Reviews in Clinical Gerontology 2015 25; 31–52 First published online 16 January 2015
© Cambridge University Press 2015 doi:10.1017/S0959259814000197

Hyponatraemia in older patients: a clinical and practical approach

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Summary

Hyponatraemia is frequent in older people and induces marked motor and cognitive dysfunction, even in patients deemed 'asymptomatic'. Nutritional status is worse than in euvolaemic-matched controls, and the risk of fracture is increased following incidental falls. Yet hyponatraemia is undertreated, in spite of the fact that its correction is accompanied by a clear improvement in symptoms. Both evaluation of neurological symptoms and classification by volaemia are essential for a correct diagnosis and treatment of the hyponatraemic elderly patient. The syndrome of inappropriate anti-diuretic hormone secretion (SIADH) is the most common cause of hyponatraemia in older people. Nutritional status and chronicity of SIADH should be taken into account when deciding therapy. We propose an 8-step approach to the management of the elderly patient with hyponatraemia.

Key words: hyponatremia, SIADH, fluid restriction, tolvaptan, hypoaldosteronism, hypertonic saline.

Introduction

Hyponatraemia is frequent in older people,[1–4] and advanced age is a risk factor for its development.[2] Even mild/moderate hyponatraemia can induce serious symptoms, often undetected in older individuals. Yet it is often overlooked, erroneously classified, inadequately diagnosed and frequently undertreated. Over the past year, comprehensive Expert Panel Recommendations as well as guidelines have been published on hyponatraemia.[5,6] A detailed roadmap has been presented on the management of inappropriate anti-diuretic hormone secretion (SIADH)-induced hyponatraemia.[7] In this review we will outline a practical, step-by-step approach for the detection, diagnosis and treatment of hyponatraemia in the elderly.

Randomized clinical trials and meta-analyses are few and far between in the field of hyponatraemia, and are limited to the use of vaptans, particularly tolvaptan, for the treatment of SIADH. When deciding what bibliography to include, we have therefore given priority to articles, expert opinions and guidelines that have modified or could modify clinical practice. We have also included the results of our own research.

Incidence of hyponatraemia in older people

Defining hyponatraemia as a serum sodium level (S_{Na}) below 135 mmol l^{-1}, the incidence of hyponatraemia has been found to be 11% in ambulatory patients over 78 years of age,[1] and close to 17% in patients over 80 years of age seen at a university hospital emergency room over a 2-year period.[2] Sixty-six per cent were females. The odds ratio (range) for hyponatraemia was 3.3 (2.8–3.8) in patients over 60 years old.[2] Prevalence on a geriatric ward and in long-term institutionalized patients has been found to be as high as 22%.[3,4] A prospective study on medical wards revealed that 6.2% of hospitalized patients over 65 years old presented marked hyponatraemia, with S_{Na} below 125 mmol l^{-1}.[8] These figures would be even higher if S_{Na} had been corrected for serum total proteins (TP), as outlined below.

Factors favouring the development of hyponatraemia include gender, chronic pain, polypharmacy, heart failure, cancer, neurological disease and a reduced renal capacity to eliminate free water.[9–11] Furthermore, elderly patients characteristically have diminished total body water. Consequently, small increases in renal water retention can exert significant clinical effects.[9]

SIADH is the most common cause of hyponatraemia in advanced age.[8,9,12] Contributing

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https://doi.org/10.1017/S0959259814000197 Published online by Cambridge University Press

factors include increased arginine vasopressin (AVP) secretion, cancer, neurological disease and polypharmacy, particularly with selective serotonin re-uptake inhibitors (SSRIs). Yet from 26 to 60% of cases of SIADH have been found to be idiopathic,[1,13,14] particularly in subjects over 81 years of age.[15] Increased AVP secretion together with inadequate renal elimination of free water have been proposed by Cowen *et al.* as an explanation for this high frequency in the older patient.[9]

Definition and detection of hyponatraemia

Hyponatraemia is usually defined as a S_{Na} below 135 mmol l^{-1}. However, adjustment must be made for hyperglycaemia-induced translocational hyponatraemia. For every 100 mg dl^{-1} of glycaemia over 100 mg dl^{-1}, 1.6 mmol l^{-1} are added to S_{Na} up to glycaemias of 400–440 mg dl^{-1}, followed by a correction of 4 mmol l^{-1} per 100 mg dl^{-1} of additional glycaemia. As a less accurate alternative, 2.4 mmol l^{-1} can be used as a correction factor.[16] Pseudohyponatraemia must be ruled out when patients have high triglyceride or high total protein levels (TP) and indirect electrode measurements of S_{Na} are used[17] (Fig. 1), although their effect is usually minor. The importance of correcting S_{Na} for low TP is often overlooked, although low TPs are frequently encountered in elderly patients. Under these circumstances, indirect electrode measurement can mask hyponatraemia and its severity substantially.[18] Whole blood gas sodium determinations are not influenced by TP.

The finding of a minimum hospital and post-surgical mortality in patients with S_{Na} between 138 and 142 mmol l^{-1} ([19,20]) has led to questioning the validity of the reference range of 135–145 mmol l^{-1} as normal or ideal. In fact, elderly patients with SIADH can already have increased body water and effective circulating volume (EFCV) with haemodilution when presenting a S_{Na} of 135 mmol l^{-1} as opposed to 140, as shown in data from a 96-year-old patient (Table 1). In any event, a S_{Na} below 135 mmol l^{-1} as corrected for TP, lipids and glycaemia, indicates frank hyponatraemia.

Clinical manifestations of hyponatraemia in older people

Severe/marked hyponatraemia can cause death through cerebral herniation induced by brain oedema. Cerebral atrophy protects the older patient from herniation, since the cranium has 'more space' to accommodate oedema. However, intracranial haemorrhage or tumours can place elderly patients at high risk. Furthermore, hypoxaemia, the most important risk factor for death in a patient with marked hyponatraemia (relative risk of 13.47 (4.7–38.4)),[21] is not uncommon in older patients. Insufficiently aggressive treatment is associated not only with increased mortality, but also with a high rate of permanent neurological sequelae. Ayus and Arieff found that post-menopausal women with marked hyponatraemia had a much higher rate of death or institutionalization following an insufficient correction rate with fluid restriction than those who developed marked overcorrection following treatment with intravenous (i.v.) saline.[22]

Over the past decade, substantial progress has been made in understanding the consequences even of mild hyponatraemia, and the beneficial effects of treatment. Renneboog *et al.* found that patients with mild/moderate chronic 'asymptomatic' hyponatraemia present cognitive impairment upon testing, whereas the same patients with eunatraemia do not.[23] Patients admitted to a geriatric unit with $S_{Na} \leq 131$ scored significantly worse on all tests performed (Activities of Daily Living, Mini Mental State Examination, Clock Completion Test, Geriatric Depression Score, Tinetti Mobility Test, and the Timed Up & Go Test) compared with matched eunatraemic controls.[24] Gait instability is frequent in patients with mild/moderate hyponatraemia, and induces falls. In fact, 'asymptomatic' hyponatraemic patients were 67 times more likely to fall than normonatraemic controls in Renneboog's study. Furthermore, gait instability also improves upon correction of hyponatraemia.[23]

Our own clinical experience seems to support these findings. Elderly patients with chronic SIADH followed up in our hyponatraemia clinic (many previously diagnosed as having 'mild chronic asymptomatic hyponatraemia') show progressive improvement of cognitive and motor function over time, following maintenance of strict eunatraemia (S_{Na} between 137 and 141 mmol l^{-1}) on chronic tolvaptan therapy. Interestingly, maximum benefits are observed after 2–4 months of continued therapy (Table 2).

Verbalis *et al.* demonstrated that sustained severe hyponatraemia induces marked osteoporosis in experimental animals, with

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Table 1. *Data from a 96-year-old patient with idiopathic SIADH of the elderly, on tolvaptan, and 14 days after discontinuation of medication*

	On tolvaptan	Off tolvaptan
S Na mmol/L	140	135
S K mmol/L	4.5	4.7
S uric acid mg/dl	5.5	4.7
S urea mg/dl	28	24
S creatinine mg/dl	0.93	0.79
EGF MDRD-4 ml/min	75	91
Bilirubin mg/dl	0.7	0.4

S, serum; Na, sodium level; K, potassium level; EGF, estimated glomerular filtration rate.

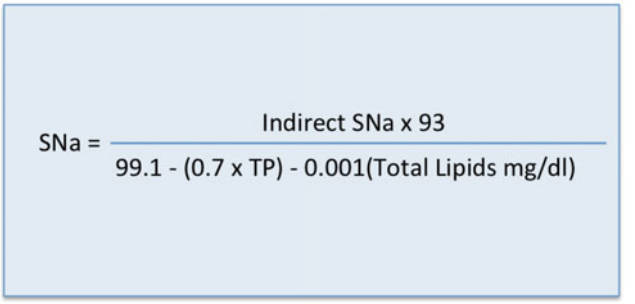


Figure 1. Formula for calculation of serum sodium level when using indirect electrode measurement. From Liamis G, *et al. Am J Nephrol* (2013). TP, total proteins in g dl^{-1}; S_{Na}, serum sodium in mmol l^{-1}.

an increase in the number of osteoclasts and reabsorptive activity. In humans, mild hyponatraemia is associated with osteoporosis in the NHANES III database, with an adjusted odds ratio for osteoporosis at the femoral neck of 2.87 among hyponatraemic subjects.[25] The Rotterdam study did not detect increased osteoporosis in hyponatraemic subjects,[26] possibly because of a high rate of thiazide use.[27] Furthermore, only one S_{Na} was available, and sustained hyponatraemia was not demonstrated. The risk of fractures is increased in patients with hyponatraemia,[26] due to a high rate of spontaneous falls, and possibly due to hyponatraemia-induced osteoporosis. Patients with hip fracture following an incidental fall are 4.8 times as likely to present hyponatraemia as matched controls.[28]

Mild hyponatraemia can induce marked anorexia and hyponatraemic patients on a geriatric ward present significantly lower mini-nutritional assessment scores than matched eunatraemic controls.[24] Non-correction of S_{Na} for TP can also cause the frequency/severity of hyponatraemia to be underestimated. Correct evaluation of nutritional status is therefore essential, as are the detection and treatment of hyponatraemia in the malnourished elderly.

All degrees of hyponatraemia are associated with an increased mortality rate.[29,30] However, active correction of hyponatraemia reduces mortality to a third in hospitalized patients with S_{Na} below 125 mmol l^{-1}.[31] The relationship between mild/moderate hyponatraemia and mortality is less clear. Hyponatraemia could simply be a marker of the severity of underlying disease. However, extracellular hyponatraemia directly inhibits rat cardiomyocyte voltage-gated L-type calcium channels *in vitro* in a concentration-dependent manner, thus compromising contractility[32] and mild/moderate hyponatraemia is a predictor of non-response to cardiac resynchronization therapy.[33] Correction of moderate hyponatraemia with chronic tolvaptan therapy reduced cardiovascular mortality and hospital re-admissions by 40% in patients with heart failure.[34] Therefore, mild/moderate hyponatraemia could contribute directly to morbidity and mortality in patients with heart failure.

