of S_{Na} levels. In even milder cases, oral hydrocortisone can be given at a dose of 20 mg tid.

Application of Algorithm 2

The aim of algorithm 2 is to achieve eunatremia in patients with SIADH-induced mild or moderate hyponatremia not posing as a medical emergency.

Correction of hypokalemia

If hypokalemia is present, Potassium Chloride supplements should be given, taking care NOT to administer potassium bicarbonate, or potassium supplements that result in the generation of bicarbonate, since the latter will increase renal sodium excretion, and can induce metabolic alkalosis⁵².

Solute Administration

Patients with SIADH should have an adequate oral salt intake. A hospital diet frequently provides less than 4 grams of sodium chloride a day. Furthermore, many patients eat considerably less than what is provided, and will have an even lower sodium intake. We recommend the association of NaCl supplements, for a minimum consumption of 5 to 8 grams of salt daily.

The administration of large amounts of solute can be used for the treatment of SIADH – induced hyponatremia, acting through the induction of increased renal obligatory water clearance. In this case, oral salt supplementation can range from 3 to 4 grams every 8 hours, and must be even higher in exceptional cases. Close monitoring of blood pressure is essential. Another solute that has been given for the treatment of SIADH hyponatremia is oral urea, at doses of 30 g a day, usually given in two 15 g doses⁵³. Urea could be the therapy of choice in children

with SIADH⁵⁴. However, its low palatability has limited its use.

Fluid Restriction

Currently, fluid restriction is the cornerstone of treatment of SIADH-induced hyponatremia not requiring urgent intervention. By fluid restriction we mean the reduction of all liquids administered to the patient, be it with iv medication, oral liquids, or the intrinsic water content of foods. To adequately initiate fluid restriction, iv medication must be concentrated whenever feasible, and non-essential oral and iv medication discontinued. Oral liquid intake must be limited and foods with a high water content eliminated from the diet (soups, mashed foods, coffee, tea, gelatins, semi-liquid desserts, melons, citric fruits, etc.).

In our experience, the Furst formula⁵⁵ is useful in predicting which patients will respond adequately, and is calculated by dividing the sum of U_{Na} and U_K (mmol/L) by S_{Na} . Patients with a result less than 0,5 can be limited to 1000 ml of total liquid intake, whereas those between 0,5 and 1 need to be limited to 500 ml of liquid a day. Patients with a result of 1 or more will not respond to fluid restriction, since their nephrons are not capable of eliminating electrolyte-free water. In this case fluid restriction to 500 ml daily is used to prevent worsening of hyponatremia, not to correct it. The response of a specific patient to fluid restriction is not constant, and can vary from one day to another. Therefore, for a correct use of the Furst formula, electrolytes must be measured in serum and urine frequently. We consider a positive response to be an average 2 mmol/L rise in S_{Na} per day over a 2-day period.

Fluid restriction is not practical in all patients, and is simply incompatible with necessary medication or artificial nutrition in others. Another group does not tolerate or does not respond to the required fluid restriction. Furthermore, fluid restriction to 500 ml makes meals less palatable, and can worsen the nutritional status of the patient if used for more than a few days. In these cases, together with those presenting a Furst formula result of 1 or more, alternative therapies must be initiated.

Furosemide Therapy

Furosemide can be useful as a short-term treatment for SIADH hyponatremia when the U_{Osm} is sufficiently high, as it induces an increase in renal free water clearance. For this loop diuretic to be effective, U_{Osm} must be over 350 mOsm/Kg, and preferably over 400 mOsm/Kg. Sodium losses must be compensated by sufficient oral salt intake.

Furosemide can be administered iv or orally, in doses ranging from 20 mg iv every 8 to 24 hours, or 40 mg every 8 to 24 hours p.o., although higher doses have been successfully given^{56,57}. The use of this loop diuretic is particularly helpful in patients in whom SIADH will presumably be of limited duration (days), as is the case of patients with pneumonia or drug-induced SIADH when the medication can be discontinued (table 3).

Furosemide can also be useful in patients with serum sodium levels below 120 mmol/L presenting with moderate or mild symptoms, sodium levels higher than 115 mmol/L, and a low risk for herniation (ie the elderly). In this case serum sodium should be repeated 3 to 6 hours after an iv dose.

