

# Diagnosis and Treatment of Hyponatremia: Compilation of the Guidelines

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## ABSTRACT

Hyponatremia is a common water balance disorder that often poses a diagnostic or therapeutic challenge. Therefore, guidelines were developed by professional organizations, one from within the United States (2013) and one from within Europe (2014). This review discusses the diagnosis and treatment of hyponatremia, comparing the two guidelines and highlighting recent developments. Diagnostically, the initial step is to differentiate hypotonic from nonhypotonic hyponatremia. Hypotonic hyponatremia is further differentiated on the basis of urine osmolality, urine sodium level, and volume status. Recently identified parameters, including fractional uric acid excretion and plasma copeptin concentration, may further improve the diagnostic approach. The treatment for hyponatremia is chosen on the basis of duration and symptoms. For acute or severely symptomatic hyponatremia, both guidelines adopted the approach of giving a bolus of hypertonic saline. Although fluid restriction remains the first-line treatment for most forms of chronic hyponatremia, therapy to increase renal free water excretion is often necessary. Vasopressin receptor antagonists, urea, and loop diuretics serve this purpose, but received different recommendations in the two guidelines. Such discrepancies may relate to different interpretations of the limited evidence or differences in guideline methodology. Nevertheless, the development of guidelines has been important in advancing this evolving field.

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Hyponatremia (serum sodium [ $S_{Na}$ ] <136 mmol/L) is a common water balance disorder that often poses a diagnostic or therapeutic challenge.<sup>1</sup> This may explain why management of hyponatremia is still suboptimal, as also recently illustrated by a hyponatremia registry.<sup>2</sup> Hyponatremia is not a disease but rather a pathophysiologic process indicating disturbed water homeostasis.<sup>3</sup> Therefore, hyponatremia should be further classified in order to provide directions for diagnosis and treatment (Table 1). These classifications illustrate that hyponatremia is a very heterogeneous disorder. This has complicated clinical

studies, because “the” patient with hyponatremia does not exist. Instead, the underlying disease that is complicated by hyponatremia usually characterizes patients with hyponatremia.<sup>4,5</sup> The most common causes of hyponatremia are the syndrome of inappropriate antidiuresis (SIAD), diuretic use, polydipsia, adrenal insufficiency, hypovolemia, heart failure, and liver cirrhosis (the latter two are often collectively referred to as “hypervolemic hyponatremia”). Although recent years have seen several developments in the diagnosis and treatment of hyponatremia, the evidence base is still limited. To capture the current

approach to hyponatremia, two sets of guidelines have been developed, one by professional organizations from within the United States (“United States guideline”) and one from within Europe (“European guideline,” in which the authors of this review participated).<sup>6–9</sup> The professional organizations involved in the United States guideline were Tufts University Office of Continuing Education and In 2 MedEd; the initiative was also supported by an unrestricted educational grant from Otsuka America Pharmaceutical.<sup>9</sup> The professional organizations involved in the European guideline were the European Renal Association–European Dialysis and Transplantation Association, the European Society of Endocrinology, and the European Society of Intensive Care Medicine.<sup>6–8</sup> The United States guideline refrained from using a quality-of-evidence scoring system due to the limited evidence. Instead, the guideline was on the basis of expert panel recommendations, which relied on a critical evaluation of relevant literature by the panel members. The European guideline did perform systematic reviews of the available evidence using the Grading of

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**Table 1.** Classifications of hyponatremia

Classification	Criteria	Limitations of Clinical Utility
Moderate (125–129 mmol/L) versus severe/profound <sup>a</sup> (<125 mmol/L)	Absolute $S_{Na}$ concentration	Symptoms do not always correlate with degree of hyponatremia
Acute versus chronic Symptomatic versus asymptomatic	Time of development (cutoff 48 h) Presence of symptoms	Time of development not always known Many symptoms aspecific; chronic hyponatremia may be symptomatic
Hypotonic, isotonic, or hypertonic	Measured serum osmolality	Ineffective osmoles (e.g., urea, ethanol) are also measured
Hypovolemic, euvolemic, hypervolemic	Clinical assessment of volume status	Clinical assessment of volume status has low sensitivity and specificity

<sup>a</sup> $S_{Na} < 125$  mmol/L is defined as “severe hyponatremia” by the United States guideline, and as “profound hyponatremia” by the European guideline.<sup>7,9</sup>

