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Special considerations of hyponatremia in the elderly patient

Julie Refardt[a,b,*]

[a] Department of Internal Medicine, Section of Endocrinology, Erasmus Medical Center, Rotterdam, the Netherlands
[b] Department of Clinical Research University of Basel, University Hospital Basel, Basel, Switzerland

Hyponatremia is the most common electrolyte disorder, particularly in older adults. Its high prevalence in this population is driven by underlying conditions such as heart and kidney failure, as well as by factors like polypharmacy and malnutrition. Rising global temperatures have also been linked to increased hyponatremia rates. Chronic hyponatremia is associated with elevated risks of falls, osteoporosis, fractures, cognitive and muscular impairment, and mortality. Despite these adverse outcomes, the condition is often underdiagnosed and undertreated, partly due to the complexity of its evaluation. Simplified, step-by-step diagnostic algorithms in future guidelines may help address this gap. Evidence increasingly supports the clinical benefits of correcting hyponatremia, prompting investigation into novel therapies. Among these, SGLT2 inhibitors and protein supplementation are especially promising, offering efficacy not only in raising plasma sodium but also in providing broader health benefits. This review explores the impact of hyponatremia in the elderly, summarizes its leading causes, and evaluates diagnostic strategies alongside the advantages and limitations of current treatment options.

Introduction

Hyponatremia is the most common electrolyte disorder in both inpatient and outpatient settings, with risk increasing markedly with age [1]. Among institutionalized geriatric patients, prevalence can reach up to 50 % [2]. The syndrome of inappropriate antidiuresis (SIAD) is the leading cause in older populations [3], often triggered by polypharmacy and a range of age-associated disorders. Other common causes include chronic heart, liver, and kidney disease, as well as malnutrition, all of which predispose to hyponatremia [4].

Prevalence rises during summer months, particularly in older adults [5,6], and is projected to increase substantially with global warming [6]. Hyponatremia is significantly associated with higher overall mortality [7] and worse outcome [8–11]. In addition, it has been linked to neurocognitive and neuromuscular impairments as well as reduced bone quality, explaining together the increased risk of falls [12], fractures [13] and attention deficits [12] in this population. Correction of hyponatremia has been shown to improve these impairments [12,14] and enhance quality of life [15].

Despite these data, chronic hyponatremia often remains untreated [16]. The complexity of its correct diagnosis, which is further complicated by interfering medications and comorbidities, is certainly an important factor here. In addition, until recently treatment options were limited. However, there have been interesting developments in recent years, with new data on existing treatments, but also new options using the sodium-glucose transport protein 2 (SGLT2) inhibitors [17,18] empagliflozin or protein supplementation [19] to correct SIAD-induced hyponatremia. These developments are likely to have a positive impact on treatment frequency.

This review aims to provide an overview of the most common causes of hyponatremia in the elderly, offer assistance with correct diagnosis, and discuss the advantages and limitations of current treatment options and any necessary dose adjustments.

* Corresponding author at: Department of Internal Medicine, Section of Endocrinology, Erasmus Medical Center, Rotterdam, the Netherlands.
E-mail address: j.refardt@erasmusmc.nl.

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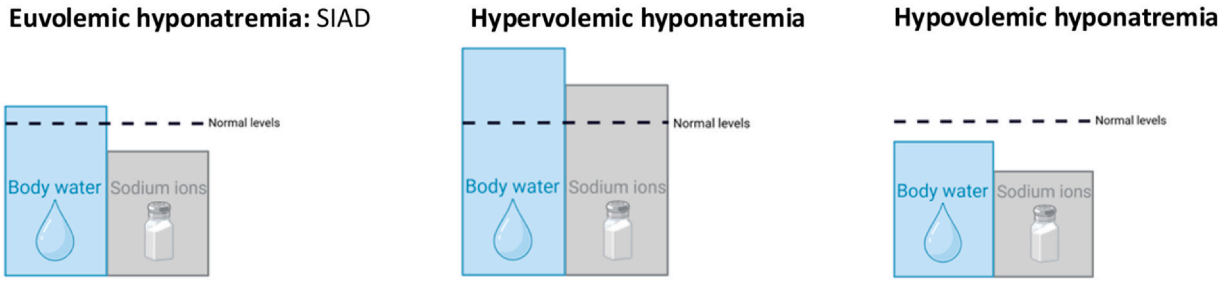

Fig. 1. Pathophysiology of the most common hyponatremia etiologies. Boxes showing changes in total body water (blue boxes) and total body amount of sodium-determining cations (grey box) as compared with normal physiological levels (dotted line).

