Recent developments in the management of acute and chronic hyponatremia

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Purpose of review
The aim of the study is to review recent studies on the management of acute and chronic hyponatremia.

Recent findings
In acute symptomatic hyponatremia, bolus infusion of hypertonic saline improves hyponatremia and neurological status more quickly than continuous infusion. In chronic hyponatremia, newly identified predictors of nonresponse to fluid restriction include a high urine osmolality (>500 mOsm/kg) and high urine sodium (>133 mmol/l). Vasopressin-receptor antagonists effectively raise the serum sodium concentration in patients with euvolemic or hypervolemic hyponatremia but have a risk of overcorrection, even at low doses. Several observational studies now support the use of urea for a more gradual correction of hyponatremia without a risk of overcorrection. Recently identified risk factors for overcorrection include lower serum sodium at presentation, polydipsia, hypovolemia, and early urine output during treatment. Specific treatments with potential efficacy are the use of intravenous albumin for hyponatremia because of liver cirrhosis, and fludrocortisone for hyponatremia in tuberculous meningitis.

Summary
The recent data will help to further optimize and personalize the management of patients with acute and chronic hyponatremia. However, most data are still observational and retrospective. Therefore, the field is in need of prospective studies comparing interventions for chronic hyponatremia and focusing on patient-relevant outcomes.

Keywords
fluid restriction, hypertonic saline, urea, vasopressin-receptor antagonist

INTRODUCTION

Hyponatremia is classified as acute or chronic hyponatremia depending on whether it develops within 48 h or not. Although the 48-h cut-off is not strict, this is the average time that cells require to adapt to a hypotonic extracellular fluid (ECF). The clinical implication of this classification is that patients with acute hyponatremia have a risk of cerebral edema (brain cell swelling). For acute hyponatremia to cause cerebral edema, two additional factors are required, including hypotonicity of the ECF and a sufficient biochemical severity of hyponatremia. Hyponatremia is usually hypotonic (i.e., associated with a reduced effective plasma osmolality), but nonhypotonic causes exist which do not have a risk of cerebral edema. Because hypotonic hyponatremia is the predominant form of hyponatremia, this review will focus on hypotonic hyponatremia only. The biochemical severity of hyponatremia is divided in mild (serum sodium 130–135 mmol/l), moderate (serum sodium 125–129 mmol/l), and profound (serum sodium <125 mmol/l) hyponatremia [1]. Thus, patients with acute profound hypotonic hyponatremia are at risk of developing cerebral edema. The basis for the treatment of acute hyponatremia is to reduce brain cell swelling by infusing hypertonic saline. This treatment is given regardless of the underlying cause of hyponatremia. Conversely, in chronic hyponatremia, brain cells have adjusted to their hypotonic environment through the release of intracellular osmoles. In this adjusted

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KEY POINTS

- Bolus infusion of hypertonic saline improves hyponatremia and neurological status more quickly than continuous infusion.
- Predictors of nonresponse to fluid restriction are high urine osmolality (>500 mOsm/kg) and high urine sodium (>133 mmol/l).
- VRAs effectively correct euvolemic and hypervolemic hyponatremia but have a risk of overcorrection, even at low doses.
- Several observational studies support the use of urea for a more gradual correction of hyponatremia without a risk of overcorrection.
- Risk factors for overcorrection include lower serum sodium at presentation, polydipsia, hypovolemia, and early urine output during treatment.