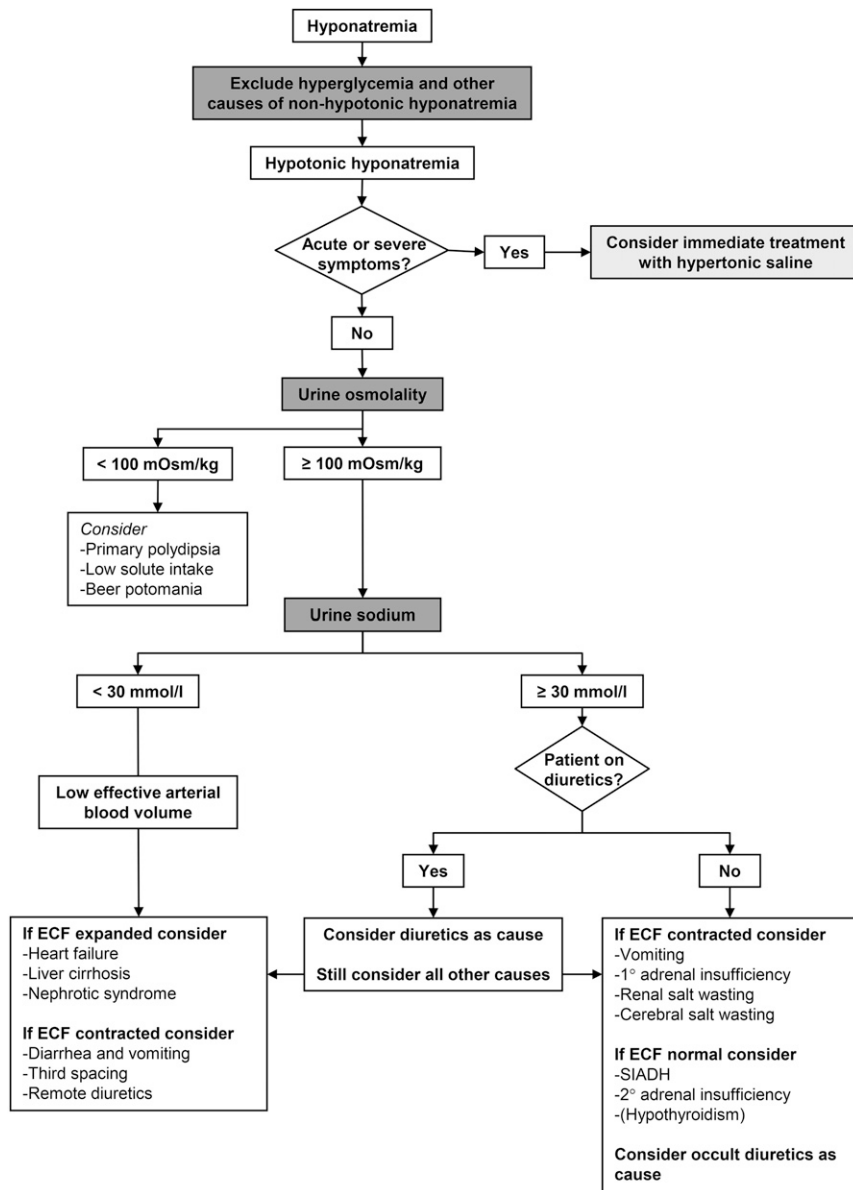
Recommendations Assessment Development and Evaluation scoring system. Both guideline committees were interdisciplinary, and the European guideline was endorsed by the European societies of nephrology, endocrinology, and intensive care.<sup>6–8</sup> This brief review will compare the two guidelines to discuss the diagnosis and treatment of hyponatremia, while also highlighting recent developments. Because of the breadth of both guidelines, this review will focus on the salient features. To place both guidelines in perspective we will integrate in our discussion the pertinent comments published after their release.<sup>10–13</sup>

## DIFFERENTIAL DIAGNOSIS OF HYPONATREMIA

Although the United States guideline did not present a diagnostic algorithm, the classifications of hyponatremia on the basis of tonicity and volume status were discussed.<sup>9</sup> The initial differentiation in hypotonic and nonhypotonic hyponatremia is important, because management is different.<sup>14</sup> Nonhypotonic hyponatremia is usually caused by hyperglycemia, but may also be caused by the administration of mannitol or hypertonic radiocontrast.<sup>7</sup> In these settings, management is usually conservative, although a decrease in extracellular tonicity may occur during treatment.<sup>15</sup> Nonhypotonic hyponatremia can also be caused by pseudohyponatremia, a laboratory artifact that may occur with high concentrations of triglycerides, cholesterol,