- Euvolemic hyponatremia (SIAD): Characterized by inappropriate arginine vasopressin (AVP) secretion leading to water retention, resulting in dilutional hyponatremia.
- Hypervolemic hyponatremia: Low effective arterial blood volume stimulates neurohormonal mechanisms, including AVP and renin–angiotensin–aldosterone system (RAAS) activation, resulting in excessive fluid retention and sodium dilution.
- Hypovolemic hyponatremia: extensive extracellular fluid loss triggers AVP-mediated water retention and RAAS activation to conserve salt and water.

Prevalence, causes and pathophysiology of hyponatremia in the elderly

Age per se is a strong risk factor for hyponatremia. Beyond the age of 50 years, the risk of hyponatremia rises progressively [20–22]. This association is especially pronounced in hospitalized patients; where individuals over 80 years have been found to have a 10-fold higher risk for developing profound hyponatremia compared to younger patients [23]. Since the number of comorbidities is also a risk factor for hyponatremia [20,24], it is not surprising that hyponatremia prevalence varies between departments, with the highest rates found in intensive care and internal medicine wards [25]. Hyponatremia rates are also elevated in geriatric nursing homes with a prevalence of up to 50 % [2].

In terms of etiology SIAD is the most common cause of hyponatremia, followed by hypovolemia and hypervolemia [26–28] (Fig. 1). In hospitalized patients, hyponatremia prevalence increases during summer, with mean outdoor temperatures above 20°C marking a threshold beyond which rates rise sharply [6, 29]. This is of importance in light of global warming: climate models impressively demonstrate that hospitalization rates due to hyponatremia will increase by 6.3 % with a 1°C rise and by 13.9 % with a 2°C rise [30]. In addition, a two-third increase in prevalence of profound hyponatremia is expected [6]. Elderly patients are especially vulnerable for heat induced hyponatremia according to a recent systematic review [31]. Other risk factors are chronic kidney disease and medications such as diuretics and antidepressants. Mechanisms for heat-induced hyponatremia include disproportionate intake of hypotonic fluids relative to salt loss through sweat, heat-induced stress, and non-osmotic release of arginine vasopressin due to vasodilation [32].

In addition to the pathomechanisms described above, older patients are more susceptible to developing hyponatremia due to age-related changes. For one, thirst-sensation - normally triggered by high blood osmolality [33] or low blood volume [34,35] is weaker than in younger people [33]. At the same time, arginine vasopressin (AVP) release is more sensitive to increases in osmolality [36]. Kidney function is also altered: both the ability to concentrate [33] and to dilute [37,38] urine is reduced. In addition, older adults have less lean body mass, so even small changes in total body water can cause larger shifts in plasma sodium levels [39,33].

Any change in the above parameters can lead to hyponatremia, which explains why older people are more susceptible to its occurrence. These factors also explain why hyponatremia is mainly caused by an excess of free water rather than sodium depletion.

Diagnostic challenges in the assessment of hyponatremia in the elderly

The first step in assessing hyponatremia is to measure plasma osmolality, followed by urine osmolality if hypotonic hyponatremia is confirmed [40]. The latter directly reflects AVP activity and is thus helpful to determine the cause. Low ($\leq$100 mOsm/kg) urine osmolality levels point to suppressed AVP as seen in primary polydipsia, low solute intake, or beer potomania (heavy beer drinking with poor nutrition) [40]. However, in older adults - because kidneys dilute urine less efficiently - a threshold of $\leq$ 200 mOsm/kg may be more appropriate. Elevated ($>$ 100–200 mOsm/kg) urine osmolality on the other hand indicates increased AVP activity. This may be appropriate, as in hypovolemia or conditions with low effective arterial volume (e.g. heart failure, cirrhosis), or inappropriate such as in SIAD [41, 42]. Unfortunately, measuring AVP directly or its stable surrogate marker copeptin has not proven helpful in this differentiation [43,44]. Accordingly, it is generally advised to measure urine sodium as a next step. Urine sodium reflects the renin-angiotensin-aldosteron system and natriuretic peptide activity [40]. A low ($\leq$30 mmol/l) level suggests either true hypovolemia or low effective arterial blood volume as described above [40], while an elevated level ($>$ 30 mmol/l) indicates increased AVP activity such as in adrenal insufficiency or SIAD [40].