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Table 2. *Evolution of clinical characteristics of patients with chronic SIADH on tolvaptan therapy following 1, 2 and 3–4 months of continued therapy*

	Year Prior to tolvaptan therapy			Eunatremia on tolvaptan therapy		
Age Gender	SNa mmol/L	Clinical Manifestations during the year prior to admittance	Nadir SNa* mmol/L	1 month SNa mmol/L	2 months SNa mmol/L	3–4 months SNa mmol/L
82 F	127–134	Frequent falls, with 4 visits to ER. Apathy, few household chores, confusion. Does not leave home. DEPENDENT.	127	Happier, steady gait, cleaning curtains, household chores. SNa 141	Feels alive again, starts going out, cleans windows and doors. SNa 141	"I've been given my life back" INPEPENDENT SNa 140–141
80 M	130–133	Unsteady gait, apathy, passivity, anorexia. Spends most time in an armchair. DEPENDENT.	120	More active, Improved appetite, gait. SNa 140	Eating well, going out. "I am no longer afraid to start something new, to go out." SNa 140	Is feeling very good. INDEPENDENT SNa 139
76 F	132–133	Impaired speech, drowsiness, dizziness, disorientation, bradypsychia, no household chores. Does not leave home. DEPENDENT.	120	More alert, spontaneous and coherent speech SNa 143	Does household chores, no dizziness, alert, smiling, joking. SNa 143	Is still accompanied when shopping. PARTIALLY INDEPENDENT SNa 139
91 M	131–133	Anorexia, weight loss, asthenia, general weakness, disorientation, depression. Six months in an armchair. DEPENDENT	112	More awake, eating, sleeping and walking better, more optimistic. SNa 139	Happy, active, spends little time at home, "unrecognizable" to the family. Starts resuming care of blind spouse SNa 138	Does all the shopping, does household chores. "We haven't seen him this way in years" INDEPENDENT AND CARETAKER SNa 138
87 F	127–133	Unsteady gait with 2 serious falls. Apathy, does few household chores. PARTIALLY DEPENDENT	130	Improved gait, no falls, still apathetic. SNa 134	More enthusiastic, does all household chores, goes shopping. SNa 138.	Active. Has resumed care of spouse with Alzheimer's Diesease. INDEPENDENT, CARETAKER SNa 138
82 F	132–134	Speech not always logical. Passive, has stopped going out and household chores. Spends most of her time in an armchair. Floating sensation. DEPENDENT	116	Active, steady gait, has resumed household chores. Reads the newspaper. SNa 141	Shopping, going out for lunch with friends, reading novels, happy, active. INDEPENDENT. SNa 141	Rereading classical literature, going out for dinner, goes to the sierra, takes charge anew of family finances. FAMILY DEPENDS ON HER. SNa 140

S_{Na}, serum sodium level; ER, emergency room.

Classification and diagnosis of hyponatraemia

Classification of the hyponatraemic patient by volaemia

This is essential for correct diagnosis and treatment. Patients are classified as hypervolaemic (increased total body water due to heart failure, ascites, substantial oedema), hypovolaemic (decreased body water), or euvolaemic. The first two cases are characterized by decreased EFCV, with baroreceptor-induced elevation in circulating AVP levels. AVP, through its G-protein-coupled, transmembrane V2 receptor, increases Na absorption at the ascending loop of Henle, and stimulates the insertion of aquaporin-2 channels into the luminal (apical) membrane of the principal cells of the collecting duct of the distal nephron.[35] Water reabsorption is induced, down an osmotic gradient between the collecting duct and the renal medulla (RM) and hyponatraemia ensues.[5,36] Euvolaemic patients, on the other hand, often present an elevated EFCV.[37]

Physical examination

Examination is essential for classifying volaemia. Detecting patients with hypervolaemia is usually straightforward. However, distinguishing hypovolaemic from euvolaemic patients can be difficult.[5] We have found that manual appraisal of ocular pressure (OP) is extremely useful in distinguishing hypovolaemia from euvolaemia in older patients.[7] The examiner gently touches each ocular globe through the patient's closed eyelid. Hypovolaemic patients present a low ocular pressure, whereas euvolaemic hyponatraemic patients have a normal OP. In fact, in states where EFCV is elevated, as occurs in SIADH, patients usually present a normal OP with ocular globe elasticity, or 'rebound'. We also use inspection to ascertain central venous pressure (CVP)[7]: in the recumbent hypovolaemic patient, the waves of the CVP are detected below the sternal angle, whereas CVP is normal in the euvolaemic patient. Skin turgor, on the other hand, is frequently reduced in older patients and should not be used to classify volaemia.

Hypovolaemic hyponatraemia: differential diagnosis and laboratory tests (see Table 3)

Patients with low EFCV (due to hyper- or hypovolaemia) tend to present a rise in serum urea and creatinine levels as S_{Na} descends, whereas euvolaemic patients with SIADH, primary polydipsia or acute water intoxication will generally present a reduction in serum urea, creatinine and uric acid levels as S_{Na} goes down. Figure 2 illustrates this point.

Patients with a low EFCV usually present low urinary sodium levels, below 20 mmol l^{-1},[5] as the renin–angiotensin–aldosterone axis (RAAS) is stimulated, leading to angiotensin II and aldosterone-induced sodium retention by the nephron. Furthermore, more sodium is reabsorbed due to a slower flux through the descending and ascending loops of Henle. However, urinary sodium levels can be high in patients with hypovolaemic hyponatraemia characterized by renal sodium loss,[5] as in diuretic use, hypoaldosteronism, hypoaldosteronism with glucocorticoid deficiency (primary adrenal insufficiency), cerebral/renal salt wasting or bicarbonate administration.

Patients over 65 years of age have been found to be ten times more likely to develop *diuretic-associated hyponatraemia* than younger subjects, with women exhibiting a relative risk of three.[38] In close to 75% of cases, thiazides are the diuretics employed. A retrospective cohort study detected that up to 30% of adults of all ages receiving thiazides developed hyponatraemia over a 5-year period.[39] Elderly subjects with a history of thiazide-induced hyponatraemia exhibit a decreased capacity for diluting urine upon receiving thiazide and an oral water load.[40] In fact, increased thirst could be a factor in thiazide-related hyponatraemia, together with up-regulation of aquaporin-2 expression.[41] The time elapsed since initiation of thiazide use to presentation of hyponatraemia is variable. A low BMI could be a risk factor.[27] The associated use of angiotensin converting enzyme inhibitors (ACEi),[42] or angiotensin II receptor blockers (ARBs)[43] can increase the risk and/or severity of hyponatraemia, as can hypokalaemia.[42]

We have observed that close to 60% of elderly patients with marked thiazide-related hyponatraemia are hypovolaemic, as classified by an initial physical examination that includes OP and CVP, with the remaining 40% euvolaemic.[44] In 27 elderly patients (median age 80 years; range 65–84 years) with a median initial S_{Na} of 116 mmol l^{-1} (109–119), urinary Na tended to be lower in the hypovolaemic group: 40 mmol l^{-1} (18–69) *vs* 61 mmol l^{-1} (43–85) ($P = 0.09$).

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Table 3. *The differential diagnosis of hyponatraemia with low effective circulating volume*

Low Effective Circulating Volume									
CLASSIFICATION		PHYSICAL EXAM			LAB TESTS				
	Causes	Ocular Pressure	Central Venous Pressure	Ascitis Edema	P_{Osm} (mOsm/Kg)	U_{Na} (mmol/L)	U_{Osm} (mOsm/kg)	Urea Creatinine	Uric acid
HYPER VOLEMIA	Heart failure, Cirrhosis, Hypoalbuminemia	↓	Can be ↑	YES	VARIES	< 20	VARIES	↑	↑
HYPO VOLEMIA	**No Renal Na Losses:** • Burns • Hemorrhage • Gastroenteritis • Vomiting • Pancreatitis • Low Na Intake	↓	↓	NO	VARIES	< 20	VARIES	↑	↑
	Renal Na Losses: • Diuretics • Hypoaldosteronism • Addison's • Salt-Wasting • Bicarbonate	↓	↓	NO	VARIES	> 20	Usually > 250	↑	Usually ↑

P_{osm}, measured plasma osmolality; U_{Na}, orinary sodium; U_{osm}, measured urinary osmolality.

Over 44% presented severe initial neurological symptoms. S_{Na} was significantly lower in patients with hypokalaemia: 113 mmol l^{-1} (109–115) *vs* 119 mmol l^{-1} (110–22) ($P = 0.041$). Eighty-five per cent of patients were women. Over 61% of patients were receiving hydrochlorothiazide. A low solute intake (from salt and protein) was present in the days prior to admission in 66%, and could be a precipitating event, as renal elimination of water becomes more difficult (see below).

Hypoaldosteronism (type IV renal tubular acidosis) is often overlooked as a cause of hyponatraemia and hyperkalaemia (or kalaemia in upper limits of normal) in patients with hypovolaemic hyponatraemia.[45,46] Hypoaldosteronism can be detected in up to 3.8% of hospitalized patients,[47] the majority between 60 and 80 years of age. Patients typically present with hyperkalaemia alone, yet when hypovolaemia is present, AVP elevation can induce hyponatraemia. After first ruling out primary adrenal insufficiency (Addison's disease), the transtubular potassium gradient (TTKG) can be calculated to assess the activity of the mineralocorticoid receptor, as a more precise measure of renal potassium excretion than urinary potassium alone. If, instead of a normal gradient (eight to nine), the calculated level is below five, the patient presents 'hypoaldosteronism', either due to a low aldosterone level, or mineralocorticoid resistance.[47–49]

Cerebral salt wasting (CSW) is an infrequent cause of hypovolaemic hyponatraemia. In a recent prospective study of 100 consecutive patients with hyponatraemia following subarachnoid haemorrhage, not a single case was detected.[50]

Euvolaemic hyponatraemia: differential diagnosis and laboratory tests (Table 4)

The most common causes of euvolaemic hyponatraemia (EH) are what we will refer to as 'euvolaemic ADH states': patients present normal or elevated EFCV induced by AVP, inadequately inhibited by a descent in plasma osmolality. This category includes patients with SIADH (including type D, or the nephrogenic syndrome of inappropriate anti-diuresis – NSIAD),[51] post-surgical hyponatraemia (sometimes considered to be a form of SIADH), patients with ACTH deficit, and physiologic stimuli of AVP secretion (nausea, vomiting or pain).