state, brain cells become sensitive to the rapid correction of hyponatremia, which may result in osmotic demyelination. Although cerebral edema and osmotic demyelination are relatively rare [2], they represent the two neurological complications that need to be treated or avoided in patients with hyponatremia [3]. Although the distinction between acute and chronic hyponatremia is logical from a pathophysiological and therapeutic perspective, the differentiation in clinical practice is often challenging. The time in which hyponatremia developed is often unknown and several symptoms can occur both in acute and chronic hyponatremia [4,5]. Therefore, some investigators prefer to classify hyponatremia as symptomatic or asymptomatic [6▪]. A similarly challenging issue is whether chronic hyponatremia requires treatment. Although chronic hyponatremia is associated with increased mortality [7], it is unclear if this is directly related to hyponatremia or to the severity of the underlying disorder causing hyponatremia [8,9]. This may be the reason that over 10% of patients with hyponatremia receive no management at all [10]. One metaanalysis suggested that the correction of hyponatremia confers a survival benefit, but this analysis was limited by the retrospective and observational nature of the studies included [11]. Despite adjustment to hypotonicity, patients with chronic hyponatremia can also exhibit neuromuscular or neurological symptoms [4,5], and this could provide a rationale for treatment. Similar to acute hyponatremia, symptoms are more likely to occur when chronic hyponatremia is profound. Furthermore, in patients with chronic hyponatremia an acute further decrease in serum sodium may occur ('acute on chronic' hyponatremia) which can produce symptoms. The treatment of chronic hyponatremia is preferably cause-directed (e.g., by treatment of the underlying disease or discontinuation of a causative drug). However, chronic hyponatremia frequently occurs in disorders that are often irreversible, including liver cirrhosis, heart failure, and the syndrome of inappropriate antidiuresis (SIAD). These causes of hyponatremia are also referred to as euvolemic hyponatremia (SIAD) and hypervolemic hyponatremia (liver cirrhosis and heart failure). Treatment usually relies on fluid restriction or the stimulation of renal water excretion. The latter can be achieved by various approaches, including loop diuretics, urea, or vasopressin-receptor antagonists (VRAs). These general principles on the management of hyponatremia are also covered by the United States (2013) and European (2014) guidelines on hyponatremia [1,12]. However, several recent studies have appeared that are likely to refine our management of patients with hyponatremia. These novel insights on the acute and chronic management of hyponatremia will be the focus of this review.

ACUTE HYPONATREMIA

Hypertonic saline (usually 3% NaCl) is the treatment of choice for patients with acute hyponatremia, especially if they are symptomatic. In recent years, the approach of giving a bolus of hypertonic saline rather than a continuous infusion has been advocated [13] and this was also endorsed by the European guideline [1]. The bolus infusion does not require calculations and has the advantage of an immediate effect with little risk of overcorrection. However, few empirical data were available to support this approach. Recently, however, a study compared bolus infusion (100 ml, repeated up to two times) with continuous infusion (20 ml/h) in patients with symptomatic hyponatremia because of SIAD (Figure 1) [14▪▪]. To do so, 22 patients were treated prospectively with bolus infusion and were then compared with a retrospective cohort that received a continuous infusion of hypertonic saline. The bolus infusion produced a faster rise in serum sodium than the continuous infusion, with quicker restoration of Glasgow Coma Scale (GCS), and without osmotic demyelination (Figure 1). However, the administration of a third bolus was associated with a greater need of dextrose or desmopressin to prevent overcorrection. An ongoing clinical trial is expected to identify the best initial approach more definitely because it is randomizing patients with symptomatic hyponatremia to receive rapid intermittent correction or slow continuous correction [15]. The