However, diuretics – a common drug in the elderly - artificially increase urinary sodium and can mask the real cause of hyponatremia. Instead, the measurement and calculation of fractional urea and uric acid is advised, since these are less influenced by diuretics [45]. Low fractional urea and uric acid levels ($<$ 35 % and $<$ 8 % respectively), suggest hypovolemia, while elevated levels ($>$ 55 % and $>$ 12 % respectively) indicate SIAD.

Although volume status assessment is routinely performed in clinical care, it has low sensitivity and specificity, particularly when distinguishing between euvolemia and mild hypovolemia [46]. This poses an additional diagnostic challenge in older patients, who often have non-hypovolemic orthostatic hypotension and nonspecific reduced skin turgor [47]. Here, point-of-care ultrasound might proof helpful [48].

In addition to increased AVP sensitivity, reduced renal concentrating ability, and the use of multiple medications that complicate correct diagnosis, older patients also suffer more frequently from multifactorial hyponatremia [49]. Accordingly, regular re-evaluation is recommended in cases of non-response to therapy.

Aetiologies of hyponatremia

Syndrome of inappropriate antidiuresis (SIAD)

As discussed above, SIAD is characterized by an inadequate AVP activity despite normal or low plasma osmolality and normal blood volume. This persistent AVP activity causes the kidneys to reabsorb free water, leading to water retention and a mild expansion of the extracellular fluid (Fig. 1). The body responds to this expansion by increasing sodium excretion (secondary natriuresis), which reduces total body sodium [50]. Because extracellular volume is determined by both sodium and water content, the loss of sodium offsets the extra water, so patients appear clinically euvolemic rather than overtly fluid overloaded. The net effect is dilution of plasma sodium, producing hypotonic hyponatremia [42].

SIAD can develop secondary to a wide range of conditions, including malignancies, pulmonary disorders, central nervous system diseases, and physiological stressors such as pain or nausea. It can also be triggered by certain medications [51,52]. These include AVP analogues (desmopressine) that interact with vasopressin-2 receptors in the renal collecting ducts, drugs that increase central AVP release (e.g., vincristine, ifosfamide), and agents that directly stimulate vasopressin-2 receptors (e.g., selective serotonin reuptake inhibitors, carbamazepine) [53].

Older adults are particularly vulnerable to SIAD because of their frequent polymorbidity and polymedication. Concerningly, awareness of these medication side effects is low [54].

It is important to note, that SIAD is a diagnosis of exclusion that requires the presence of normal cortisol levels [55]. This is particularly relevant in view of the high use of all kind of steroids (cremes, inhalers, injections, tablets, etc) in elderly patients. In case no triggering factor can be identified – so called idiopathic SIAD – a diagnostic work up including evaluation for possible malignancy