When ADH is inadequately detectable in euvolaemic hyponatraemic patients, AVP via

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Figure 2. The relationship between serum sodium and urea in hyponatraemia. A, relationship between serum urea (mg dl^{-1}) and sodium (mmol l^{-1}) levels of a 78-year-old hypovolaemic patient with a salt-wasting nephropathy as i.v. isotonic saline is added, raising serum sodium, or discontinued, with fall of serum sodium. B, relationship between serum urea (mg dl^{-1}) and sodium (mmol l^{-1}) levels in an initially 94-year-old patient with chronic idiopathic SIADH, over a 1-year period.

its V2 receptor directly increases the osmolality of the RM, through stimulus of Na absorption at the ascending loop of Henle, and induces water reabsorption from the collecting duct, as in hypovolaemic hyponatraemia. The higher the AVP levels, the more aquaporin-2 channels are inserted into the apical membrane of the principal cells of the collecting duct, and a higher degree of anti-diuresis will ensue. When sufficient aquaporin-2 channels are open, osmolality in

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Table 4. *The differential diagnosis of euvolaemic hyponatraemia*

"Euvolemic" : normal or elevated Effective Circulating Volume								
CLASSIFICATION	PHYSICAL EXAM			LAB TESTS				
Causes	Ocular Pressure	Central Venous Pressure	AscitisEdema	P_{Osm} (mOsm/Kg)	U_{Na} (mmol/L)	U_{Osm} (mOsm/kg)	Urea Creatinine	Uric acid
Renal Failure (Without Heart Failure)	N	N	Can present Edema	VARIES	> 20	↑	↑↑	↑↑
Primary Polydipsia (Worse if Low Solute Intake, Stress)	N	N	NO	↓	< 20 < 10	< 100	↓	↓
Acute Water Intoxication (Can stimulate AVP via nausea)	N	N	NO	↓	VARIES	VARIABLE	↓	↓
Low Na/Solute Intake, with adequate fluid intake	N	N	NO	↓	< 20	VARIABLE	VARIABLE	VARIABLE
ADH Family: SIADH, NSIAD, Post-op ACTH deficit, Nausea, Vomiting, Pain	N	N	NO	↓	>40 if sufficient Na Intake	> 100	↓	↓
Others: Thiazides, Severe Hypothyroidism	N	N	NO	↓	Usually > 40	> 100	↓	↓

P_{osm}, measured plasma osmolality; U_{Na}, urinary sodium; U_{osm}, measured urinary osmolality; ADH, anti-diuretic hormone; SIADH, the syndrome of inappropriate anti-diuretic hormone secretion; NSIAD, the nephrogenic syndrome of inappropriate anti-diuresis.

the distal collecting duct (i.e. urine) will have entered into equilibrium with the osmolality of the RM.[52] Thus urine osmolality (U_{osm}) will directly reflect the osmolality of the RM, and indirectly indicate circulating AVP levels. Urinary sodium is over 40 mmol l^{-1} when salt intake is sufficient, but can go below 20 mmol l^{-1} in cases of severe salt depletion. Plasma osmolality is below 275 mosmol kg^{-1}, and U_{osm} above 100 mosmol kg^{-1}.[5,53] Activating mutations of the V2 receptor mimic AVP action in NSIAD.

ACTH deficiency (secondary adrenal insufficiency) can be indistinguishable from SIADH, since hyponatraemia is induced by elevated AVP secretion, although some patients will have low BP and blood glucose, or signs of hypopituitarism. The 'culprit' AVP in this case is synthesized by parvocellular neurons of the dorsomedial paraventricular hypothalamic nucleus, in neurons that also synthesize CRH. An integral part of the hypothalamic–pituitary–adrenal axis, parvocellular AVP will rise with CRH in conditions of stress and of hypocortisolaemia, as long as the parvocellular neurons are intact.[54,55] Thus patients with suspected SIADH must be screened for ACTH deficit by measurement of serum cortisol, and/or a short synacthen test. A morning serum cortisol level >300 nmol l^{-1} (11 μg dl^{-1}) has been considered sufficient to rule out the need for immediate glucocorticoid therapy,[50] although higher levels (>469 nmol l^{-1} or >17 μg dl^{-1}) could be preferable in patients in situations of stress. If ACTH deficit is recent, a short synacthen test will not be adequate for diagnosis.

Pain and nausea must be controlled prior to diagnosing SIADH, since they are potent stimulators of AVP secretion. In experimental animals, nociceptive pain is a particularly potent stimulator of parvocellular AVP.[56]

Thiazides can induce euvolaemic hyponatraemia. However, we have yet to see a single case of 'rebound' ocular pressure in these patients, in spite of normal OP and CVP (authors' unpublished data). Patients on diuretics can have underlying SIADH. Yet, until the diuretic has been discontinued and its effect has passed, SIADH cannot be diagnosed.[5] Severe hypothyroidism can also induce euvolaemic hyponatraemia, although infrequently. One study found that for every mU l^{-1} elevation in TSH levels, S_{Na} descent was limited to 0.14 mmol l^{-1}.[65]

The diagnosis of SIADH is therefore one of exclusion – patients must be euvolaemic, have a normal adrenal and renal function, have pain and

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nausea under control, have severe hypothyroidism ruled out, not be on diuretics, and present a low plasma osmolality with an inadequately concentrated urine.

The differential diagnosis of CSW with SIADH should not be difficult. CSW patients are clearly hypovolaemic, with low OP and CPV, have polyuria, with an elevation of urea/creatinine levels as S_{Na} lowers.[57] However, as opposed to other cases of hypovolaemia, uric acid levels also descend, presumably due to proximal tubule loss.[58,59] Intravenous isotonic saline corrects hyponatraemia and the elevation in serum urea/creatinine as volaemia is restored. Since saline does not correct uricosuria, uric acid levels remain low until CSW is resolved. In SIADH, serum uric acid lowers, as do serum urea/creatinine, rising as hyponatraemia is corrected.

Primary polydipsia can be seen in elderly people. As part of the syndrome of 'diabetes insipidus', it is characterized by polydipsia and polyuria. Patients usually present S_{Na} in the low–normal range, or only slightly below 135 mmol l^{-1}, since decreased serum osmolality inhibits AVP secretion and polyuria ensues. However, these patients can develop marked hyponatraemia when polydipsia is accompanied by a low solute intake. The minimum U_{osm} is 50–60 mosmol kg^{-1} with normal renal function. In other words, the nephron needs at least 60 mosmol of solute to eliminate a litre of water[60] in a normal kidney. Each molecule of sodium, chloride, potassium and urea contribute a mosmole. In absence of sufficient protein (urea) and salt intake, ingested liquid will not be excreted adequately and severe hyponatraemia can ensue. Elderly people already have a diminished capacity for free-water clearance. Thus decreased protein intake (urea), together with a low-salt diet, can induce marked hyponatraemia when maintaining liquid intake. Stress, pain or nausea, stimulating AVP regardless of plasma osmolality, can also induce marked hyponatraemia in the polydipsic patient, by opening aquaporin-2 channels. Urine is typically dilute, with Na below 20 and even 10 mmol l^{-1}, and U_{osm} below 100 mosmol kg^{-1}.[5]

Acute water intoxication can be seen in elderly patients during or following the preparation of colonoscopy. When assessing the severity of hyponatraemia in this disorder, the velocity of S_{Na} descent must be considered, when information is available. A patient with initially moderate neurological symptoms can deteriorate rapidly if water is still being absorbed from the gastrointestinal tract.[61] Peripheral venous natraemia is often inaccurate, as recently absorbed water will first dilute arterial blood.[62] Therefore, arterial gas sodium measurement is preferable to assess the true degree of hyponatraemia. Gastric distension, nausea and vomiting can induce AVP secretion and urine sodium/osmolality can be high (over 40 mmol l^{-1} and 100 mosmol kg^{-1}, respectively). However, in other cases, urine can be dilute.

Low sodium intake (LSI) alone is not a cause of hyponatraemia. Hyponatraemia can be induced when LSI is associated with external sodium losses (diuretics, fistulae) and/or low protein intake. However, low salt intake is often blamed for hyponatraemia in elderly patients receiving artificial nutrition, in spite of the accompanying generation of urea. The sodium content of parenteral nutrition is not related to the low S_{Na} often observed.[63] Patients with hyponatraemia receiving artificial nutrition should be correctly classified (as hyper-, hypo- or eunatraemic) and diagnosed, since a correct diagnosis will be required for adequate therapy.[64]

Approach to the management of the elderly hyponatraemic patient (Fig. 3)

When evaluating a patient with hyponatraemia, it is important to first consider the severity of the neurological symptoms, take a short history when possible and determine volaemia by physical examination. Based on this information, together with the whole blood or serum sodium level corrected for glycaemia, a decision can be made as to whether 3% hypertonic saline infusion (HSS) is indicated.

Step 1: Evaluate neurological symptoms (Fig. 4).[5,7] Starting with an initial classification, we consider a series of parameters that make marked hyponatraemia more likely to induce death or permanent neurological sequelae if not aggressively treated.[7] When one of these parameters is present we 'upgrade' or 'correct' severity.

Step 2: Evaluate volaemia by physical examination, including OP and CVP. Patients with heart failure are treated specifically. Patients with other types of hypervolaemia and severe hyponatraemia can be treated as hypovolaemics initially.

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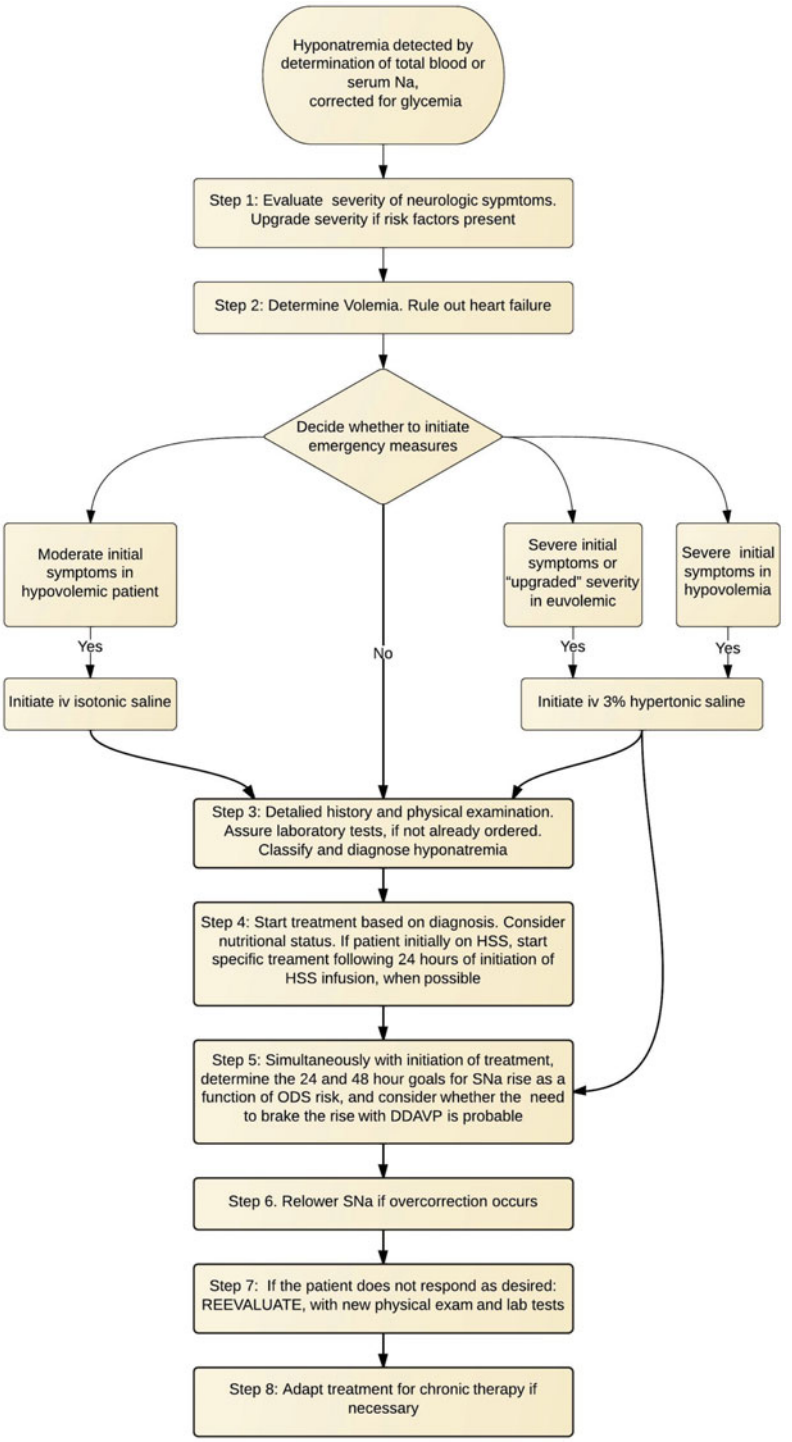