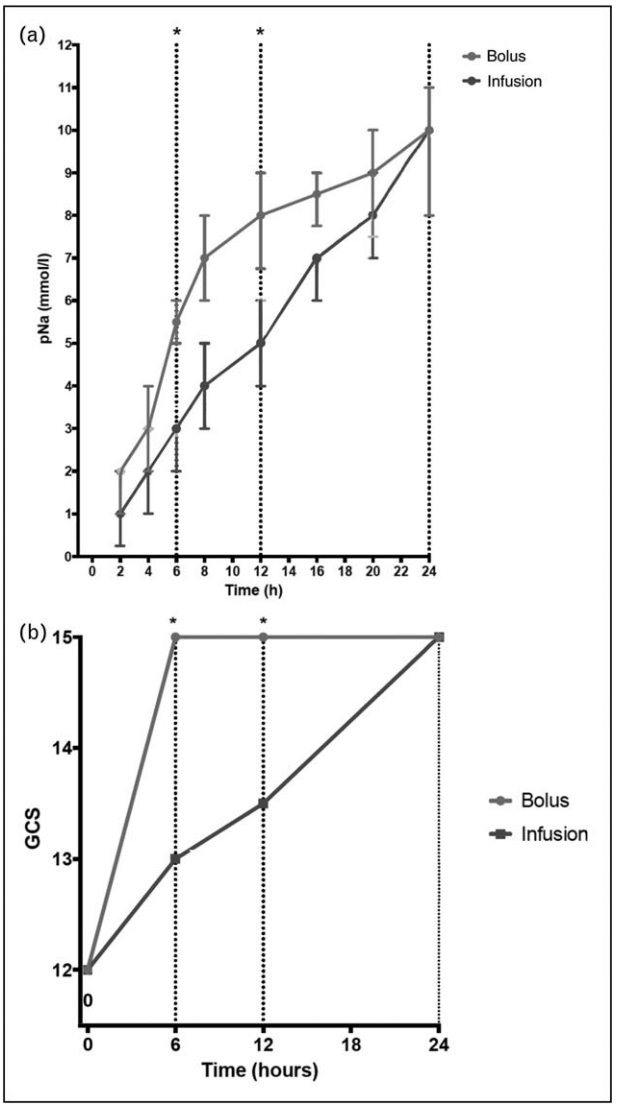

FIGURE 1. Serial measurements of plasma sodium (a) and serial assessments of Glasgow Coma Scale (b) in patients with symptomatic hyponatremia treated with hypertonic saline as a bolus (light grey line) or as a continuous infusion (dark grey line). Reprinted from [14▪▪], with kind permission. Asterisks indicate significant differences between groups.

primary outcome in this study is the incidence of overcorrection over 2 days, whereas evolution of the GCS is one of the secondary outcomes. The study aims to include 178 patients and has currently enrolled 152 patients (personal communication with Dr. Kim). A different approach – 500 ml 3% NaCl over 6 h – has been reported previously to also improve neurological status without causing osmotic demyelination [16]. However, the correction rate at 24 h was at the upper limit of current recommendations (10 ± 1 mmol/l), which may be undesirable in patients in whom the differentiation between acute and chronic hyponatremia is difficult. The very low serum sodium concentrations of the patients included in this study (114 ± 1 mmol/l) suggest that some patients had a component of chronic hyponatremia. Hypertonic saline is often also the predominant form of therapy in neurocritically ill patients. This was illustrated by a study in 116 hyponatremic patients with subarachnoid hemorrhage, traumatic brain injury, or intracranial tumors who were admitted to the neurological intensive care unit [17]. Hypertonic saline was started at an average serum sodium concentration of 133 mmol/l and this treatment was prompted by a decline in the serum sodium concentration (59%), or the presence of cerebral edema (18%). Of interest, a small randomized trial showed that in a specific setting of acute hyponatremia, namely exercise-associated hyponatremia, oral hypertonic saline was equally effective as intravenous hypertonic saline in raising serum sodium [18].

CHRONIC HYPONATREMIA

Fluid restriction

Fluid restriction is recommended as first-line treatment for chronic hyponatremia secondary to SIAD and also recommended in hypervolemic hyponatremia [1]. However, fluid restriction is not always effective, either because it is difficult to adhere to, or because urinary concentration exceeds the ability to achieve a negative water balance by fluid restriction. In the Hyponatremia Registry (a multinational registry for treatment of euvolemic or hypervolemic hyponatremia), fluid restriction for SIAD failed to increase serum sodium by at least 5 mmol/l in 55% of treatment episodes [19]. A recent study identified a high urine osmolality and high urine sodium as predictors of nonresponse to fluid restriction [20]. A urine osmolality of at least 500 mOsm/kg predicted nonresponse with a specificity of almost 90%. Of interest, however, urine sodium was a better predictor than urine osmolality, even in the context of diuretic use. Thus, a high urine sodium (>130 mmol/l) appears to signal a greater degree of antidiuresis with increased probability of nonresponse to fluid restriction. In line with this observation was the finding that nonresponders to fluid restriction had a significantly lower mid-regional proatrial natriuretic peptide, which suggests ECF expansion. Decaux *et al.* [21] reached a similar conclusion by showing that fluid restriction was effective in patients with chronic SIAD only when urine osmolality was less than 400 mOsm/kg. Although fluid restriction remains an effective treatment for euvolemic and hypervolemic hyponatremia, the degree of antidiuresis – as assessed by urine

osmolality and sodium – should be factored in to determine its expected effect.