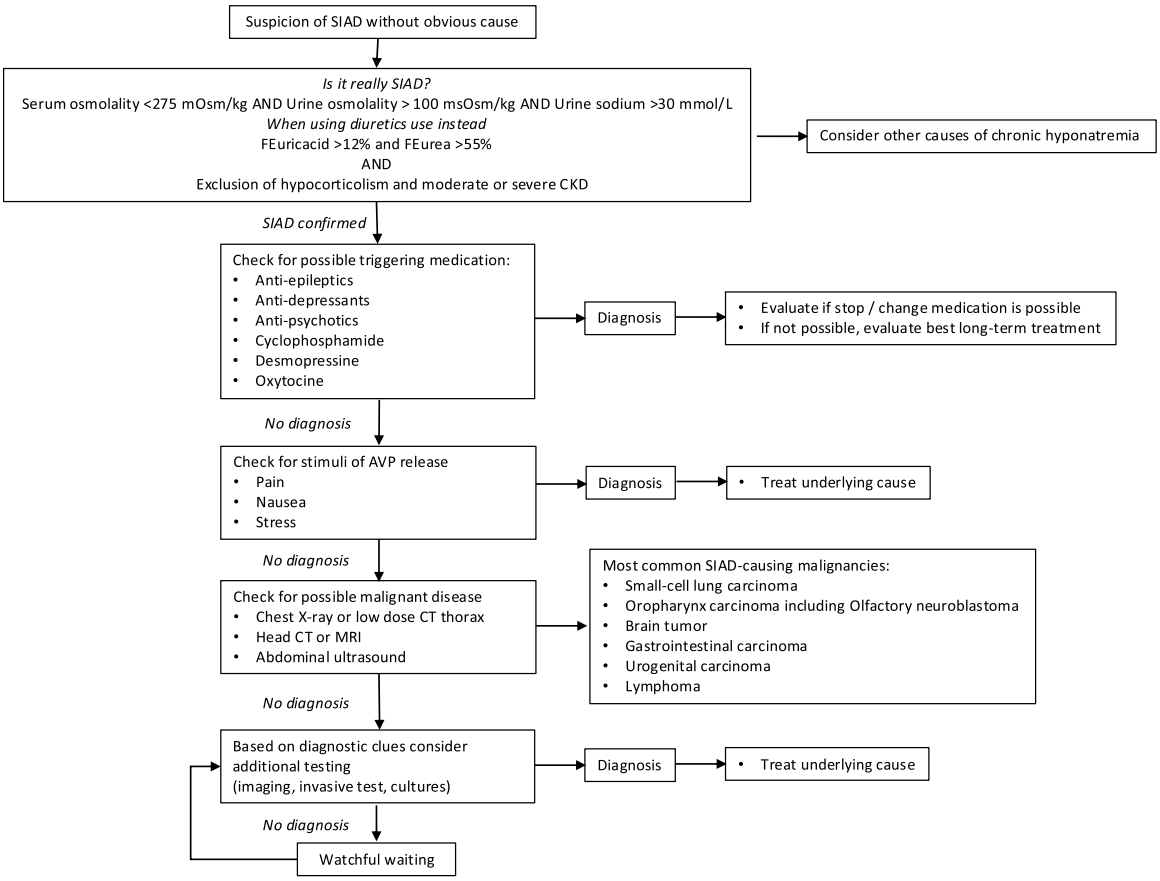

Fig. 2. Proposed diagnostic algorithm in patients with idiopathic SIAD.

is recommended (Fig. 2).

Hypovolemic hyponatremia

Hypovolemic hyponatremia occurs when the body loses more sodium than water [56], for example in cases of gastroenteritis or bleeding or third-space fluid shifts (i.e.burns, sepsis) [50] (Fig. 1). Thiazide and thiazide-like diuretics are a common cause of hyponatremia [57,58] as it occurs in up to 20 % of the patients taking them [59]. While thiazide induced hyponatremia usually develops within weeks, also more delayed occurrences are possible [57,58,60,61]. Again, age in addition to female sex is a risk factor [57,59,62]. Re-exposure should be avoided since most patients become again hyponatremic [63]. Patients with thiazide-associated hyponatremia can be euvolemic or hypovolemic as its etiology can be multifactorial. It may result from the loss of urine sodium leading to mild volume depletion and a reduced ability of the distal convoluted tubule to dilute urine [58]. Additionally, a genetic mutation in the prostaglandin transporter of the collecting duct can raise urinary prostaglandin E2 levels, which increases aquaporin 2 activity without involving AVP. This boosts water reabsorption in the kidneys, leading to dilutional hyponatremia [64].

High water and low solute intake

Hyponatremia due to high water Intake occurs when water ingestion exceeds the maximal excretable urine volume, which is determined by solute intake [65]. This means, that patients with low solute intake are at higher risk of developing hyponatremia. This applies to all patients with malnutrition, such as chronic illness-related anorexia, beer potomania and the so called “tea and toast syndrome” often occurring in elderly patients [66]. In the latter, insufficient salt and protein intake and the reduced dilution capacity of aging kidneys impair water excretion. Accordingly, a detailed nutritional history should be part of the routine examination of patients with hyponatremia.

Hypervolemic hyponatremia

Hypervolemic hyponatremia involves an overall increase in total body sodium, accompanied by a relatively greater water excess (Fig. 1). This imbalance is driven by activation of the renin–angiotensin–aldosterone system (RAAS) in response to reduced effective arterial blood volume, together with AVP–mediated water retention and reduced glomerular filtration [67]. This typically occurs in patients with heart failure or liver cirrhosis, with older patients being at higher risk due to the age-related changes described above. The treatment of heart failure and liver cirrhosis includes loop diuretics and mineralocorticoid receptor antagonists. This can further reduce effective arterial blood volume and disrupt sodium homeostasis, especially in cases of excessive intake of hypotonic fluid.

In summary, older adults are at heightened risk for hyponatremia due to any cause due to age-related physiological changes and a higher burden of comorbidities, with the syndrome of inappropriate antidiuresis (SIAD) being the most frequent underlying cause.