Figure 3. A step-by-step approach to the management of hyponatraemia in the older patient

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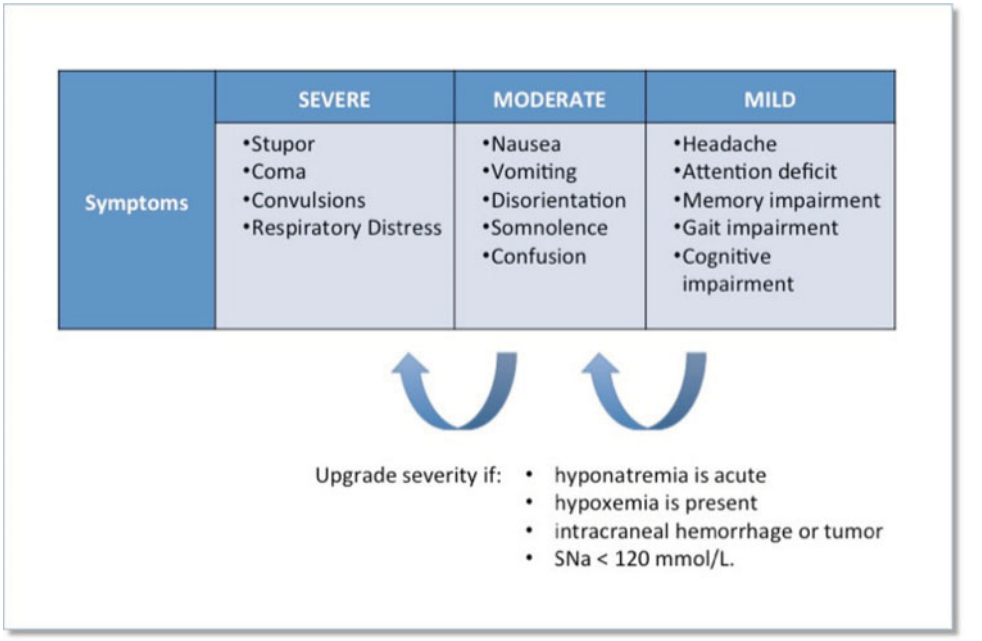


Figure 4. Evaluation of neurological symptoms. Adapted from Runkle *et al., Medicina Clinica* (2013).

Base indication for and use of 3% hypertonic saline i.v. on Steps 1 and 2. Patients with euvolaemic or hypovolaemic hyponatraemia with severe neurological symptoms should immediately be started on HSS as treatment for cerebral oedema.[5,7] Patients with euvolaemic hyponatraemia 'upgraded' to severe should also start on HSS. Euvolaemic patients should not be treated with isotonic saline – not only can this therapy be inadequate for treatment of cerebral oedema, it can worsen it, by lowering S_{Na}.[66] Patients with hypovolaemic hyponatraemia and moderate initial symptoms should receive i.v. isotonic saline. Before initiating HSS or isotonic saline, blood must be drawn for haemoglobin total proteins, urea, creatinine, glucose, electrolytes and osmolality. Cortisolaemia, thyroid hormones and transaminase levels should be measured as soon as possible.

When initial neurological symptoms are severe, or moderate symptoms present in patients with acute hyponatraemia or hypoxaemia, i.v. bolus HSS therapy should be considered.[5,7] There is a growing body of experience with the use of 100 ml i.v. bolus therapy, initially employed in exercise-associated hyponatraemia.[67] The bolus can be administered three times, at 10-min intervals. Intravenous bolus therapy is stopped after neurological symptoms have improved, or after three bolus injections.[5] The recent European guidelines recommend bolus therapy with 150 ml.[6] We prefer the use of 100 ml, given the absence of evidence/experience for the 150 ml regimen. In other cases, HSS can be infused at a rate of 0.5–2 ml kg^{-1} h^{-1}.[5,7]

Urine should be collected for electrolyte and osmolality analysis as soon as HSS therapy is initiated, if not obtained previously. Diuresis must be closely monitored, since HSS can induce polyuria (particularly in patients with prior low solute intake), with an increased risk for overcorrection of S_{Na}. An indwelling bladder catheter may be indicated. Desmopressin (DDAVP) (1 mg i.v. or s.c.) should be administered if polyuria is detected.[7,68,69] S_{Na} or blood Na must be determined 2 h following HSS initiation and ideally every 2 h during HSS infusion. A specific roadmap for the use of hypertonic saline has recently been published.[7]

Step 3: Following start of HSS, or if HSS is not indicated, complete detailed history and physical examination. On-line primary care records should be accessed when available to ascertain the patient's medication history and other relevant data. Laboratory tests are ordered if not yet

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underway, both for diagnosis and management, as outlined above. Based on results, an initial classification and diagnosis should be made.

Step 4: Initiate therapy based on diagnosis. In patients that have started HSS, tests will help determine therapy to be instituted on the following day, since the initiation of additional treatments conducive to rises in S_{Na} should be avoided until 24 h have elapsed from the start of HSS infusion, to avoid overcorrection. Specific therapies are discussed below. Avoid treatments/measures that could worsen the patient's nutritional status. Evaluate the need for nutritional supplements when deciding therapy.

Step 5: Set goals for S_{Na} rise. When starting treatment, regardless of the type of therapy, 24- and 48-h objectives for S_{Na} increment should be determined, based on the assessed risk for development of osmotic demyelination syndrome (ODS) (Table 5).[5] The initial frequency of S_{Na} determinations should be a function of the risk for overcorrection. Patients at high risk (adrenal insufficiency, discontinuation of medication with a short half-life, patients with marked hypovolaemic hyponatraemia, etc.) should be monitored every 6–8 h (unless they are receiving HSS, thereby needing continuous monitoring). If the 24-h objective for S_{Na} increment is met before 24 h have elapsed from initiation of treatment, therapy should be discontinued when possible, and/or DDAVP (1 mg every 6–8 h i.v. or s.c.) should be administered to brake the rise.[7]

Step 6: Promptly lower S_{Na} if overcorrection occurs. This measure has been found to be effective in the prevention of ODS.[69–71] A high U_{osm} indicates anti-diuresis, facilitating reabsorption of administered liquids and i.v. dextrose alone can suffice (6 cm^3 kg^{-1} h^{-1} for 2 h). However, in patients with U_{osm} below 500 mosmol kg^{-1}, we recommend the association of DDAVP to i.v. dextrose, to assure adequate water reabsorption.[7] When using DDAVP, the initial dextrose infusion rate should be lower, starting at 2–3 ml kg^{-1} h^{-1} for 2–3 h. S_{Na} should be repeated at the end of dextrose infusion and dextrose reinitiated until the initial S_{Na} goal is reached. Intravenous furosemide can rapidly brake the descent in S_{Na} following DDAVP administration, if necessary.[7]

Step 7: Re-assess and reclassify patients if response to therapy is inadequate, repeating the physical examination/laboratory tests (i.e. start again).

Step 8: Determine whether the patient is a candidate for long-term, maintenance therapy. Decide whether treatment should be modified to permit chronic use.

Treatment of mild/moderate hypovolaemic hyponatraemia

Hypovolaemic patients with mild/moderate symptoms will initially be treated with i.v. isotonic saline as needed. In mild hyponatraemia, abundant oral liquids and salt sometimes suffice (salted broths, soups, etc. – 'Granny's remedy'). Specific therapy should be administered as a function of diagnosis and the cause of hyponatraemia addressed. Patients with marked hyponatraemia (S_{Na} below 125 mmol l^{-1}) treated with i.v. isotonic saline frequently 'overshoot' the maximum recommended 24-h rise in S_{Na} levels, and S_{Na} should be monitored (i.e. every 6–8 h) to assess the need for interrupting the infusion or adding DDAVP.

Treatment of special cases

Hypoaldosteronism. Increased liquid and salt intake is necessary (either i.v. or orally). Medication that interferes with the RAAS and lowers aldosterone levels, or drugs that interfere with mineralocorticoid action, should be discontinued whenever possible. The former category includes NSAIDs, ACE inhibitors, ARBs, and heparin. The latter group includes NSIADs, spironolactone, eplerenone, amiloride, triamterene, trimethoprim and pentamidine.[49,72] Some patients will need administration of the mineralocorticoid fludrocortisone, at a starting dose of 0.05 mg daily. Fludrocortisone is also used for the differential diagnosis of hypoaldosteronism due to low aldosterone levels *versus* mineralocorticoid resistance, as patients with the latter will not respond.[49] Aldosterone/renin levels can also be measured. However, in hospitalized patients these determinations are not always readily available or even reliable, since reference ranges are not based on values for recumbent patients. Marked hyponatraemia is rare in patients with hypoaldosteronism, and patients are at a low risk for overcorrection. Out-patients should carry a clinical report with their diagnosis and a list of medications to be avoided.

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Table 5. *Correction goals and limits in chronic hyponatraemia*

Risk of ODS	24 h Goal	24 h Limit	48 h Goal	48 h Limit
Low	4–8	10–12	+ 4–8	18
High	4–6	8	+ 4–6	+ 8

Values are given in mmol l^{-1}. The 24-h goal should be met within the first 6 h of therapy if hyponatraemia is severe. ODS, osmotic demyelination syndrome. Adapted from Verbalis *et al. Am J Med* (2013) with authors' permission.