Vasopressin-receptor antagonists

VRAs have been approved for the treatment of chronic hyponatremia secondary to euvolemic (Europe, USA) and hypervolemic (USA) causes. Four VRAs are available, including tolvaptan, lixivaptan, satavaptan, and conivaptan [22]. Tolvaptan, lixivaptan, and satavaptan are selective vasopressin V2-receptor antagonists and available as oral preparation. In contrast, conivaptan also targets the V1a receptor and is only available for intravenous administration. The efficacy of VRAs to increase serum sodium has clearly been demonstrated in several placebo-controlled trials and confirmed in several metaanalyses [23–25]. Four additional meta-analyses have appeared in the last three years [26–28,29▪]. Zhang *et al.* [27] metaanalyzed 18 trials and – as expected – showed that VRAs significantly increase serum sodium and 24-h urine output, while decreasing body weight. These effects occurred regardless of the type of VRA, the type of hyponatremia (euvolemic or hypervolemic), and whether concurrent water restriction was prescribed. Drug-related adverse effects included a rapid correction of serum sodium, and symptoms related to the aquaretic effects (dry mouth, thirst, constipation). The metaanalysis of Li *et al.* [26] generally had the same findings but was restricted to tolvaptan, the most commonly used VRA. The two other meta-analyses reviewed treatment for nonhypervolemic chronic hyponatremia in general, which mainly concerned VRAs for SIAD [24,25]. One of these metaanalyses provided the clinically useful observation that a lower pretreatment serum sodium predicts a greater increase in serum sodium with VRA treatment (Figure 2) [29▪]. Two previous studies reported a similar finding [30,31]. The additional conclusion of the two metaanalyses emphasized the lack of benefit on patient-important outcomes and lack of comparative studies of VRAs versus other active treatments. Indeed, no clinical trial or meta-analysis has shown that VRAs improve outcomes beyond serum sodium. Recent studies in patients with liver cirrhosis or heart failure have explored potential additional benefits. According to

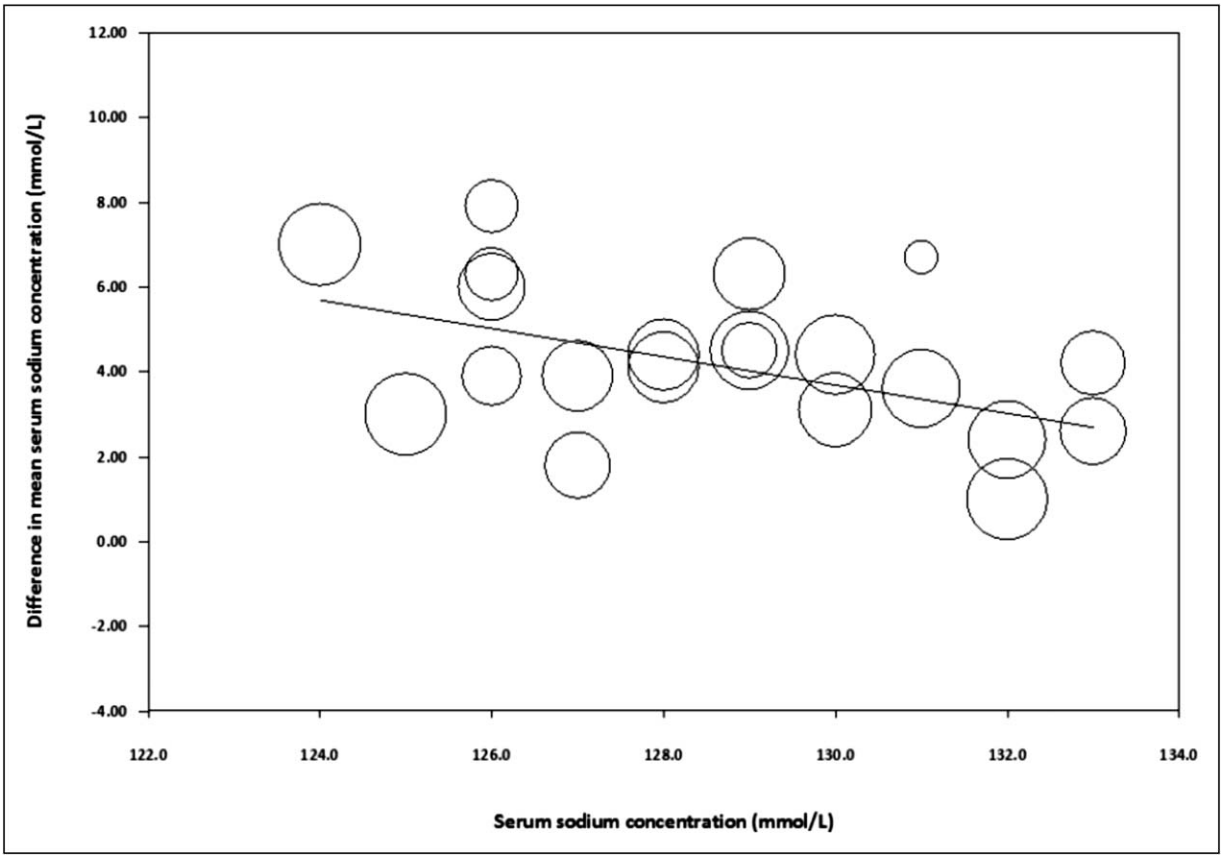

FIGURE 2. Metaregression analysis showing the effect of baseline serum sodium concentration on the change in natremia during treatment with vasopressin-receptor antagonists. A lower serum sodium concentration at baseline is associated with a greater increase in serum sodium with treatment. Reprinted from [29▪], with kind permission.