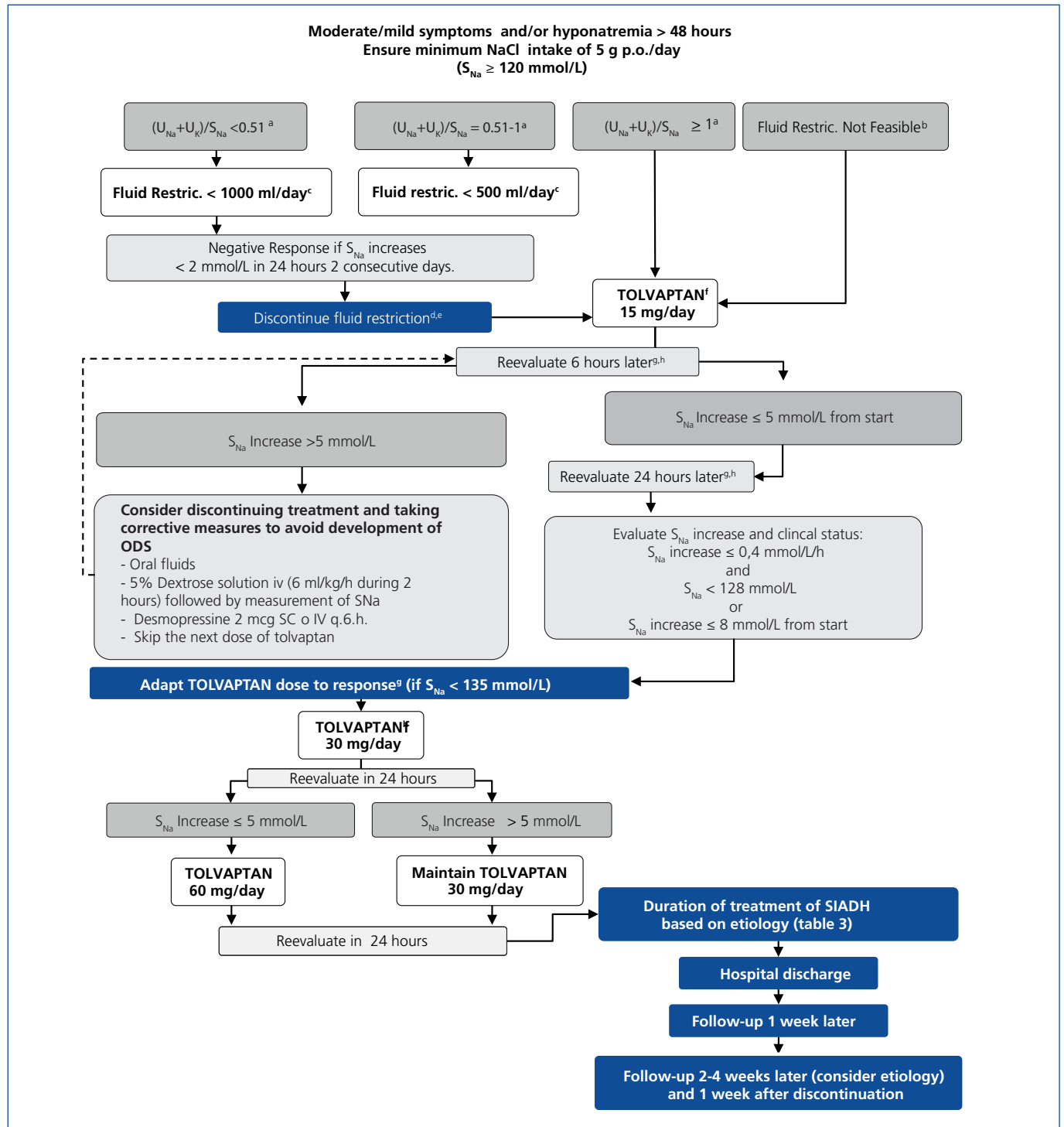
Tolvaptan Therapy

We recommend the use of tolvaptan, the selective V2 receptor inhibitor⁵⁸, in patients with SIADH who are not candidates for fluid restriction or furosemide. The drug is particularly useful in patients that will need treatment of their hypotonic hyponatremia for several days, or longer, as occurs in patients with chronic SIADH.