Addison's disease. Patients with Addison's disease must be treated specifically with glucocorticoid/mineralocorticoid therapy and i.v. saline and dextrose as needed, liquid and salt intake assured. Overcorrection is an important risk when initiating therapy and the physician should be ready to add DDAVP (1 mg every 6–8 h) as needed to brake the rise.

Diuretics should be discontinued and isotonic saline administered as needed in the hypovolaemic patient. The danger of early overcorrection is higher when patients are receiving short-acting hydrochlorothiazide than when using chlorthalidone. Patients who have developed thiazide-related hyponatraemia are at a high risk for a new episode. Thiazides should not be reintroduced.

Cerebral salt wasting: i.v. isotonic saline is the basis of treatment. In some cases fludrocortisone can be helpful once hypovolaemia is corrected.[73]

Hypokalaemia alone induces or worsens hyponatraemia and its correction will raise S_{Na}. Given that hypokalaemia is a risk factor for development of ODS, treatment should be limited to oral potassium chloride (KCl) supplements whenever possible, since KCl in isotonic saline will increase the risk for overcorrection. When i.v. saline infusion is deemed essential, DDAVP will often be necessary to brake the rise.

Treatment of hypervolaemic hyponatraemia

Patients with heart failure are initially treated with classic therapy directed towards increasing EFCV, lowering afterload. Reduction of preload with furosemide is also part of standard therapy. Patients with a history of low salt intake and aggressive diuretic therapy often become resistant to furosemide. Tolvaptan has been used successfully in these patients,[34] although it is not authorized for the treatment of heart failure in Europe. There is also experience with the administration of hypertonic saline and high doses of furosemide in refractory heart failure patients with hyponatraemia.[74]

Treatment of euvolaemic hyponatraemia

Pain and nausea must be controlled and a minimum salt intake assured (at least 6 g daily). Patients with acute hyponatraemia due to acute water intoxication have a low risk for ODS and a high risk for herniation or permanent neurological sequelae if undertreated. Therefore, aggressive initial correction of hyponatraemia is in order, as mentioned above. Patients with primary polydipsia and marked hyponatraemia can present important elevations of S_{Na} upon reduction of oral fluid intake. Strict fluid restriction is to be avoided in these cases. Instead, S_{Na} should be carefully monitored and desmopressin should be considered.

Patients with ACTH deficit should be treated with glucocorticoids, either orally (hydrocortisone at initial doses of 20 mg t.i.d.), or i.v. Patients are at high risk for overcorrection. S_{Na} levels should be monitored every 6–8 h to determine the need for associated DDAVP therapy, to brake the rise.

Treatment of SIADH (Table 6)

If initial therapy is HSS, no other treatment should be associated when HSS is discontinued until 24 h have elapsed from initiation of infusion to avoid overcorrection, with the possible exception of fluid restriction when indicated.[7] S_{Na} levels should be monitored every 6 h following HSS, to detect the need for DDAVP administration upon reaching the 24-h goal for correction before 24 h have elapsed and to detect any repeated descent of S_{Na}. Medication that can induce SIADH should be discontinued whenever possible: ACEi and SSRIs

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Table 6. *Treatment of SIADH with mild/moderate hyponatraemia*

Characteristics	Treatment
Pain or nausea	Analgesia/antiemetics
Hypokalemia	Oral Potassium Chloride
Medication that can induce SIADH	Discontinue if feasible
Short-term SIADH + U Osm >> 350 mOsm/kg. BP controlled	Furosemide + 6–9 g salt suplements + partial fluid restriction
U Osm < 350 mOSm/kg, Fürst <0.5; less than 300 ml needed for iv medication, good teeth, good nutritional status, not in a hurry	Fluid restriction to 1 litre (never use to 500 ml for more than a few hours)
Impending or initiated "disasters" (surgery, chemotherapy, preparation of colonoscopy, artificial nutrition, prior episodes of heart failure, etc)	Tolvaptan
Lack of response to FR and furosemide	Tolvaptan
Chronic SIADH with persistent hyponatremia	Tolvaptan
Non-response to tolvaptan	Urea

Assure adequate salt intake. Our protocol for the treatment of SIADH. Adapted from Runkle *et al. Medicina Clínica* (2013). FR, fluid restriction; U_{osm}, urine osmolality; Fürst, Fürst formula, *Am J Med Sci* (2000); SIADH, the syndrome of inappropriate anti-diuretic hormone secretion.

should be stopped immediately and omeprazole replaced by ranitidine. Neurological opinion should be called in to consider modifications in anti-epileptic medication. Given the number of drugs that can cause SIADH, the most practical way to ascertain whether a specific therapy could be causal is to directly access an online database or PubMed. Physicians are often wary of interrupting ACEi therapy. However, given the increased EFCV that characterizes most patients with SIADH, patients' RAAS is usually inhibited and agents such as aliskiren, ACEi and ARBs will be of limited use, even if not directly inducing SIADH (ACEi). Amlodipine can be given to control hypertension.

Diagnostic work-up to detect the cause of SIADH, unless evident, should include brain computerized tomography (CT) or MRI scan, cervicothoracic CT, abdominal CT or ultrasound and PSA and the underlying cause treated. Establishing the cause of SIADH is often the most challenging part of patient evaluation.

When HSS has not been used, or a minimum of 24 h have elapsed following its initiation, specific therapy for SIADH with mild/moderate hyponatraemia should be initiated.

Fluid restriction

Although fluid restriction (FR) is considered to be the mainstay of therapy, before its initiation the physician should ascertain whether its use can be harmful for the patient, and if it is feasible. Ideally, the nutritional status of the patient should be evaluated before initiating FR, and the need for nutritional supplements or artificial nutrition ascertained. Malnutrition is frequent in elderly patients and the evidence in favour of the use of nutritional/protein supplements is strong.[75] Since supplements are usually in given in 400–500 ml daily, their administration makes fluid restriction untenable. Furthermore, extreme fluid restriction to 500 ml day^{-1} can be accompanied by a decreased intake of solid foods.[76]

Not all patients respond to FR – their nephrons may be incapable of eliminating free water. The calculation of the Fürst formula can be useful to detect patients with a low probability of response[77] (Fig. 5). Even applying the Fürst formula, many patients do *not* present a rise in S_{Na}. Another pitfall for the use of FR is that the patient's response varies and the formula must be recalculated, as shown in the Fürst formulas of a 95-year-old patient with idiopathic SIADH over an 18-month period (Table 7).

Response to FR, when present, can be slow. It should not be used when it implies delaying or withholding needed therapy, such as surgery, chemotherapy, or artificial nutrition. Furthermore, a slow response to fluid restriction can increase hospital length-of-stay and thereby increase costs. To correctly apply FR, all i.v. and oral liquids

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Table 7. *Response to strictly-complied-with fluid restriction in a patient initially 92 years old with chronic SIADH, over a 33-month period*

	11/ 2008	12/ 2008	07/ 2009	02/ 2010	12/ 2010	02/ 2010	05/ 2011	05/ 2011	07/ 2011	07/ 2011	08/ 2011	08/ 2011
SNa mmol/L	**116**	**120**	**129**	**111**	**119**	**121**	**126**	**132**	**128**	**129**	**120**	**119**
UNa mmol/L	58	85	67	30	47	82	130	40	152	163	135	100
SK mmol/L	4.5	4.3	4.9	4.6	4.8		4.6	4.2	4.7	4.3	4.3	4.9
UK mmol/L	48	19.7	45	43	49	53	29	21	49.5	53	54.6	37
SCl mmol/L	83	89	98	77	85	93	91	96	98	97	89	89
POsm mOsm/kg		246			247	257	253	269				247
UOsm mOsm/kg		294			315	395		260		574		409
Urea mg/dl	18	26	38	30	24	22	18	31	25	27	26	25
Glycemia mg/dl	76	76	103	91	83	74	77	80	110	102	99	88
FURST formula	**0.9**	**0.88**	**0.86**	**0.66**	**0.8**	**1.13**	**1.31**	**0.46**	**1.57**	**1.67**	**1.58**	**1.15**

The Fürst formula varies between 0.46 and 1.67. S_{Na}, serum sodium; S_K, serum potassium; U_{Na}, urinary sodium; U_K, urinary potassium; S_{Cl}, serum chloride; P_{osm}, plasma osmolality; U_{osm}, urine osmolality.

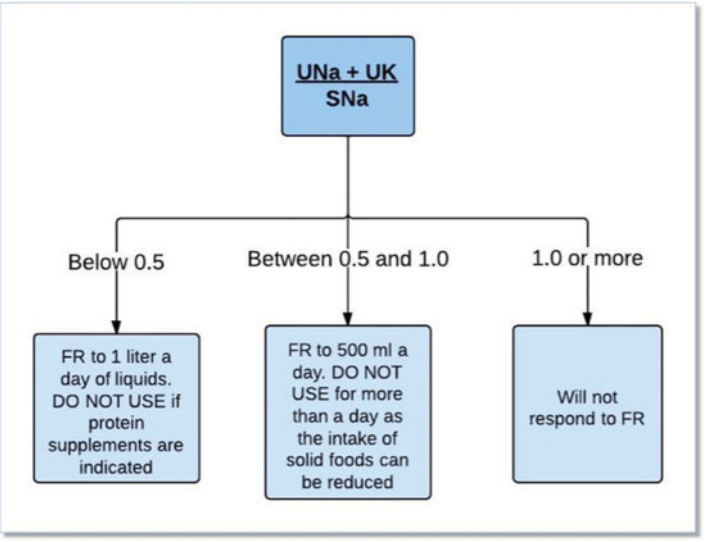


Figure 5. Use of the Fürst formula[77]. FR, fluid restriction; U_{Na}, urinary sodium in mmol l^{-1}; U_K, urinary potassium in mmol l^{-1}; S_{Na}, serum sodium in mmol l^{-1}.

must be taken into account (Fig. 6). Need for i.v. medication, even when concentrated, can make FR unfeasible. Fluid restriction can induce thirst, often intense, and patient compliance can be poor.

Furosemide

This can be useful in the treatment of short-term SIADH in hospitalized patients.[7,78,79] Furosemide interferes with the reabsorption of Na in the ascending loop of Henle, thus lowering RM osmolality. Much of the unabsorbed Na will reach the collecting duct, as the RAAS is usually inhibited in SIADH. Since in SIADH the osmolality in the distal portion of the collecting duct will often have reached equilibrium with that of the RM, a transitory decrease in RM osmolality, together with a transitory rise in collecting duct osmolality, will give rise to the elimination of free water down an osmotic gradient with ensuing diuresis. However, this effect is only observed in patients with high U_{osm}, well over 350 mmol l^{-1}.