registries, the current treatment of hyponatremia in these disorders is frequently ineffective [32,33]. Three studies suggest a survival benefit with the use of VRAs in patients with liver cirrhosis and hyponatremia [34–36]. However, the study designs of two of these studies preclude causal inference, because they were retrospective [35], nonrandomized [34], or of small sample size [34,35]. The third study was a double-blind, placebo-controlled randomized trial which found that 7-day treatment of tolvaptan in patients with liver cirrhosis and ascites improved 6-month survival rate [36]. It remains uncertain if such a short treatment episode can be linked causally to improved longer term outcomes. Indeed, Pose *et al.* [37] found very limited to no effect of tolvaptan in patients with liver cirrhosis and severe hyponatremia. A larger study found that tolvaptan was effective in only 52% of patients with liver cirrhosis, ascites, and diuretic resistance [38]. Notably, this study found that a urine sodium to potassium ratio of at least 2.5 predicted treatment response to tolvaptan [38]. Because this ratio is a marker of aldosterone action, this finding suggests that primarily patients without significant secondary hyperaldosteronism respond to tolvaptan. In patients with acute heart failure, a double-blind, randomized trial investigated whether tolvaptan (30 mg/day) improved dyspnea [39]. In addition to acute heart failure, inclusion criteria were hyponatremia, reduced kidney function (estimated glomerular filtration rate <60 ml/min/1.73 m^2), or diuretic resistance. Despite weight loss, tolvaptan was not associated with greater early improvement in dyspnea (the primary outcome). Two other studies explored whether tolvaptan may improve decongestion in patients with combined chronic heart failure (CHF) and chronic kidney disease (CKD). The first study compared the introduction of tolvaptan ($\leq$15 mg/day) to an increase in the dose of furosemide in patients with CHF and CKD (stage G3b-5) [40]. The study found that tolvaptan produced a greater diuretic effect than increased furosemide. The second study was a retrospective study that evaluated the use of tolvaptan (initial dose 15 mg/day) as addition to the diuretic regimen in patients with CHF (primarily New York Heart Association Class III) and CKD (primarily stage G5) [41]. Despite the severity of the underlying conditions, tolvaptan still produced an aquaretic effect with a rise in serum sodium and decrease in body weight, although this occurred at the expense of a reduction in kidney function. Another focus of recent studies has been to prescribe tolvaptan in a reduced starting dose (3.75 or 7.5 mg/day instead of 15 mg/day). One retrospective case series showed that this lower dose on average leads to comparable correction rates but