Initiation and monitoring of tolvaptan therapy. We prefer to start tolvaptan in patients in whose Nap has already risen above 119 mmol/L, since patients with lower serum sodium levels seem to be at a higher risk for overcorrection, in our experience as well as in that of others (Dr. Volker Burst, University of Cologne, personal communication).

Tolvaptan therapy must always be initiated while the patient is hospitalized. Care should be taken to assure that during the first day of tolvaptan administration patients not only have free access to liquids, but also are actively encouraged to drink *ad libitum*, since maximum aquaresis is observed precisely on day 1, when excess circulating water is greatest. Patients who have previously been on fluid restriction are prone to not drinking as much as they desire and must be closely monitored. If a patient has a limited capacity to drink (ie oral or gastrointestinal disease) 5% dextrose solution should be associated from the start. Patients with a nasogastric tube will also need increased liquids. In these cases, diuresis is helpful in estimating increased fluid needs.

The initial recommended dose is of 15 mg p.o., although several groups prefer to start treatment with 7.5 mg^{59,60}, (Dr. Volker Burst, personal communication). It is preferable to administer tolvaptan early in the morning (7 to 9 AM), to facilitate monitoring of the patient's response, and to assure adequate nocturnal rest. We recommend measuring serum sodium, potassium and P_{Osm} as well as

**Algorithm 2. Non-acute treatment.**

^a Furst H, et al. Am J Med Sci 2000;319(4):240-244; ^b Parenteral nutrition, or iv liquids that prevent fluid restriction, or patient intolerance; ^c Consider furosemide if Osmou >350 mOsm/Kg; ^d The patient must be able to drink ad libitum; ^e See warnings on text; ^f Tolvaptan summary of characteristics (Samsca®). Laboratorios Otsuka. ^g Measure electrolytes and Osmolality in plasma and urine; ^h Measure diuresis and liquid intake every 6 horas. If balance excessively negative: take corrective measures; especially important in patients with initial $S_{Na} < 125$ mmol/L.

Available at URL: <http://www.ema.europa.eu>. Access: November 2011.

S_{Na} : serum sodium concentration; U_{Na} and U_K =Urine concentrations of sodium and potassium mmol/L; Osmou: urine osmolality; ODS: osmotic demyelination syndrome; SC: subcutaneous; IV: intravenous; SIADH: syndrome of inappropriate antidiuretic hormone secretion.

sodium, potassium and osmolality in urine at baseline, and 6 hours after the initial dose, with monitoring of fluid intake and diuresis every 6 hours.

Patients whose S_{Na} has not increased by more than 5 mmol/L at 6-hours post-tolvaptan, and are drinking freely can be monitored by fluid intake/diuresis alone, with S_{Na} repeated 24 hours after the initial dose. If at 6 hours from baseline, S_{Na} has risen more than 5 mmol/L, we recommend initiating corrective measures in order to prevent an excessive rise in the 24-hour serum sodium levels, given that in our experience on day one of tolvaptan therapy S_{Na} will rise at nighttime, when the patient's fluid intake is low. These measures include an increase in oral fluid intake, and 5% dextrose solution iv infusion, at a rate of 3-4 ml/Kg/hour for 2 hours, followed by a new determination of S_{Na} . We have found the association of desmopressin (iv or sc) to be useful in avoiding overcorrection of S_{Na} in spite of V2 blockade, at doses of 2-4 mcg every 6 hours as needed. When using desmopressin, we recommend starting with a lower rate of dextrose infusion: 2 3ml /Kg/hour for 2 hours, followed by measurement of S_{Na} . The rate of infusion

is then increased every 2 hours as necessary to relower sodium levels with a goal of attaining a maximum increment of 4 mmol/L over baseline. Patients whose S_{Na} has risen more than 5 mmol/L over the first 6 hours should have S_{Na} measured once more 12 hours from baseline. Not all patients drink as needed and thus some present a excessively negative fluid balance. They will also require a new 12 h measurement of S_{Na} .