Effects of hyponatremia and its correction

Clinical symptoms of hyponatremia are mainly determined by the rate of sodium decline. In acute cases (< 48 h), the brain’s ability to adapt to the rising osmotic gradient across the blood–brain barrier is overwhelmed, causing water to shift into brain tissue and resulting in cerebral oedema. This may raise intracranial pressure, producing headaches, restlessness, and confusion, and can progress to brain herniation and death if not promptly treated [40,68]. In contrast, when hyponatremia develops gradually over several days, the brain adapts by expelling sodium and, subsequently, organic osmolytes, thereby lowering intracerebral osmolality and reducing the risk of oedema [69]. As a result, chronic hyponatremia often appears clinically silent. Despite this apparent lack of acute symptoms, accumulating evidence links chronic hyponatremia to neurocognitive and neuromuscular impairments [12,14,70], reduced bone health [71], a higher incidence of falls and fractures [12,72–74], and diminished quality of life [15]. Also noteworthy is the fact that most of the patient populations studied had an average age of around 70 years, emphasizing the susceptibility of the elderly population to this condition. Moreover, although most supporting data are observational, active correction of hyponatremia has been associated with reversal of many of these adverse outcomes [12,18,75].

Neurocognitive and neuromuscular function

A well-known example is the study by Renneboog et al. [12], which examined a group of 122 older adults with clinically silent, chronic mild-to-moderate hyponatremia admitted to the emergency department. Falls were far more common in these patients than in their peers with normal sodium levels, and the risk was elevated regardless of hyponatremia severity. Other research has confirmed this pattern: even mild hyponatremia has been linked to a substantially higher likelihood of falls, both in hospitalised patients and in those living independently in the community [76–78]. In fact, the increased risk associated with mild hyponatremia was comparable to the effect of more than a decade of ageing [79].

The impact of correcting hyponatremia was strikingly shown in a small case control study of 16 patients with mild to moderate hyponatremia [80]. In this study, patients performed worse on gait tests, with results comparable to those seen in normonatremic controls who were mildly alcohol-intoxicated. After sodium levels were normalized, balance abnormalities resolved. A follow-up study by the same group highlighted that older adults with moderate hyponatremia experienced greater impairment in gait and cognitive performance than younger individuals, underscoring the heightened vulnerability of the ageing brain to sodium fluctuations [81].

Beyond these reports, evidence of treatment benefits after correcting hyponatremia remains limited. One small outpatient study found that individuals with mild-to-moderate hyponatremia experienced symptoms such as headache, confusion, and gait instability, along with poorer performance on neurocognitive and muscular tests compared with healthy peers [14]. While treatment improved

symptoms in all patients, gains in neurocognitive function were minimal. In another study of fourteen patients with hyponatremia and liver cirrhosis treated with the vasopressin receptor antagonist tolvaptan, improvements were seen in cognition, quality of life, and brain MRI findings [15]. More recent observational research has similarly shown that correcting moderate-to-severe hyponatremia can enhance cognitive performance and produce measurable changes in brain structure and neuronal activity [82].

Randomized evidence is particularly limited and often derived from secondary analyses. In the SALT trials [83], patients receiving the vasopressin antagonist tolvaptan experienced both increased sodium levels and notable improvements in mental health scores compared with placebo. The INSIGHT study [84], which examined tolvaptan's impact on cognition and postural stability in people with clinically asymptomatic hyponatremia, found a trend toward better neurocognitive performance alongside sodium correction. Another crossover trial tested the SGLT2 inhibitor empagliflozin in chronic SIAD-related hyponatremia; while sodium levels improved after four weeks of treatment, effects on gait were absent and cognitive gains were minimal [18]. The lack of stronger evidence likely reflects the observational nature of much of the research, the fact that many participants did not achieve normonatremia, and that no randomized trial to date has been designed specifically to detect changes in neurocognitive or neuromuscular function.

Bone health

Multiple studies and meta-analyses have shown a consistent link between chronic hyponatremia and a higher risk of osteoporosis and fractures [13,74,85–87]. Research in older adults has found that this increased fracture risk persists even when bone density is similar to that of individuals with normal sodium levels [88], suggesting other mechanisms are involved. One meta-analysis also linked hyponatremia to a greater likelihood of falls [73], with gait instability likely contributing to the elevated fracture risk. Additional evidence indicates that both the severity and duration of hyponatremia further elevate the risk of osteoporosis and fragility fractures [89]. Beyond falls, bone loss itself may be directly promoted by hyponatremia, as bone serves as the body's largest reservoir of osmotically inactive sodium [90]. Experimental studies in rats support this idea, showing marked bone loss and increased osteoclast activity after prolonged hyponatremia [91].