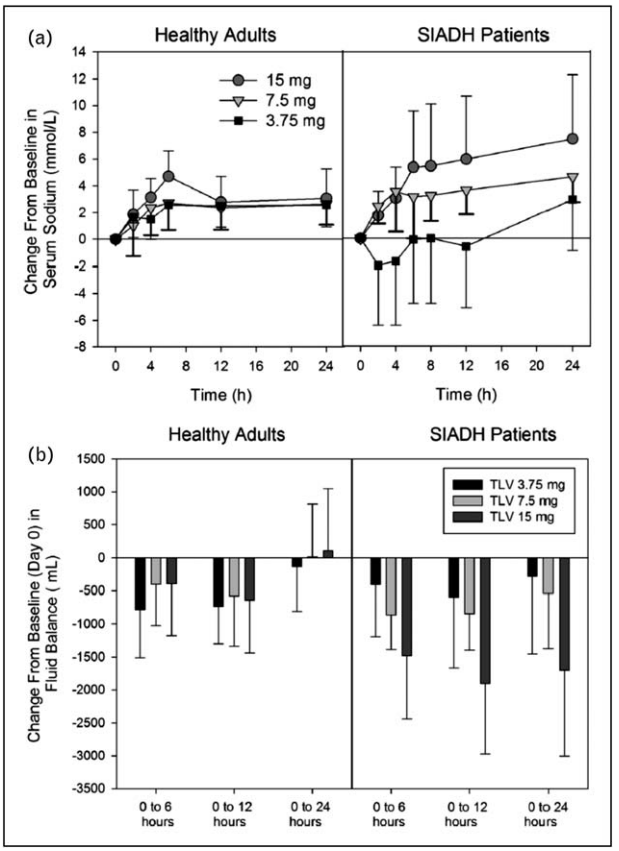

FIGURE 3. Changes in serum sodium (a) and fluid balance (b) in healthy controls and patients with syndrome of inappropriate antidiuresis after receiving 3.75, 7.5, or 15 mg tolvaptan. Reprinted from [45▪▪], with kind permission.

may prevent overcorrection [42]. A similar experience was reported in patients presenting to the emergency department with euvolemic or hypervolemic hyponatremia [43]. The standard dose led to overcorrection (>12 mmol/l/day) in 41.7% of the patients, whereas the low dose caused no overcorrection. The approach of giving a lower starting dose also resulted in a gradual and persistent correction of euvolemic or hypervolemic hyponatremia in seven elderly male patients (age > 90 years) [44]. To address the effects of different doses more extensively, Shoaf *et al.* [45▪▪] performed a study on the pharmacokinetic and pharmacodynamic effects of 3.75, 7.5, and 15 mg tolvaptan in healthy adults and patients with SIAD (Figure 3). In 29 patients with SIAD, all three doses still caused overcorrection (serum sodium $\geq$8 mmol/l in 8 h or $\geq$12 mmol/l in 24 h) in one, one, and two patients, respectively. Overcorrection was not observed in the healthy controls. This difference was explained by the observation that the healthy controls but not patients with SIAD increased fluid intake after tolvaptan

(Figure 3). In patients with hyponatremia, the initial rise in serum sodium will remain in the hypotonic range and will therefore not trigger a thirst response. Conversely, in some patients with SIAD hyponatremia has been shown to be resistant to tolvaptan, likely because of excessive ectopic production of vasopressin [46]. In summary, VRAs have uncertain effects on outcomes other than serum sodium but do have a risk of overcorrection [47]. This complicates the overall positioning of these agents in the management of chronic hyponatremia [1,47,48]. Exceptions for individual cases exist as illustrated by the report of a patient in whom tolvaptan allowed the continuation of bortezomib treatment after it had caused hyponatremia [49]. Two recent studies suggest the use of VRAs in hospitalized patients may also be cost-effective by reducing length of hospital stay [50,51], although this was classified as low certainty evidence [29▪]. A complicating factor in the debate on the positioning of VRAs in the management of chronic hyponatremia is that the majority of studies, including the Hyponatremia Registry, are directly or indirectly supported by the pharmaceutical companies producing these agents [29▪].

Urea

Urea has long been recognized as an osmotic diuretic that effectively increases serum sodium in patients with euvolemic or hypervolemic hyponatremia [52,53]. However, its use was not widespread because of inexperience and poor palatability of urea powder. In the European guideline urea was recommended as a second-line treatment for moderate or profound hyponatremia secondary to SIAD [1]. The guideline also offered a urea prescription that can be consumed as liquid formulation. In addition, oral urea is currently commercially available (ure-Na). Recently, several groups have reported favorable results with the use of urea in patients with chronic hyponatremia. In 58 patients with hyponatremia primarily because of SIAD urea (7.5–90 g/day) increased serum sodium from a median of 124–131 mmol/l [54▪]. In an additional analysis, urea only-treated patients were matched and compared with urea-untreated patients. The urea-treated patients had a greater increase in serum sodium and a trend toward achieving normonatremia more often. Another retrospective study reported the effects of 78 treatment episodes with urea in 69 patients with hyponatremia primarily because of SIAD who did not respond to fluid restriction (median nadir serum sodium 122 mmol/l) [55▪]. When urea was used as second-line treatment, it led to a significantly greater increase in serum sodium than fluid restriction (Figure 4). After 72 h, 64.1% had a serum sodium at least 130 mmol/l. The third retrospective analysis included 36 cancer patients with profound chronic hyponatremia secondary to SIAD [56▪]. In these patients, urea (15–30 g/day) increased serum sodium from 123 ± 4 to 128 ± 3 mmol/l after 24 h. Normonatremia was reached by 56, 86, 92% of patients within 14, 30, and 60 days of treatment, respectively (Figure 4). Importantly, in all three studies, no overcorrection or serious adverse events were reported. Drug taste, however, was still an