If 24 hours following the first dose serum sodium levels have increased more than 10 mmol/L, tolvaptan should not be readministered on that day, and corrective measures used as needed, although discontinuation of tolvaptan administration is usually sufficient to relower S_{Na} to desired levels. The drug can be reintroduced on the following day. If S_{Na} has increased by less than 10 mmol/L, a new dose of 15 mg should be administered, and S_{Na} monitored on the following day. When the rise in serum sodium levels is insufficient, the daily dose of tolvaptan can be increased to 30 mg, with a maximum dose of 60 mg/day. Experience with tolvaptan in Europe is still somewhat limited, and its use will surely undergo modifications in the future, particularly regarding doses.

Table 3. Probable duration of syndrome of inappropriate antidiuretic hormone secretion treatment as indicated by etiology

Etiology	Probable duration of SIADH	Relative Risk of chronic SIADH
ADH-secreting tumors (ectopic SIADH) (<i>oat-cell</i> , etc.)	Function of the duration of the underlying disease	1.0
Medication-induced, with continued use of the drug (carbamazepine, etc.)	Duration of treatment	1.0
Cerebral tumors	Function of the evolution of the underlying disease	0.8
Idiopathic SIADH of the elderly	Indefinite	0.8
Subarachnoid Hemorrhage	1-4 weeks	0.6
Stroke	1-4 weeks	0.5
Inflammatory Cerebral Lesions	Function of response to therapy	0.5
Respiratory Failure (COPD)	Function of response to therapy	0.4
HIV Infection	Function of response to therapy	0.2
Head Trauma	From 2-7 days to indefinite	0.2
Drug-induced, when the medication is discontinued. (carbamazepine, etc.)	Function of the duration of treatment	0.1
Pneumonia	2-5 days	0
Nausea, pain, prolonged exercise	Variable, depends on the cause	0
Post-operative Hyponatremia	2-3 days	0

COPD: chronic obstructive lung disease; SIADH: Syndrome of onappropriate Antidiuretic Hormone Secretion; HIV: human immunodeficiency virus.

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Tolvaptan: General Considerations. Tolvaptan has important drug interactions which must be taken into account before and during its use (Table 4). As a substrate for cytochrome P450 3A4, circulating levels of tolvaptan will increase when used with inhibitors, and will drop when associated with inducers. Tolvaptan at high doses (60 mg/day) can increase serum digoxin concentrations.

Tolvaptan should be used as monotherapy for SIADH, and never be administered jointly with hypertonic saline. On day 1 of use, it is preferable not to associate potassium supplements, nor furosemide. Tolvaptan should never be administered to a hypovolemic patient, underlying the importance of a correct diagnosis of SIADH. Tolvaptan is usually well tolerated, and in our experience is very effective for attaining strict eunatremia. However, intense thirst sometimes follows its administration. When accompanied by the ingestion of large quantities of liquid, thirst can lessen the effectiveness of the medication, as can chronic pain. Patients with SIADH type D (NSIAD due to an activating V2 receptor mutation) will probably not respond to tolvaptan treatment⁶¹.

Duration of Treatment. Out-patient follow-up. The duration of tolvaptan treatment is determined by the persistence of the underlying cause of the patient's SIADH (Table 3). When discontinuing tolvaptan, a progressive reduction in dose is always preferable to abrupt withdrawal of the medication. In patients discharged on tolvaptan therapy, we recommend repeating S_{Na} within a week, with new laboratory tests 2 to 4 weeks later, then monthly. In patients with chronic SIADH, in our experience, the tolvaptan dose can be progressively reduced once strict eunatremia is achieved. Patients with particularly low maintenance doses of tolvaptan may need higher doses once more in situations of increased liquid administration, and /or low salt intake, such as typically occurs with hospital readmission.

CONCLUSIONS

Hyponatremia is a very common disorder, yet it remains underdiagnosed, underappreciated, and often incorrectly managed. Concrete roadmaps for the treatment of hyponatremic patients are lacking. We have elaborated two complementary strategies to treat SIADH-induced hyponatremia in an attempt to increase awareness of its importance, simplify its therapy, and improve prognosis.