When using furosemide, RM osmolality must be restored via salt supplements (2–3 g t.i.d.), to

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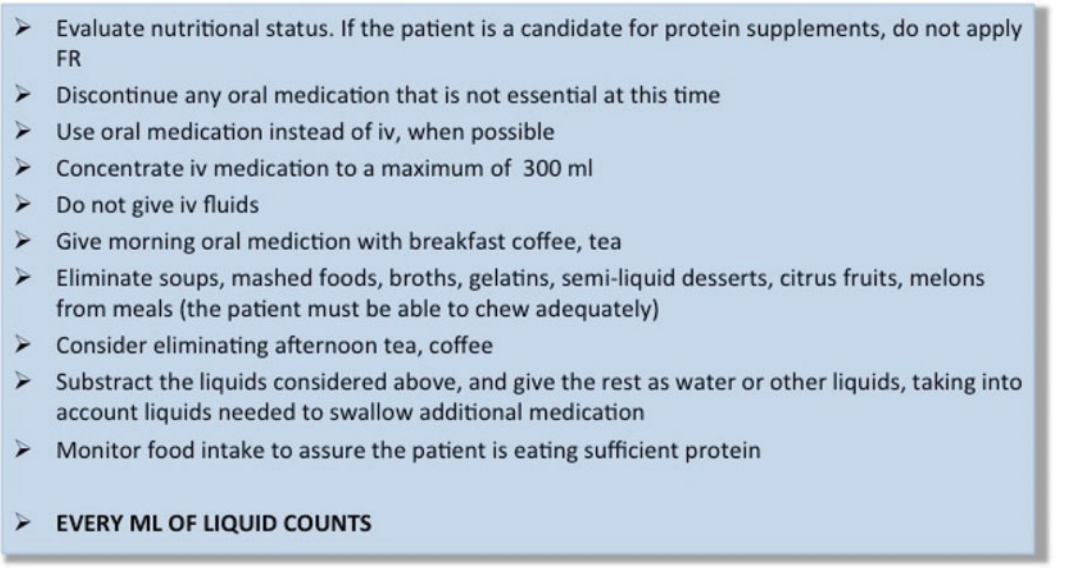


Figure 6. Fluid restriction: how to apply it

maintain response and U_{osm} monitored. When calculating the need for salt supplements, the patient's oral salt intake with hospital meals should be taken into account – how much salt is in the hospital diet, as well the salt content of the food that is actually eaten. Whenever possible, salt should be added to meals, to make hospital food more palatable and increase protein intake. Some patients do not respond to furosemide unless a sodium load (4–5 g of oral salt) is given previously (we administer the load 3 h before 20 mg of i.v. furosemide). The associated use of salt can elevate blood pressure, which should be carefully monitored.

We apply 'partial fluid restriction' – i.v. medication is concentrated and patients are not encouraged to drink liquids without thirst. However, patients are allowed to drink freely. We thus avoid a low liquid intake that could interfere with the ingestion of solid foods, placing nutritional status at risk. Protein supplements are given as needed. We find furosemide therapy preferable to fluid restriction in the elderly hospitalized patient and consider it first-line treatment. Unfortunately, furosemide is not a feasible choice for chronic, ongoing SIADH, as its use is limited in time. Doses range from 40 mg p.o. 1–3 times a day, or 20 mg i.v. 1–3 times a day.

Tolvaptan

We use tolvaptan in patients with mild/moderate SIADH-induced hyponatraemia who are not candidates for or do not respond to fluid restriction or furosemide.[7] It is also our treatment of choice in preparation for surgery, in patients that need artificial nutrition or protein supplements, and in preparation for and during chemotherapy. We have also found chronic tolvaptan therapy to be of great benefit in the treatment of elderly patients with chronic SIADH and sustained hyponatraemia (Table 2). In our series, continued tolvaptan use in patients with chronic SIADH was associated with a significant descent in emergency room visits, as well as a tendency towards reduced days of hospital stay due to readmissions.[76]

Vaptans are not recommended in European guidelines for treatment of SIADH, due to a high risk for overcorrection.[6] However, the authors chose to not specifically analyse tolvaptan, the only vaptan authorized for use in Europe. Rather, the analysis grouped together four vaptans: tolvaptan, conivaptan (authorized for i.v. use in the USA), satavaptan and lixivaptan, in spite of the fact that the latter two are not authorized for use in North America or in Europe.

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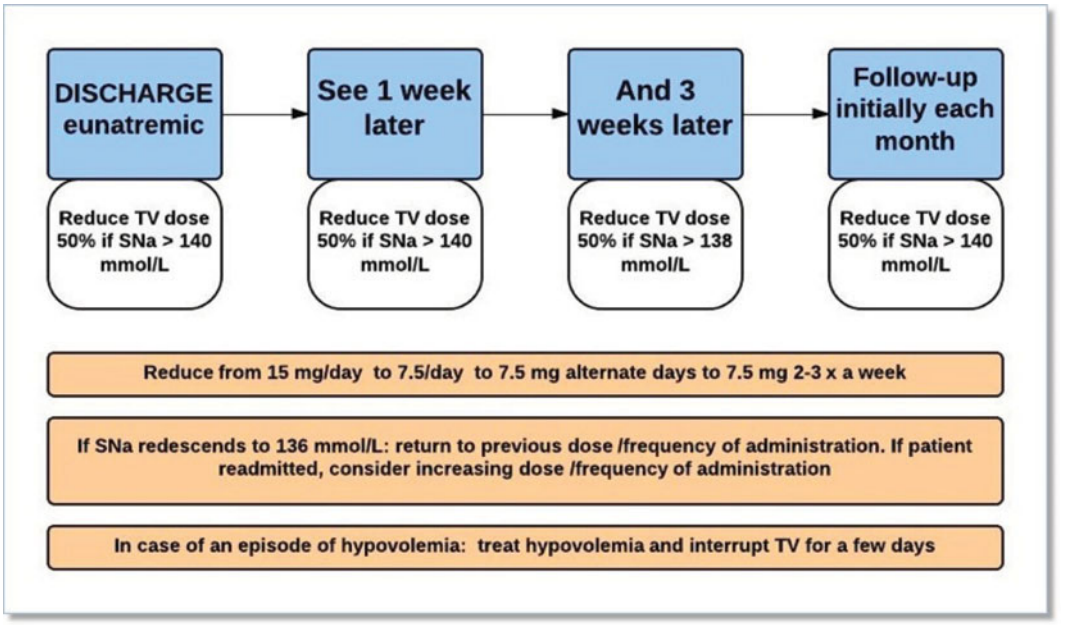


Figure 7. Our protocol for follow-up of patients on maintained tolvaptan therapy for chronic SIADH. TV, tolvaptan; S_{Na}, serum sodium

When initiating treatment with tolvaptan, fluid restriction must be discontinued and the patient encouraged to drink freely. Elderly patients (including those over 90 years of age) do note thirst when starting on tolvaptan therapy, and will increase fluid intake when allowed to. We initiate tolvaptan at a dose of 7.5 mg on day 1,[80,81] almost always increasing to 15 mg daily from day 2 onwards. S_{Na} is determined 6 h following the initial dose.[7] If S_{Na} has risen 5 mmol l^{-1} or more, we 'brake' the rise, adding 3 mg of DDAVP s.c. to i.v. dextrose (2–3 mmol kg^{-1} h^{-1} for 2–3 h) as needed. In a recent analysis of 39 patients with SIADH and mild/moderate hyponatraemia, with a median age of 78 (68–84) years, only one patient presented an increase of S_{Na} over 4 mmol l^{-1} 6 h after the initial 7.5 mg dose.[81] Not a single patient presented overcorrection of S_{Na} at 24 or 48 h. From a mean initial S_{Na} of 127.6 mmol l^{-1} (SD 3.8), the average 24- and 48-h increments were 3.89 (SD 3.2) and 5.8 (SD 3.9) mmol l^{-1}, respectively, with a maximum 24-h rise of 10 mmol l^{-1} in two patients at a low risk for ODS, and of 13 mmol l^{-1} at 48 h. The highest increments were observed in elderly patients with idiopathic SIADH. Initial S_{Na} was negatively correlated with 24-h increment. Thus a starting dose of 7.5 mg was perfectly safe, although not always effective: 10% of patients did not respond to the initial 7.5 mg dose, but did to the following 15 mg dose.

As a precaution, day 2 and day 3 tolvaptan should not be administered before assuring that the 24- and 48-h S_{Na} increment is not over maximum limits: these doses must be given after seeing the S_{Na} level. If the limit is overshot, increased fluid intake (3 to 4 glasses of water) together with a 4–6 h delay in tolvaptan administration, will permit adequate lowering of S_{Na}. Alternatively, tolvaptan can be reintroduced on the following day.[7] Tolvaptan should never be given with hypertonic saline and should not be initiated with other treatments that increase S_{Na}. Tolvaptan should never be administered to a hypovolaemic patient, nor to a patient in anuria. Although the maximum dose of tolvaptan authorized for use in SIAHD is 60 mg daily, patients with SIADH rarely need doses over 30 mg daily.

Tolvaptan can induce thirst, and dryness of mouth in patients on chronic therapy. Elevations in transaminase and bilirubin levels have been detected in patients with polycystic renal disease on chronic tolvaptan therapy, following doses of

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120 mg daily.[82] To our knowledge, not a single case of liver dysfunction has been attributed to tolvaptan in the treatment of SIADH. However, its use is not currently recommended in patients with marked liver dysfunction.

Chronic tolvaptan therapy achieves and maintains strict eunatraemia in elderly patients with chronic SIADH.[76] Doses can be lowered over time and given intermittently, while still maintaining eunatraemia in an out-patient setting. Our protocol for dose reduction is shown in Fig. 7. Our goal is to maintain S_{Na} levels of 138–140 mmol l^{-1}, thus normalizing body water. As mentioned above, cognitive and motor function improve dramatically over 2–4 months. Patients with chronic SIADH can present episodes of hypovolaemia, secondary to infection, gastrointestinal bleeding, etc. In this case tolvaptan therapy can be safely interrupted for a few days, hypovolaemia and its cause treated and tolvaptan reinitiated when euvolaemia is restored, preferably before S_{Na} falls again.

Oral urea

Oral urea can be used in the treatment of hyponatraemia.[6] However, patients often do not reach levels of eunatraemia[83] and rarely reach the S_{Na} levels associated with minimum mortality (138–142 mmol l^{-1}). Furthermore, marked hypernatraemia can be seen in patients who stop drinking or are not drinking freely, as seen in up to 14% of ICU patients with mild/moderate hyponatraemia receiving urea,[84] as well as in the case of an 80-year-old male who developed pneumonia while on chronic urea therapy and whose S_{Na} rose to 155 mol l^{-1}.[83] When a 96-year-old patient of ours on chronic out-patient tolvaptan therapy was in the same circumstance, S_{Na} levels remained normal (S_{Na} 137 mmol l^{-1}) and hypernatraemia and dehydration did not ensue (authors' unpublished data). This different response could be explained by the mechanisms of action of urea and tolvaptan. Urea induces osmotic diuresis, interfering with reabsorption of water in the entirety of the nephron. A patient who stops drinking can then develop marked hypernatraemia and dehydration. Tolvaptan, however, only blocks water reabsorption at the collecting duct: initial hypovolaemia will be compensated by increased proximal nephron water reabsorption, acting as a safety valve that is unavailable in elderly patients on urea therapy.