These findings suggest that hyponatremia-related bone loss may be reversible, although prospective data are largely limited to changes in bone formation markers. In the INSIGHT trial [84], treatment with the vasopressin antagonist tolvaptan was associated with an increase in osteocalcin, a marker of bone formation. Similar results were seen in two studies involving the SGLT2 inhibitor empagliflozin [75,92], where patients whose sodium levels normalized showed rises in markers of osteoblast activity, while those who remained hyponatremic did not. A recent cross-sectional analysis in older adults also found that even mild hyponatremia was independently associated with lower bone mineral density at the hip, though without changes in trabecular structure [93].

Beyond bone health, hyponatremia has also been linked to sarcopenia and reduced muscle strength in older patients [94]. Experimental work in ageing rats supports these observations [95], showing that hyponatremia can accelerate loss of lean mass and is associated with higher rates of hypogonadism and cardiomyopathy. Together, these factors accelerate the age-related changes.

Morbidity and mortality

Hyponatremia has been linked to poorer outcomes across a wide range of medical conditions, with multiple studies showing an association with higher mortality [9,22,96–98]. This increased risk likely reflects a complex interplay of underlying disorders and physiological factors. Observational evidence suggests that correcting hyponatremia may be beneficial in this regard. For example, in patients with SIAD, active treatment has been associated with greater sodium correction and shorter hospital stays compared with standard care [99]. In heart failure patients, failure to correct hyponatremia has been linked to a higher likelihood of readmission or death [100]. A meta-analysis of 15 observational studies indicated that hyponatremia improvement in correlates with reduced overall mortality - particularly in older adults and those with more pronounced hyponatremia [101].

Randomized controlled trials, all using vasopressin receptor antagonists (vaptans) [83, 102–105], have not demonstrated clear benefits for mortality or rehospitalization. This lack of effect may be due to the risk of overcorrection and associated adverse events [106], as well as the heterogeneous nature of hyponatremia, which likely requires a more tailored, individualized treatment approach.

Whether the link between hyponatremia and poor clinical outcomes reflects a causal relationship or merely an association remains uncertain, highlighting the need for well-designed outcome studies. Results from a large randomized trial assessing the impact of targeted hyponatremia treatment on 30-day mortality and rehospitalization [107] are expected to be published in the near future and may help clarify this issue.

Hyponatremia treatment options

Since the clinical picture depends on hyponatremia onset, treatment is also divided into these categories. In acute cases with severe manifestations, rapid hyponatremia correction with hypertonic saline takes priority over diagnostic work-up or cause-specific therapy [40]. In chronic hyponatremia, management focuses on addressing the underlying cause while raising sodium levels gradually to allow reversal of cerebral adaptations (maximum 10 mmol/l in the first 24 h and of 18 mmol/l in the first 48 h [40]). In patients with profound hyponatremia, hypokalemia, alcoholism, advanced liver disease, or malnutrition [66]^{120} who are at high risk of osmotic demyelination syndrome - a potentially devastating neurological complication caused by myelin damage from osmotic stress [108] – even slower correction rates with 6–8 mmol/l within 24 h are recommended [66]. If correction limits are exceeded, measures such as oral water intake, intravenous hypotonic fluids, or desmopressin can be used to re-lower sodium levels [109].

Hypertonic saline infusion

Acute, severely symptomatic hyponatremia is a medical emergency requiring immediate treatment with hypertonic saline. American and European guidelines [40,66] differ slightly in dosing recommendations (100 ml 3 % over 10 min versus 150 ml 3 % over 20 min respectively), but both aim for a modest (5 mmol) rapid rise in sodium to improve symptoms. The European guidelines also recommend dosage adjustment of 2 ml/kg for patients at the extremes of body size [40], as they are prone to over- or under-correction [110]. Extra caution is also advised in older or frail individuals, who are at increased risk of overcorrection due to often lower lean body mass and total body water [111]. Overall, bolus administration appears safer and preferable to continuous infusion [112,113], both can be given via a peripheral venous access [114, 115]. Some centres also use a "desmopressin clamp," giving desmopressin alongside hypertonic saline to reduce the risk of overly rapid correction [109,116]. While observational data support this approach, randomized trials are lacking.

Isotonic saline infusion

Isotonic saline, usually 0.9 % sodium chloride, is the mainstay of treatment for hypovolemic hyponatremia [117]. It replenishes both water and sodium while suppressing RAAS and AVP activation, which can trigger a water diuresis - making close sodium monitoring essential in patients with severe hyponatremia [109]. In contrast, isotonic saline should be avoided in SIAD, as the infused water cannot be adequately excreted and may further lower sodium levels [118].