In spite of the frequency and negative repercussions of hyponatremia, there is a paucity of evidence in the field of hyponatremia and its therapy. We are clearly in need

of more research directed towards gathering evidence that can optimize therapy.

We hope that the application of this protocol will simplify and help bring consistency to the treatment of SIADH-induced hyponatremia, thus reducing morbidity, and facilitating the accumulation of evidence.

Conflicts of interest

Isabelle Runkle has worked as a consultant for Otsuka and has given sessions sponsored by Otsuka, Amgen and Novartis.

Carles Villabona has worked as a consultant for Otsuka and has given sessions sponsored by Novartis, Ipsen and Otsuka.

Andrés Navarro has worked as a consultant for Otsuka.

Antonio Pose has worked as a consultant for Otsuka, Boehringer, MSD, Rovi and Almirall, and has given sessions sponsored by Otsuka, Almirall, Boehringer, Novartis, Astra, Bristol, Lilly, Bayer, Sanofi, Lacer and Novo.

Francesc Formiga has worked as a consultant for Otsuka and has given sessions sponsored by Otsuka.

Alberto Tejedor has worked as a Nephrology consultant for the Spanish Agency of Medicines and the European Medicines Agency. He has been a consultant for Otsuka and Astra Zeneca.

Esteban Poch has worked as a consultant for Otsuka and has given sessions sponsored by Otsuka.

Table 4. Tolvaptan drug interactions

- Tolvaptan should be administered with caution when used together with CYP3A4 inhibitors (such as ketoconazol, diltiazem, macrolides) since these drugs increase circulating levels of tolvaptan.
- Tolvaptan action is reduced when co-administered with CYP3A4 inducers (such as rifampicine, barbiturates) as well as when co-administered with cyclosporine.
- Grapefruit juice can increase the activity of tolvaptan, and should be avoided.
- No interactions have been observed with CYP3A4 substrates (such as warfarin or amiodarone).
- Circulating levels of lovastatin are increased.
- Doses of 60 mg increase digoxin levels, requiring that the latter be measured.