Urea is given in doses from 15 to 120 g daily.[83] Some patients do not tolerate oral urea easily and can even develop nausea when taking it. Its use does not seem practical or feasible in patients at risk for chemotherapy-induced nausea, nor in patients on artificial nutrition. We believe that urea therapy should be attempted in patients that do not respond to tolvaptan, presumably due to type D SIADH,[85] although resistance to vaptans in the latter subtype has recently been called into question.[86]

Since urea is not considered to be a medication, no randomized clinical trials have been undertaken to ascertain side-effects. However, we know that 37% of ICU patients with marked hyponatraemia have 'overcorrected' on urea therapy[84] and initial studies indicated that i.v. urea could increase calcium and magnesium renal clearance, with a fall in circulating levels of calcium, magnesium and phosphate.[87] The ensuing effect of urea on circulating parathormone levels has not been studied, to our knowledge.

Conclusion

Hyponatraemia in older people is frequent and accompanied by marked cognitive and motor dysfunction, both of which improve upon correction of S_{Na}. The initial steps in the management of hyponatraemia are the evaluation of neurological symptoms and the identification of volaemic status. SIADH is the most frequent cause of hyponatraemia in the elderly. Nutritional status, and the chronicity of anti-diuresis, should be taken into account when deciding therapy.

Conflicts of interest

Dr Runkle has served as an advisor to Otsuka, and given talks sponsored by Otsuka, Amgen, Novartis and Novo-Nordisk. Dr Gómez Hoyos has given talks sponsored by Otsuka. Dr de Miguel has given talks sponsored by Novo-Nordisk and Novartis. Dr Cuesta Hernández and Dr Chafer-Vilaplana declare no conflicts of interest.

References

1 Miller M, Hecker MS, Friedlander DA, Carter JM. Apparent idiopathic hyponatremia in an ambulatory geriatric population. *J Am Geriatr Soc* 1996; **44**: 404–8.

https://doi.org/10.1017/S0959259814000197 Published online by Cambridge University Press

2 Lindner G, Pfortmüller C, Leichtle A, Fielder G, Exadaktylos A. Age-related variety in electrolyte levels and prevalence of dysnatremias and dyskalemias in patients presenting to the emergency department. *Gerontology* 2014; published online 20 May 2014. doi: 10.1159/000360134.

3 Mannesse CK, Vondeling AM, van Marum RJ, van Solinge WW, Egberts TC, Jansen PA. Prevalence of hyponatremia on geriatric wards compared to other settings over four decades: A systematic review. *Ageing Res Rev* 2013; **12**: 165–73.

4 Miller M. Hyponatremia: age-related risk factors and therapy decisions. *Geriatrics* 1998; **53**: 32–33, 37–38, 41–42.

5 Verbalis J, Goldsmith S, Greenberg A, Korzelius C, Schrier R, Sterns R, Thompson C. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med* 2013; **126** (D suppl 1): S1–42.

6 Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn E, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, NAgler E. Clinical practice guideline and diagnosis and treatment of hyponatremia. *EJE* 2014; **170**: G1–47.

7 Runkle I, Villabona C, Navarro A, Pose A, Formiga F, Tejedor A, Poch E. El tratamiento de la hiponatremia secundaria al síndrome de secreción inadecuada de la hormona antidiurética. *Medicina Clínica* 2013; **141**: 507.

8 Shapiro D, Sonnenblick M, Galperin I, Melkonyan L, Munter G. Severe hyponatraemia in elderly hospitalized patients: prevalence, aetiology and outcome. *Int Med J* 2010; **40**: 574–580.

9 Cowen L, Hodak S, Verbalis J. Age-associated abnormalities of water homeostasis. *Endocrinol Metab Clin North Am* 2013; **42**: 349–70.

10 Beck LH. Changes in renal function with aging. *Clin Geriatr Med* 1998; **14**: 199–209.

11 Rolls BJ, Phillips PA. Aging and disturbances of thirst and fluid balance. *Nutr Rev* 1990; **48**: 137–44.

12 Rao MY, Sudhir U, Anil Kumar T, Saravanan S, Mahesh E, Punith K. Hospital-based descriptive study of symptomatic hyponatremia in elderly patients. *J Assoc Physicians India* 2010; **58**: 667–69.

13 Anpalahan M. Chronic idiopathic hyponatremia in older people due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) possibly related to aging. *J Am Geriatr Soc* 2001; **49**: 788–92.

14 Hirshberg B, Ben-Yehuda A. The syndrome of inappropriate antidiuretic hormone secretion in the elderly. *Am J Med* 1997; **103**: 270–73.

15 Arinzon Z, Feldman J, Jarchowsky J, Fidelman Z, Krasnyansky I, Adunsky A. A comparative study of the syndrome of inappropriate antidiuretic hormone secretion in community-dwelling patients and nursing home residents. *Aging Clin Exp Res* 2003; **15**: 6–11.

16 Hillier A, Abbot R, Barrett B. Hyponatremia: Evaluating the correction factor for hyperglycemia. *Am J Med* 1999; **106**: 399–403.

17 Liamis G, Liberopoulos E, Barkas F, Elisaf M. Spurious electrolyte disorders: a diagnostic challenge for clinicians. *Am J Nephrol* 2013; **38**: 50–55.

18 Chow E, Fox N, Gama R. The effect of low serum total protein on sodium and potassium measurement by ion-selective electrodes in critically ill patients. *Br J Biomed Sci* 2008; **65**: 128–31.

19 Wald R, Jaber B, Price LL, Upadhyay A, Madias N. Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med* 2010; **170**: 294.

20 Leung A, McAlister F, Rogers S, Pazo V, Wright A, Bates D. Preoperative hyponatremia and perioperative complications. *Arch Intern Med* 2012; **172**: 1474–81.

21 Nzerue C, Bonnie H, You W, Falana B, Dai S. Predictors of outcome in hospitalized patients with severe hyponatremia. *J Natl Med Assoc* 2003; **95**: 335–43.

22 Ayus JC, Arieff AI. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. *JAMA* 1999; **281**: 2299–304.

23 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.

24 Gosch M, Joosten-Gstrein B, Heppner HJ, Lechleitner M. Hyponatremia in geriatric inhospital patients: effects on results of a comprehensive geriatric assessment. *Gerontology* 2012; **58**: 430–40.

25 Verbalis JG, Barsony J, Sugimura Y, Tian Y, Adams DJ, Carter EA *et al.* Hyponatremia-induced osteoporosis. *J Bone Miner Res* 2010; **25**: 554–63.

26 Hoorn EJ, Rivadeneira F, van Meurs JB, Ziere G, Stricker BH, Hofman A, Pols HA, Zietse R, Uitterlinden AG, Zillikens MC. Mild hyponatremia as a risk factor for fractures: the Rotterdam study. *J Bone Miner Res* 2011; **26**: 1822–28.

https://doi.org/10.1017/S0959259814000197 Published online by Cambridge University Press

27 Rodenburg EM, Hoorn EJ, Ruiter R, Lous JJ, Hofman A, Uitterlinden AG, Stricker BH, Visser LE. Thiazide-associated hyponatremia: a population-based study. *Am J Kidney Dis* 2013; **62**: 67–72.
28 Tolouian R, Alhamad T, Farazmand M, Mulla ZD. The correlation of hip fracture and hyponatremia in the elderly. *J Nephrol* 2012; **25**: 789–93.
29 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.
30 Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med* 2009; **122**: 857–65.
31 Hoorn EJ, Lindemans J, Zietse R. Development of severe hyponatraemia in hospitalized patients: treatment-related risk factors and inadequate management. *Nephrol Dial Transplant* 2006; **21**: 70–76.
32 Movafagh S, Cleemann L, Morad M. Regulation of cardiac Ca2 +channel by extracellular Na+. *Cell Calcium* 2011; **49**: 162–73.
33 Arao K, Fujiwara T, Sakakura K, Wada H, Sugawara Y, Suga C, Ako J, Ishikawa SE, Momomura S. Hyponatremia as a predictor for worsening heart failure in patients receiving cardiac resynchronization therapy. *Circ J* 2013; **77**: 116–22.
34 Hauptman PJ, Burnett J, Gheorghiade M, Grinfeld L, Konstam MA, Kostic D, Krasa HB, Maggioni A, Ouyang J, Swedberg K, Zannad F, Zimmer C, Udelson JE. Clinical course of patients with hyponatraemia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. *J Card Fail* 2013; **19**: 390–97.
35 Nielsen S, Fror J, Knepper MA. Renal aquaporins: key roles in water balance and water balance disorders. *Curr Opin Nephrol Hypertens* 1998; **7**: 509–16.
36 Wong LL, Verbalis JG. Systemic diseases associated with disorders of water homeostasis. *Endocrinol Metab Clin North Am* 2002; **31**: 121–40.
37 Verbalis J. Whole-body volume regulation and escape from antidiuresis. *Am J Med* 2006; **119**: S21–29.
38 Sharabi Y, Illan R, Kamari Y, Cohen H, Nadler M, Messerli FH, Grossman E. Diuretic induced hyponatraemia in elderly hypertensive women. *J Hum Hypertens* 2002; **16**: 631–35.
39 Leung AA, Wright A, Pazo V, Karson A, Bates DW. Risk of thiazide-induced hyponatremia in patients with hypertension. *Am J Med* 2011; **124**: 1064–72.
40 Clark BA, Shannon RP, Rosa RM, Epstein FH. Increased susceptibility to thiazide-induced hyponatremia in the elderly. *J Am Soc Nephrol* 1994; **5**: 1106–11.
41 Kim GH, Lee JW, Oh YK, Chang HR, Joo KW, Na KY, Earm JH, Knepper MA, Han JS. Antidiuretic effect of hydrochlorothiazide in lithium-induced nephrogenic diabetes insipidus is associated with upregulation of aquaporin-2, Na–Cl co-transporter, and epithelial sodium cannel. *J Am Soc Nephrol* 2004; **15**: 2836–43.
42 Rastogi D, Pelter MA, Deamer RL. Evaluations of hospitalizations associated with thiazide-associated hyponatremia. *J Clin Hypertens (Greenwich)* 2012; **14**: 158–64.
43 Yamada H, Asano T, Aoki A, Ikoma A, Yoshida M, Kusaka I, Kawakami M, Kakei M, Ishikawa SE. Combination therapy of angiotensin II receptor blocker and thiazide produces severe hyponatremia in elderly hypertensive subjects. *Intern Med* 2014; **53**: 749–52.
44 Crespo Hernández I, Ruiz Gracia T, Gomez Hoyos E, Ortola Buigues A, Cuesta Hernandez M, Fernandez Capel F, de Miguel Novoa P, Sanabria Perez MC, Calle Pascual A, Runkle de la Vega I. Marked thiazide-induced hyponatremia: characteristics of a group of patients. *16th European Congress of Endocrinology* (Wroclaw, Poland), 723.
45 Talapatra I, Kalavalapalli S, Tymms DJ. Isolated hypoaldosteronism: an overlooked cause of hyponatraemia. *Eur J Internal Med* 2007; **18**: 246–48.
46 Gómez Hoyos E, Montañez Zorrilla C, Cuesta Hernández C, de Miguel Novoa P, Pelaz Berdullas L, Matía Martín P, Marcuello Foncillas C, Pérez Ferre N, Calle Pascual A, Runkle de la Vega I. Pacientes con hipovolemia, hiponatremia e hipokaliemia en límites altos: pensar en hipoaldosteronismos tras descartar enfermedad de Addison. Abs, no. 21. XI Congreso de la Sociedad de Endocrinología, Nutrición y Diabetes de la Comunidad de Madrid (SENDIMAD), November 2012.
47 Haas CS, Pohlenz I, Lindner U, Muck PM, Arand J, Suefke S, Lehnert H. Renal tubular acidosis type IV in hyperkalaemic patients – a fairy tale or reality? *Clin Endocrinol (Oxford)* 2013; **78**: 706–11.
48 Choi MJ, Ziyadeh FN. The utility of the transtubular potassium gradient in the evaluation of hyperkalemia. *J Am Soc Nephrol* 2008; **19**: 424–26.