or protein.<sup>16</sup> The United States guideline subsequently divided hypotonic hyponatremia into hypovolemic, euvolemic, and hypervolemic hyponatremia.<sup>9</sup> Although this represents the most traditional and commonly used approach to hypotonic hyponatremia, it deserves scrutiny. Hypovolemic and euvolemic hyponatremia are notoriously difficult to differentiate on the basis of physical examination,<sup>17</sup> whereas hypervolemic hyponatremia is usually clinically obvious (presence of edema or ascites). Two studies that analyzed the diagnostic performance of the clinical assessment of volume status in patients with hyponatremia reported low sensitivity (50%–80%) and specificity (30%–50%).<sup>18,19</sup> Previously, we showed that clinicians often misclassify hyponatremia when using algorithms that start with clinical assessment of volume status.<sup>20</sup> Similarly, physicians in training had a better diagnostic performance than senior physicians when using an algorithm in which urine osmolality ( $U_{Osm}$ ) and urine sodium ( $U_{Na}$ ) concentration are prioritized over assessment of volume status.<sup>21</sup> Because the kidneys will respond to hypovolemia or a low effective arterial blood volume with sodium retention,  $U_{Na} < 30$  mmol/L can be used to identify both hypovolemic and hypervolemic hyponatremia. Three caveats, however, should be emphasized: (1)  $U_{Na}$  will also be low in patients consuming a low sodium diet (rare in the western populations), (2) the (recent) use of diuretics will increase  $U_{Na}$ , and (3) patients with CKD may be

less able to reabsorb sodium.<sup>7,22</sup> In addition, advanced CKD usually impairs water excretion, complicating the evaluation of the role of vasopressin in water balance.<sup>23</sup> These considerations prompted the European guideline committee to propose an algorithm that prioritizes  $U_{Osm}$  and  $U_{Na}$  over volume status (Figure 1). It also incorporates the limitations of  $U_{Na}$ . In addition, it recommends early identification of acute or symptomatic hyponatremia to identify patients in whom immediate treatment is indicated. Two additional diagnostic tests for hyponatremia merit discussion, including a trial of volume expansion and the fractional uric acid excretion ( $FE_{UA}$ ). A trial of volume expansion with isotonic saline can be used to diagnose hypovolemic hyponatremia.<sup>18</sup> Although a rise in  $S_{Na}$  in response to isotonic saline would be consistent with hypovolemic hyponatremia, another possibility would be that the stimulus for vasopressin release in a patient with SIAD abated. Such stimuli are often nonspecific and transient, including pain or nausea.<sup>14,24</sup> In addition,  $S_{Na}$  has been shown to improve upon saline infusion in patients with SIAD with  $U_{Osm} < 500$  mOsm/kg.<sup>25</sup> Conversely, isotonic saline may sometimes worsen hyponatremia, a phenomenon called “desalination.”<sup>26</sup> In response to the United States guideline, Gross raised the issue of how to deal with mixed forms of hyponatremia, for example SIAD and hypovolemia.<sup>10</sup> Indeed, we previously showed that patients often have two to three possible causes for



**Figure 1.** Diagnostic algorithm for hyponatremia. Based on the European guideline.<sup>7</sup> ECF, extracellular fluid.

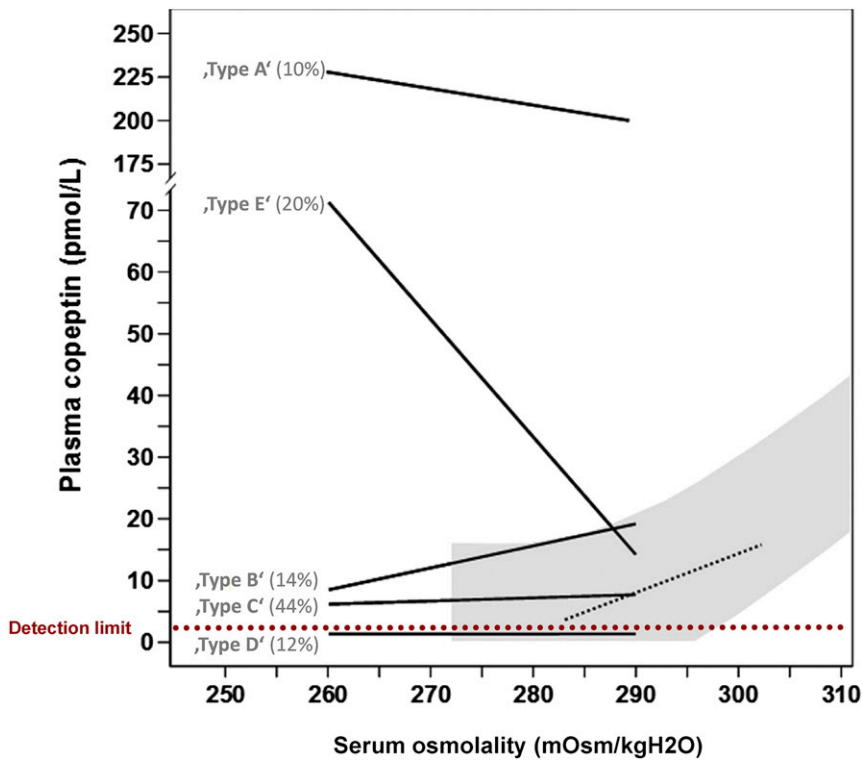
hyponatremia (although it was unclear if and to which extent each cause contributed).<sup>27</sup> In addition to a trial of volume repletion, an alternative approach to mixed pathogenesis would be to combine hypertonic saline with desmopressin.<sup>28,29</sup> Although the literature on this approach is limited, it offers a rational approach to prevent a rapid rise in  $S_{Na}$  that may occur once hypovolemia has been corrected. Fenske *et al.* found that  $FE_{UA} > 12\%$  had the highest sensitivity and specificity to diagnose SIAD with or without diuretic use.<sup>30</sup> This study is