Fluid restriction

Fluid restriction is the first-line treatment for chronic, non-severely symptomatic SIAD [55, 119]. Two randomized trials in mainly older patients showed modest improvements in sodium levels with this approach [120,121] (3 and 4 mmol/l after 4 days), but real-world effectiveness is often lower. This is particularly the case in patients with highly concentrated urine (> 500 mOsm/kg) or high urinary sodium levels (> 130 mmol/l) [122]. While generally safe, occasional cases of acute kidney injury and hypotension have been reported [123]. Typical recommendations are to limit fluid intake to around half a litre to one litre per day, or half a litre less than daily urine output [55]. The urine-to-plasma electrolyte ratio [124] can help guide the restriction level, with higher values indicating stricter limits. Maintaining strict fluid restriction over time can be challenging, and a more moderate limit may be sufficient in patients whose urine is less concentrated [125]. It should be noted that this is rarely the case in older patients due to their often-reduced thirst sensation and consequently lower fluid intake.

Loop diuretics

Loop diuretics are the mainstay in managing hypervolemic hyponatremia by reducing the kidneys ability to reabsorb water and thereby leading to aquaresis [126]. European guidelines list low-dose loop diuretics with sodium chloride tablets also as a second-line option for moderate to severe SIAD [40]. However, one trial found that adding loop diuretics - either alone or with salt tablets - to fluid restriction offered no advantage over fluid restriction alone in raising sodium levels [123].

Vasopressin receptor antagonists

Vaptans promote water excretion without sodium loss by reducing the kidney's ability to reabsorb water through the aquaporin 2 channels. Tolvaptan, taken orally, is available in both Europe and the US, while conivaptan is an intravenous option used only in the US [55]. Large clinical trials showed that tolvaptan effectively raises sodium levels in patients with SIAD, heart failure, or liver cirrhosis [127,128], leading to its approval for SIAD in Europe and for both euvolemic and hypervolemic hyponatremia in the US. However, in 2013 the FDA restricted its use in liver cirrhosis after higher doses were linked to severe liver toxicity in patients treated for polycystic kidney disease [129].

A key concern with tolvaptan is the risk of overly rapid sodium correction [130], especially for patients with profound hyponatremia [131], which is why treatment is usually started in hospital. Beginning with a lower dose (7.5 mg/day) can help reduce this risk [132]. Although even with this approach, rapid sodium rise was observed in one of five patients in a recently published study [121].

Extra caution is needed in those taking CYP3A4 inhibitors or inducers because of possible drug interactions, a common issue in older adults with multiple medications [133]. Treatment also requires that patients can drink freely and have an intact sense of thirst, which may be diminished in the elderly. The high daily cost of tolvaptan can further limit its use, particularly for older people with financial constraints. Even so, long-term success has been reported in carefully monitored cases, making it a potent treatment option in carefully selected older patients [134].

Salt tablets

Using salt tablets alone to treat SIAD is often ineffective, as each tablet provides only a small osmotic load, meaning many would be needed to significantly increase urine output. In line with this, a prospective study found no added benefit from salt tablets when combined with fluid restriction [123].

Oral urea

Administration of oral urea powder leads to osmotic diuresis due to its strong osmotic load. In most European countries, urea is provided by pharmacies as a compounded medical food, while in the US, flavoured ready-to-use formulations are available and FDA-approved [135]. European guidelines recommend its use for moderate to severe, fluid-restriction refractory SIAD [40]. Although a body weight adapted dosage is recommended (0.25–0.50 g/kg per day), a starting dose of 30 g per day is usually used which can be

increased to 60 or 90 g per day if needed. In frail elderly patients or patients at high risk for overcorrection, a lower starting dose of 15 g per day should be chosen [135].

Urea has been shown to be effective in a wide range of patients with SIAD. One prospective study found urea to be safe, well tolerated, and as effective as tolvaptan when patients received each treatment for a year in sequence [136]. Although no randomized controlled trials are available, recent meta-analyses support its safety and efficacy [137,138]. The use of urea has also been reported in hypervolemic hyponatremia due to heart failure [139–141]. However, its benefit is doubtful in patients with high baseline urea, and in liver cirrhosis it should be used only with extreme caution due to limited evidence and the risk of hepatic encephalopathy.

A common issue when using urea is its poor palatability, which can be improved by dissolving it in a strongly flavoured beverage like orange juice if no ready-to-use flavored preparation is available [40]. Otherwise, it is well tolerated and safe [142,143]. Urea may also protect against osmotic demyelination syndrome, according to a rat study that found that urea caused fewer deaths and less neurological damage than vaptans or hypertonic saline solution after rapid sodium correction [144].