https://doi.org/10.1017/S0959259814000197 Published online by Cambridge University Press

49 Bhaskar B, Fraser JF, Mullaney D. Lest we forget: heparin-induced hyperkalemia. *J Cardiothorac Vasc Anesth* 2012; **26**: 106–9.

50 Hannon MJ, Behan LA, O'Brien MM, Tormey W, Ball SG, Javadpour M, Sherlock M, Thompson CJ. Hyponatremia following mild/moderate subarachnoid hemorrhage is due to SIAD and glucocorticoid deficiency and not cerebral salt wasting. *J Clin Endocrinol Metab* 2014; **99**: 291–98.

51 Robertson G. Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. *Am J Med* 2006; **119**: S36–42.

52 Sands J, Layton H. The physiology of urine concentration: an update. *Seminars in Nephrology* 2009; **29**: 178–95.

53 Janicic N, Verbalis JG. Evaluation and management of hypo-osmolality in hospitalized patients. *Endocrinol Metab Clin North Am* 2003; **32**: 459–81.

54 Kovács KJ, Földes A, Sawchenko PE. Glucocorticoid negative feedback selectively targets vasopressin transcription in parvocellular neurosecretory neurons. *J Neurosci* 2000; **20**: 3843–52.

55 Aguilera G, Liu Y. The molecular physiology of CRH neurons. *Frontiers in Neuroendocrinology* 2012; **33**: 67–84.

56 Suzuki H, Kawasaki M, Ohnishi H, Otsubo H, Ohbuchi T, Katoh A, Hashimoto H, Yokoyama T, Fujihara H, Dayanithi G, Murphy D, Nakamura T, Ueta Y. Exaggerated response of a vasopressin-enhanced green fluorescent protein transgene to nociceptive stimulation in the rat. *J Neurosci* 2009; **29**: 13182–89.

57 Sherlock M, O'Sullivan E, Agha A, Behan LA, Rawluk D, Brennan P, Tormey W, Thompson CJ. The incidence and pathophysiology of hyponatraemia after subarachnoid haemorrhage. *Clin Endocrinol* 2006; **64**: 250–54.

58 Maesaka JK, Gupta S, Fishbane S. Cerebral salt-wasting syndrome: does it exist? *Nephron* 1999; **82**: 100–9.

59 Palmer BF. Hyponatremia in patients with central nervous system disease: SIADH *versus* CSW. *Trends Endocrinol Metab* 2003; **14**: 182–87.

60 Berl T. Impact of solute intake on urine flow and water excretion. *J Am Soc Nephrol* 2008; **19**: 1076–78.

61 Cherney DZ, Davids MR, Halperin ML. Acute hyponatraemia and 'ecstasy': insights from a quantitative and integrative analysis. *QJM* 2002; **95**: 475–83.

62 Shafiee MA, Charest AF, Cheema-Dhadli S, Glick DN, Napolova O, Roozbeh J, Semenova E, Sharman A, Halperin ML. Defining conditions that lead to the retention of water: the importance of the arterial sodium concentration. *Kidney Int* 2005; **67**: 613.

63 Gómez Hoyos E, Matía Martin P, Cuesta Hernández M, Hernández Núñez G, Larrad Saiz A, Soria Carreras P, Pérez Ferre N, Cabrerizo Garcia L, Rubio Herrera MA, Runkle de la Vega I. Prevalencia e Incidencia de Hiponatremia en pacientes con soporte nutricional artificial por vía parenteral. XXVIII Congreso Nacional SENPE (Sociedad Española de Nutrición Enteral y Parenteral). *Oviedo. Nutrición Hospitalaria* **28**, suppl 3; May 2013.

64 Gómez Hoyos E, Cuesta Hernández M, Fernández Capel F, Ruiz Gracia T, Martín Matía P, Rubio Herrera MA, Cabrerizo García L, Pérez Ferre N, Calle Pascual A, Runkle de la Vega I. Diagnosis and management of patients presenting hyponatremia while receiving parenteral nutrition. Abs no. 437, poster 694. 15th European Congress of Endocrinology, Copenhagen, 27 April to 1 May 2013. *Endocrine Abstracts* 2013; **32**: 694.

65 Warner MH, Holding S, Kilpatrick ES. The effect of newly diagnosed hypothyroidism on serum sodium concentrations: a retrospective study. *Clin Endocrinol* 2006; **64**: 598–99.

66 Musch W, Decaux G. Treating the syndrome of inappropriate ADH secretion with isotonic saline. *Q J Med* 1998; **91**: 749–53.

67 Hew-Butler T, Almond C, Ayus JC, Dugas J, Meeuwisse W, Noakes T, Reid S, Siegel A, Speedy D, Stuempfle K, Verbalis J, Weschler L. Exercise-Associated Hyponatraemia (EAH) Consensus Panel: Consensus statement of the 1st International Exercise-Associated Hyponatremia Consensus Development Conference, Cape Town, South Africa 2005. *Clin J Sport Med* 2005; **15**: 208–13.

68 Sterns R, Nigwekar SU, Hix JK. The treatment of hyponatremia. *Seminars in Nephrology* 2009; **29**: 282–99.

69 Perianayagam A, Sterns R, Silver S, Grieff M, Mayo R, Hix J, Kouides R. DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. *Clin J Am Soc Nephrol* 2008; **3**: 331–36.

70 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.

71 Gankam Kengne F, Soupart A, Pochet R, Brion JP, Decaux G. Re-induction of hyponatraemia after rapid overcorrection of hyponatremia reduces mortality in rats. *Kidney Int* 2009; **76**: 614.

https://doi.org/10.1017/S0959259814000197 Published online by Cambridge University Press

72 Perazella M. Drug-induced hyperkalemia: old culprits and new offenders. *Am J Med* 2000; **109**: 307–14.
73 Momi J, Tang CM, Abcar AC, Kujubu DA, Sim JJ. Hyponatremia – what is cerebral salt wasting? *Perm J* 2010; **14**: 62–65.
74 Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, Argano C, Tuttolomondo A, Paterna S. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J* 2003; **145**: 459–66.
75 Stratton R, Hébuterne X, Elia M. A systematic review and meta-analysis of the impact of oral nutritional supplements on hospital readmissions. *Ageing Res Rev* 2013; **12**: 884–97.
76 Gómez Hoyos E, Cuesta Hernández M, Ruíz Gracia T, de Miguel Novoa MP, Molino González A, Díaz Pérez JA, Calle Pascual A, Runkle de la Vega I. Manejo diagnóstico y terapéutico de la hiponatremia (HN) por el Síndrome de secreción inadecuada de ADH (SIADH) por el Servicio de Endocrinología y Nutrición (EN) del Hospital Clínico San Carlos. 55 Congreso de la SEEN, Granada, 15–17 May 2013.
77 Furst H, Hallows KR, Post J, Chen S, Kotzker W, Goldfarb S, Ziyadeh FN, Neilson EG. The urine/plasma electrolyte ratio: a predictive guide to water restriction. *Am J Med Sci* 2000; **319**: 240–44.
78 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; **285**: 89–90.
79 Decaux G. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by long loop diuretics. *Nephron* 1983; **35**: 82–88.
80 Cuesta M, Gomez-Hoyos E, Montañez C, Martin P, Marcuello C, de Miguel P, Calle A, Runkle I. An initial dose of 7.5 mg Tolvaptan is safe and effective in the treatment of hyponatremia caused by SIADH. 15th International Congress of Endocrinology jointly with the 14th European Congress of Endocrinology (Florencia, May 2012). *Endocrine Abstracts* 2012: **29**: P1149.
81 Runkle I, Gomez Hoyos E, Recio Blázquez L, Cuesta Hernández M, de Miguel Novoa MP, Ruiz Gracia T, Sanabria Perez C, Santiago Perez A, Matia Martin P, Calle Pascual A. Experiencia con una dosis inicial de 7.5 mg de tolvaptan en el tratamiento de la hiponatremia secundaria al SIADH. 56 congreso de la SEEN, Valencia, 21–23 May 2014.
82 Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS; TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; **367**: 2407–18.
83 Soupart A, Coofernils M, Couturier B, Gankam-Kengne F, Decaux G. Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin J Am Soc Nephrol* 2012; **7**: 742–47.
84 Decaux G, Andres C, Gankam Kengne F, Soupart A. Treatment of euvolemic hyponatremia in the intensive care unit by urea. *Critical Care* 2010; **14**: R184.
85 Vandergheynst F, Brachet C, Heinrichs C, Decaux G. Long-term treatment of hyponatremic patients with nephrogenic syndrome of inappropriate antidiuresis: personal experience and review of published case reports. *Nephron Clin Pract* 2012; **120**: 168–72.
86 Fenske WK, Christ-Crain M, Hörning A, Simet J, Szinnai G, Fassnacht M, Rutishauser J, Bichet DG, Störk S, Allolio B. A copeptin-based classification of the osmoregulatory defects in the syndrome of inappropriate antidiuresis. *J Am Soc Nephrol* 2014; **25**: 2376–83.
87 Better OS, Gonick HC, Chapman LC, Varrady PD, Kleeman CR. Effect of urea-saline diuresis on renal clearance of calcium, magnesium, and inorganic phosphate in man. *Proc Soc Exp Biol Med* 1966; **121**: 592–96.

https://doi.org/10.1017/S0959259814000197 Published online by Cambridge University Press