of interest because it formally tested the diagnostic performance of several parameters using receiver operating curves. More recently, a larger study confirmed that  $FE_{UA} > 12\%$  had the best sensitivity and specificity for SIAD.<sup>31</sup> In absolute terms, however, the performance of  $FE_{UA}$  was still moderate, and  $U_{Na} > 30$  mmol/L and  $FE_{Urea} > 55\%$  had better sensitivity and specificity for SIAD, respectively. We frequently analyze  $FE_{UA}$  in patients with hyponatremia, but mainly use it as supporting information.  $FE_{UA}$  is high in both SIAD and

cerebral salt wasting, but normalizes in SIAD only during treatment.<sup>32</sup> Of note, however, is that even in neurosurgical patients with hyponatremia, cerebral salt wasting is rare and has remained an enigmatic and not widely accepted clinical entity.<sup>33,34</sup>

**VASOPRESSIN**

Arginine vasopressin (the antidiuretic hormone) plays a central role in the pathogenesis of hyponatremia. In one study, nonosmotic secretion of vasopressin was detected in 97% of patients with hyponatremia.<sup>35</sup> Because hypotonicity normally suppresses vasopressin, the reasons for nonosmotic vasopressin release should be considered.<sup>36</sup> “Appropriate” vasopressin release is due to hypovolemia or low effective arterial blood volume, both of which activate baroreceptors to cause vasopressin release. Although one might expect thiazide-induced hyponatremia to be due to hypovolemia secondary to saluresis, this is not the case.<sup>37</sup> Instead, the pathogenesis appears to be a combination of polydipsia and impaired urea-mediated water excretion.<sup>37,38</sup> “Inappropriate” vasopressin release is usually caused by the effect of an underlying disease or drugs on central osmoreceptors; alternatively, vasopressin can be produced ectopically (e.g., in small cell lung cancer or olfactory neuroblastoma).<sup>3,39,40</sup> In addition, hypocortisolism increases vasopressin release, because corticotropin-releasing hormone normally suppresses vasopressin.<sup>41</sup> Although rare, secondary and even primary adrenal insufficiency may mimic SIAD and can be missed without appropriate testing.<sup>42–44</sup> Although the kidney usually limits the degree of hyponatremia in SIAD (“vasopressin escape”<sup>45</sup>), it can also cause antidiuresis independent of vasopressin.<sup>46,47</sup> A specific example is gain-of-function mutations of the vasopressin type 2 receptor causing hereditary hyponatremia (“nephrogenic SIAD”).<sup>48</sup> Despite the pathogenetic role of vasopressin in hyponatremia, plasma vasopressin is rarely measured in clinical practice. This has



**Figure 2.** Copeptin-based classification of five subtypes of the syndrome of inappropriate antidiuresis (SIAD). The shaded gray area and the black dashed line show the normal physiologic relationship between serum osmolality and plasma copeptin (as surrogate marker for vasopressin). In SIAD type B this relationship is intact, but the osmotic threshold for vasopressin release has decreased. In SIAD types A and C vasopressin release is no longer regulated by serum osmolality. In SIAD type D plasma copeptin levels are undetectable. In SIAD type E the normal relationship between serum osmolality and copeptin has reversed. This phenomenon has been coined “barostat reset,” as it may indicate increased sensitivity of baroreceptors to increased vasopressin release. Percentages indicate how often each subtype was present in one study of 50 patients. Data on the basis of Fenske *et al.*<sup>55</sup> and figure modified from Fenske *et al.*<sup>116</sup> with permission.