REFERENCES

- Schwartz W, Bennett W, Curelop S, Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *Am J Med* 1957;23:529-42.
- Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic syndrome. *Am J Med* 1967;42:790-806.
- Feldman BJ, Rosenthal SM, Vargas GA, Fenwick RG, Huang EA, Matsuda-Abedini M, et al. Nephrogenic syndrome of inappropriate antidiuresis. *N Engl J Med* 2005;352:1884-90.
- Zerbe R, Stropes L, Robertson GL. Vasopressin function in the syndrome of inappropriate antidiuresis. *Annu Rev Med* 1980;31:315-27.
- Robertson GL. Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. *Am J Med* 2006;119:S36-S42.
- Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006;119:71.e1-8.
- Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. *QJM* 2008;101:583-8.
- Sandhu HS, Gilles E, DeVita MV, Panagopoulos G, Michelis MF. Hyponatremia associated with large-bone fracture in elderly patients. *Int Urol Nephrol* 2009;41:733-7.
- Hoorn EJ, Rivadeneira F, van Meurs JB, Ziere G, Stricker BH, Hofman A, et al. Mild hyponatremia as a risk factor for fractures: the Rotterdam Study. *J Bone Miner Res* 2011;26:1822-8.
- Verbalis J, Barsony J, Sugimura Y, Tiang Y, Adams D, Carter E, et al. Hyponatremia-induced osteoporosis. *J Bone Miner Res* 2010;25:554-63.
- Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med* 1985;102:164-8.
- Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med* 2009;122:857-65.
- Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med* 2010;170:294-302.
- Sajadieh A, Binici Z, Mouridsen MR, Nielsen OW, Hansen JF, Haugaard SB. Mild hyponatremia carries a poor prognosis in community subjects. *Am J Med* 2009;122:679-86.
- Arieff A. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986;314:1529-35.
- Upadhyay A, Jaber B, Madias N. Incidence and prevalence of hyponatremia. *Am J Med* 2006;119:S30-S35.
- Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta* 2003;337:169-72.
- Whyte M, Down C, Miell J, Crook M. Lack of laboratory assessment of severe hyponatremia is associated with detrimental clinical outcomes in hospitalized patients. *Int J Clin Pract* 2009;63:1451-5.
- Hoorn E, Lindemans J, Zeitse R. Development of severe hyponatremia in hospitalized patients: treatment-related risk factors and inadequate management. *Nephrol Dial Transplant* 2006;21:70-6.
- Ellison D, Berl T. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007;356:2064-72.
- Rozen-Zvi B, Yahav D, Gheorghide M, Korzets A, Leibovici L, Gaftor U. Vasopressin receptor antagonists for the treatment of hyponatremia: systematic review and meta-analysis. *Am J Kidney Dis* 2010;56:325-37.
- Verbalis J, Goldsmith S, Greenberg A, Schrier R, Sterns R. Hyponatremia treatment guidelines 2007: Expert panel recommendations. *Am J Med* 2007;120:S1-S21.
- Vexler ZS, Ayus JC, Roberts TP, Fraser CL, Kucharczyk J, Arieff AI. Ischemic and hypoxic hypoxia exacerbate brain injury associated with metabolic encephalopathy in laboratory animals. *J Clin Invest* 1994;93:256-64.
- Ayus JC, Arieff AI. Pulmonary complications of hyponatremic encephalopathy: noncardiogenic pulmonary edema and hypercapnic respiratory failure. *Chest* 1995;107:517-21.
- Ayus JC, Arieff AI. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. *JAMA* 1999;281:2299-304.
- Ayus JC, Armstrong D, Arieff AI. Hyponatremia with hypoxia: Effects on brain adaptation, perfusion, and histology in rodents. *Kidney Int* 2006;69:1319-25.
- Arieff A. Influence of hypoxia and sex on hyponatremic encephalopathy. *Am J Med* 2006;119:S59-S64.
- Nzerue C, Baffoe-Bonnie H, You W, Falana B. Predictors of outcome in hospitalized patients with severe hyponatremia. *J Natl Med Assoc* 2003;95:335-43.
- Ayus JC, Olivera J, Frommer J. Rapid correction of severe hyponatremia with intravenous hypertonic saline solution. *Am J Med* 1982;72:43-8.
- Rose B. Treatment of hyponatremia. UpToDate 2000. Available at: [http://cmbi.bjmu.edu.cn/uptodate/critical care/Fluid and electrolyte disorders/Treatment of hyponatremia- Sodium deficit and rate of correction.htm](http://cmbi.bjmu.edu.cn/uptodate/critical%20care/Fluid%20and%20electrolyte%20disorders/Treatment%20of%20hyponatremia-%20Sodium%20deficit%20and%20rate%20of%20correction.htm).
- Rose B. Treatment of Hyponatremia. UpToDate edition 17, 2010.
- Sterns R, Nigwekar SU, Hix JK. The treatment of hyponatremia. *Sem Nephrol* 2009;29:282-99.
- Moritz M, Ayus JC. The pathophysiology and treatment of hyponatraemic encephalopathy: an update. *Nephrol Dial Transplant* 2003;18:2486-91.
- Schrier RW, Bansal S. Diagnosis and management of hyponatremia in acute illness. *Curr Opin Crit Care* 2008;14:627-34.
- Cherney DZ, Davids MR, Halperin ML. Acute hyponatraemia and 'ecstasy': insights from a quantitative and integrative analysis. *QJM* 2002;95:475-83.
- Shafiee MA, Charest AF, Cheema-Dhadli S, Glick DN, Napolova O, Roozbeh J, et al. Defining conditions that lead to the retention of water: the importance of the arterial sodium concentration. *Kidney Int* 2005;67:613-21.
- Perianayagam A, Sterns R, Silver S, Grieff M, Mayo R, Hix J, et al. DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. *Clin J Am Soc Nephrol* 2008;3:331-6.
- Koenig MA, Bryan M, Lewin JL, Mirski MA, Geocadin RG, Stevens RD. Reversal of transtentorial herniation with hypertonic saline. *Neurology* 2008;70:1023-9.
- Kang SH, Kim HW, Lee SY, Sun IO, Hwang HS, Choi SR, et al. Is the sodium level per se related to mortality in hospitalized patients with severe hyponatremia? *Clin Nephrol* 2012;77:182-7.