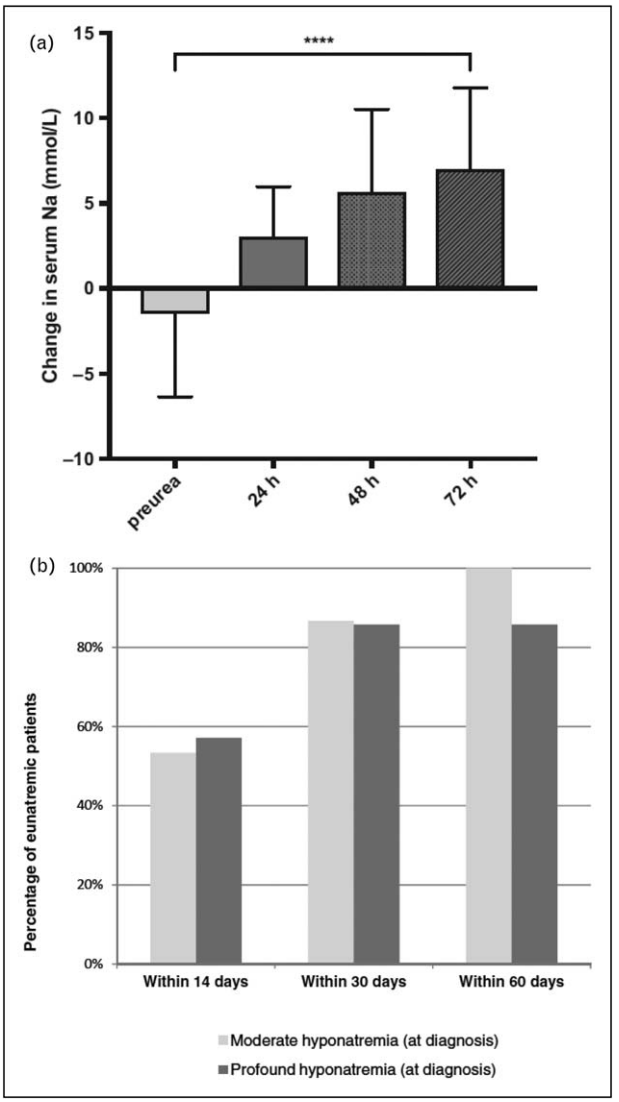

FIGURE 4. Results of two studies evaluating the efficacy of urea for chronic hyponatremia. Cumulative change in mean serum sodium over each 24-h period for patients failing fluid restriction ($n = 56$, a). Percentage of patients with moderate and profound hyponatremia who reached normonatremia within 14, 30, and 60 days of urea treatment ($n = 36$, b). Reprinted from [55▪] and [56▪], with kind permission.

issue in some patients and sometimes led to discontinuation of urea. Of interest, in experimental animals, neurological outcomes are better when overcorrection is induced with urea than with VRAs or hypertonic saline [57]. Urea is sometimes also given in other settings of hyponatremia. For example, Annoni *et al.* [58] reported their experience with giving urea by nasogastric tube in patients with acute brain injury who also developed hyponatremia secondary to SIAD. They showed that urea not only increased serum sodium but also decreased intracranial pressure.

Preventing and treating overcorrection

In patients with profound chronic hyponatremia, overcorrection during treatment is common. Recent estimates from two studies indicate it occurs in 41 or 16% of patients, depending on whether overcorrection is defined as a rise in serum sodium of more than 8 or more than 10 mmol/l in the first 24 h [59▪,60]. In one of these studies, 295 patients also underwent brain magnetic resonance imaging [59▪]. In these patients, radiological evidence of osmotic demyelination was observed in nine patients, clinical symptoms were present in eight patients of whom five patients recovered. Several risk factors for overcorrection were identified, including a lower serum sodium at presentation, younger age, female gender, polydipsia, lower comorbidity, a urine sodium less than 30 mmol/l, and early urine output during treatment. A brisk water diuresis and overcorrection can occur if patients with chronic polydipsia suddenly cease fluid intake or if appropriate vasopressin release because of hypovolemia (low urine sodium) abates after intravenous fluid resuscitation. In patients with hypovolemic hyponatremia who developed overcorrection during treatment, the use of desmopressin appears safe and effective, although randomized trials are lacking [61].