Protein supplementation

Proteins are a natural source of urea, as they are broken down into nitrogen, which the liver converts into urea for excretion. About 10 g of protein produces 50 mmol of urea [56]. In rat models of SIAD [145], both a high-protein diet and a low-protein diet supplemented with oral urea raised plasma sodium, reduced natriuresis, and increased medullary urea compared with a low-protein diet alone. A recent prospective clinical study involving seventeen outpatients with chronic SIAD confirmed these findings. Consuming 90 g of protein per day over a period of seven days increased sodium and urea levels to a similar extent as consuming 30 g of urea per day [19]. A positive side effect of a high-protein diet is an increase in muscle mass and strength, which could reduce the risk of falls in this frail population group. However, these results must first be confirmed in a larger and longer-term study.

SGLT2 inhibitors

SGLT2 inhibitors promote glucose excretion in the urine, thereby leading to osmotic diuresis and excretion of electrolyte-free water [146–148]. Originally developed as oral diabetes drugs, they also slow chronic kidney disease progression and offer cardiovascular protection also in people without diabetes [149–152]. In two placebo-controlled trials in patients with SIAD adding the SGLT2-inhibitor empagliflozin improved sodium levels [153,154]. While the first study was conducted on hospitalized patients, was limited to four days, and also included fluid restriction, the second study was conducted on outpatients over a period of four weeks and without fluid restriction. The increase in sodium was moderate (4 mmol/l) in the outpatient study, but the treatment was well tolerated. In addition, the possibility of treating SIAD with SGLT2 inhibitors is interesting due to their cardiorenal protective effect, which could have a positive impact on the common comorbidities in older SIAD patients. Although data for other SGLT2 inhibitors are lacking, a similar effect as empagliflozin treatment can be assumed. Potential adverse effects of SGLT2 inhibitors, including genitourinary infections and ketoacidosis, should be considered, as with their use for any other indication.

Conclusions

Hyponatremia is the most common electrolyte disorder, particularly among older adults. SIAD is now the leading cause, driven by polypharmacy and multiple comorbidities, though hypervolemic and hypovolemic forms must also be considered. Its prevalence rises during warmer months and is expected to grow further with global warming.

Symptoms depend on the speed of onset: acute cases can cause cerebral oedema and require urgent treatment with hypertonic saline, which takes priority over further diagnostics or cause-specific therapy.

Although once considered asymptomatic, chronic hyponatremia is now linked to neurocognitive and neuromuscular impairment, reduced bone density, higher fracture risk, poorer quality of life, increased rehospitalizations, and greater mortality. Observational studies suggest these outcomes can improve when sodium levels are corrected, though randomized controlled trial data remain limited. Until stronger evidence is available, managing chronic hyponatremia should be seen as part of supporting healthy ageing. Appropriate differential diagnosis is a prerequisite, as the appropriate treatment is different in various aetiologies of hyponatremia. Several treatment modalities of chronic hyponatremia are available, with the mainstays being isotonic saline infusion in hypovolemic hyponatremia, fluid restriction and loop diuretics in hypervolemic hyponatremia, and fluid restriction, urea or vaptans in patients with SIAD. In addition, protein supplementation and SGLT2 inhibitors have appeared in the last years as treatment alternatives that could represent an attractive and holistic option, especially in older patients.

Research Agenda

Future trials should investigate

- Biomarkers to aid in the differential diagnosis of hyponatremia
- Combinations of established treatments as well as longer-termed clinical studies on SGLT2-inhibitors and protein supplementation.
- Evaluation of biomarkers for early detection of osmotic demyelination syndrome to guide sodium correction rate
- Possible protective role of urea for osmotic demyelination syndrome
- Prospective trials to evaluate the reversibility of neurocognitive and neuromuscular deficits in hyponatremic patients

Practice Points

- Older adults face a heightened risk of hyponatremia due to age-related changes in AVP regulation and urine concentration abilities, as well as higher rates of comorbidities, polypharmacy, and malnutrition.
- Chronic hyponatremia is linked to higher mortality and morbidity, including neuromuscular and cognitive decline as well as osteoporosis.
- Evidence suggests that correcting hyponatremia may improve neuromuscular and neurocognitive function and benefit bone health
- A step-wise diagnostic approach is helpful when evaluating hyponatremia
- New evidence is available for SIAD treatment, with SGLT2 inhibitors and protein supplementation offering broader health benefits in the elderly population.

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