40. Karp BI, Laureno R. Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. *Medicine (Baltimore)* 1993;72:359-73.
41. Ashrafian H, Davey P. A review of the causes of central pontine myelinolysis: Yet another apoptotic illness? *Eur J Neurol* 2001;8:103-9.
42. Kleinschmidt-Demasters BK, Rojiani AM, Filley CM. Central and extrapontine myelinolysis: then... and now. *J Neuropathol Exp Neurol* 2006;65:1-11.
43. Soupart A, Penninckx R, Crenier L, Stenuit A, Perier O, Decaux G. Prevention of brain demyelination in rats after excessive correction of chronic hyponatremia by serum sodium lowering. *Kidney Int* 1994;45:193-200.
44. Gankam Kengne F, Soupart A, Pochet R, Brion JP, Decaux G. Re-induction of hyponatremia after rapid overcorrection of hyponatremia reduces mortality in rats. *Kidney Int* 2009;76:614-21.
45. Soupart A, Penninckx R, Stenuit A, Perier O, Decaux G. Reinduction of hyponatremia improves survival in rats with myelinolysis-related neurologic symptoms. *J Neuropathol Exp Neurol* 1996;55:594-601.
46. Soupart A, Ngassa M, Decaux G. Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia. *Clin Nephrol* 1999;51:383-6.
47. Oya S, Tsutsumi K, Ueki K, Kirino T. Reinduction of hyponatremia to treat central pontine myelinolysis. *Neurology* 2001;57:1931-2.
48. Croxson M, Lucas J, Bagg W. Diluting delirium. *N Z Med J* 2005;118:U1661.
49. Yamada H, Takano K, Ayuzawa N, Seki G, Fujita T. Relowering of serum Na for osmotic demyelinating syndrome. *Case reports in neurological medicine* 2012;2012:704639.
50. Sterns R, Emmett M, Forman J. Osmotic demyelination syndrome and overly rapid correction of hyponatremia. *UpToDate* 2012.
51. Nieman L, Lacroix A, Martin K. Treatment of adrenal insufficiency in adults. *UpToDate* 2012.
52. Lindinger MI, Franklin TW, Lands LC, Pedersen PK, Welsh DG, Heigenhauser GJ. NaHCO(3) and KHCO(3) ingestion rapidly increases renal electrolyte excretion in humans. *J Appl Physiol* 2000;88:540-50.
53. Decaux G, Brimouille S, Genette F, Mockel J. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by urea. *Am J Med* 1980;69:99-106.
54. Huang EA, Feldman BJ, Schwartz ID, Geller DH, Rosenthal SM, Gitelman SE. Oral urea for the treatment of chronic syndrome of inappropriate antidiuresis in children. *J Pediatr* 2006;148:128-31.
55. Furst H, Hallows KR, Post J, Chen S, Kotzker W, Goldfarb S, et al. The urine/plasma electrolyte ratio: A predictive guide to water restriction. *Am J Med Sci* 2000;319:240-4.
56. Decaux G, Waterlot Y, Genette F, Hallemans R, Demanet JC. Inappropriate secretion of antidiuretic hormone treated with furosemide. *Br Med J (Clin Res Ed)* 1982;10:89-90.
57. Decaux G. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by long loop diuretics. *Nephron* 1983;35:82-8.
58. Verbalis JG, Alder S, Schrier RW, Berl T, Zhao Q, Czerwiec FS; SALT Investigators. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. *Eur J Endocrinol* 2011;164:725-32.
59. Gross P, Wagner A, Decaux G. Vaptans are not the mainstay of treatment in hyponatremia: perhaps not yet. *Kidney Int* 2011;80:594-600.
60. Cuesta M, Gomez-Hoyos E, Montañez C, Martin P, Marcuello C, de Miguel P, et al. An initial dose of 7.5 mg Tolvaptan is safe and effective in the treatment of hyponatremia caused by SIADH. Presented at ECE/ICE. Florence, Italy. May 2012.
61. Decaux G, Vanderghyest F, Bouko Y, Parma J, Vassart G, Vilain C. Nephrogenic syndrome of inappropriate antidiuresis in adults: High phenotypic variability in men and women from a large pedigree. *J Am Soc Nephrol* 2007;18:606-12.