Cause-specific treatments

Data on the treatment of specific causes of hyponatremia have become available in recent years. This includes the treatment of hyponatremia secondary to liver cirrhosis, neurological disorders (tuberculous meningitis and subarachnoid hemorrhage), systemic juvenile idiopathic arthritis, and thiazide-induced hyponatremia. In a large cohort of patients with liver cirrhosis and hyponatremia (serum sodium < 130 mmol/l), the effect of intravenous albumin was analyzed [62▪]. Despite a higher MELD score, lower kidney function, and lower serum sodium, patients receiving albumin had a greater increase in serum sodium and greater resolution of hyponatremia than patients who did not receive albumin. In turn, hyponatremia resolution was an independent predictor of 30-day survival. In contrast, a placebo-controlled trial that tested the combination of albumin and midodrine against placebo did not find a lower rate of liver cirrhosis complications (hyponatremia, renal failure, infections, hepatic encephalopathy, or gastrointestinal bleeding) [63]. An observational study in 10 patients with liver cirrhosis and hyponatremia did observe an increase in serum sodium (124–130 mmol/l) after the combination of midodrine and octreotide [64]. Glucocorticoids and mineralocorticoids are occasionally used to prevent or treat hyponatremia secondary to neurological disease. To test this more rigorously, patients with tuberculous meningitis and suspected cerebral salt wasting (defined as hyponatremia, polyuria, and exclusion of other causes of hyponatremia) were randomized to receive fludrocortisone or no fludrocortisone (18 patients in each arm) [65▪]. All patients also received isotonic saline and oral sodium chloride supplementation. Fludrocortisone resulted in a significantly earlier normalization of serum sodium (4 versus 15 days) and caused fewer infarcts in the deep border zone (watershed cerebral infarction, 6 versus 33%). Adverse reactions occurred in three patients (hypokalemic hypertension or pulmonary edema), which led to discontinuation of fludrocortisone in two patients. In contrast, a recent systematic review found no effects of fludrocortisone or hydrocortisone in preventing hyponatremia after subarachnoid hemorrhage [66]. In the pediatric literature, an interesting case of systemic juvenile idiopathic arthritis with hyponatremia because of SIAD was reported that resolved with the interleukin 6 inhibitor tociluzimab [67]. The case is of interest because it illustrates that high interleukin 6 levels may explain SIAD secondary to inflammation [68]. Finally, the treatments for thiazide-induced hyponatremia were evaluated in the Hyponatremia Registry [69]. Next to discontinuing the diuretic, additional treatment is often necessary to normalize serum sodium. For this purpose, hypertonic saline was most effective but also associated with high overcorrection rates ($>20\%$). Isotonic saline with or without fluid restriction was also effective, whereas fluid restriction alone was ineffective. The ineffectiveness of fluid restriction is somewhat surprising given a recent study that proposes thiazide-induced hyponatremia is caused by prostaglandin-mediated antidiuresis [70]. A recent balance study suggested that thiazide-induced hyponatremia has a biochemical profile similar to SIAD but is caused by cation depletion and therefore responsive to solute repletion [71].

CONCLUSION

The most notable findings in recent years are the evidence supporting bolus infusion of hypertonic saline for acute symptomatic hyponatremia [14▪▪] (Figure 1), the identification of predictors of nonresponse to fluid restriction in patients with chronic hyponatremia [20], the support of urea as treatment to more gradually correct chronic hyponatremia without overcorrection [54▪,55▪,56▪] (Figure 4), the potential efficacy of specific treatments for hyponatremia because of liver cirrhosis (intravenous albumin) [62▪], and tuberculous meningitis (fludrocortisone) [65▪]. These findings will be useful to optimize and personalize treatment of acute and chronic hyponatremia. However, the majority of these studies were observational and retrospective. Therefore, higher quality evidence is warranted. An ongoing clinical trial is expected to provide this evidence for the management of acute hyponatremia [15]. In chronic hyponatremia, however, the comparative efficacy of the available treatments has been poorly investigated. In addition, the potential benefits of correcting chronic hyponatremia beyond normalization of serum sodium are unknown. Hopefully, this answer can be provided by an ongoing trial that is randomizing patients between a targeted correction of serum sodium and standard care and will analyze the effects on the rate of death or rehospitalization within 30 days (ClinicalTrials.gov, NCT03557957).

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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