two reasons. First,  $U_{Osm}$  accurately reflects vasopressin activity, and, therefore, this more readily available parameter can be used instead. Second, vasopressin is difficult to measure reliably in nonexpert laboratories, because it binds to platelets, it is unstable in isolated plasma, and commercial assays are not very sensitive for low concentrations.<sup>49</sup> These limitations, however, have largely been resolved by the development of an assay for copeptin.<sup>50</sup>

## COPEPTIN

Enzymatic cleavage of the vasopressin prohormone produces not only vaso-

pressin, but also neurophysin and copeptin (also called C-terminal proarginine vasopressin).<sup>51</sup> Because copeptin is more stable, it can be measured more easily. Copeptin can therefore be used as a surrogate marker for vasopressin. Although both guidelines only briefly discuss copeptin, emerging data justify a brief discussion on the diagnostic utility of this novel marker. Fenske *et al.* found that plasma copeptin levels were higher in patients with hypo- or hypervolemic hyponatremia than in patients with SIAD.<sup>52</sup> This was demonstrated previously<sup>35</sup> and likely reflects an “osmoreceptor gain,” the phenomenon in which angiotensin II amplifies vasopressin release in the context of a

low effective arterial blood volume.<sup>53,54</sup> Because hypovolemic hyponatremia is characterized by high plasma copeptin and low  $U_{Na}$ , the plasma copeptin to  $U_{Na}$  ratio may be especially useful to differentiate it from SIAD. Although the study by Fenske *et al.* did indeed demonstrate this,<sup>52</sup> the specificity of copeptin/ $U_{Na}$  for SIAD in a more recent and larger study was less high.<sup>31</sup> An interesting approach was the use of plasma copeptin to differentiate SIAD subtypes.<sup>55</sup> Using hypertonic saline, SIAD subtypes were defined on the basis of their relationship between serum osmolality and plasma copeptin (Figure 2). As expected, low plasma copeptin levels are diagnostic for hyponatremia due to polydipsia.<sup>31,52</sup> Arguably, the need for a novel diagnostic marker for this cause of hyponatremia is limited, as it is usually obvious from the clinical setting and the low  $U_{Osm}$ . In addition to plasma copeptin, two additional circulating markers were recently evaluated in patients with hyponatremia, including apelin and midregional proatrial natriuretic peptide (MR-proANP).<sup>56,57</sup> Physiologically, apelin and vasopressin are regulated in opposite directions by volemic and osmotic stimuli.<sup>56</sup> Apelin not only inhibits vasopressin release centrally, but also counteracts the antidiuretic effect in the kidney.<sup>58</sup> However, in patients with hyponatremia due to SIAD or heart failure, plasma apelin was insufficiently suppressed, possibly contributing to antidiuresis in these settings.<sup>56</sup> Similar to plasma copeptin, MR-proANP levels were higher in patients with hypovolemic or hypervolemic hyponatremia than in patients with SIAD (although these levels were still higher than in healthy subjects).<sup>57</sup> High MR-proANP in hypovolemic hyponatremia is counterintuitive, but may be explained by lower GFR secondary to volume depletion.<sup>59</sup> Although plasma copeptin, apelin, and MR-proANP increase insight into the pathophysiology of hyponatremia, the true diagnostic potential of these parameters remains to be determined. In addition, one single parameter is unlikely to achieve optimal

**Table 2.** Comparison of the United States and European guidelines

Subject	United States Guideline	European Guideline
Acute or symptomatic hyponatremia	Severe symptoms: Bolus 3% NaCl (100 ml over 10 min × 3 as needed)  Moderate symptoms: Continuous infusion 3% NaCl (0.5–2 ml/kg per h)	Severe symptoms: Bolus 3% NaCl (150 ml over 20 min 2–3 times as needed)  Moderate symptoms: Bolus 3% NaCl (150 ml 3% over 20 min once)
Chronic hyponatremia SIAD	Fluid restriction (first line) Demeclocycline, urea, or vaptan (second line)	Fluid restriction (first line) Urea or loop diuretics + oral NaCl (second line) Do not recommend or recommend against vaptan <sup>a</sup> Recommend against lithium or demeclocycline
Hypovolemic hyponatremia	Isotonic saline	Isotonic saline or balanced crystalloid solution
Hypervolemic hyponatremia	Fluid restriction Vaptans <sup>b</sup>	Fluid restriction Recommend against vaptan
Correction rates	Minimum: 4–8 mmol/L per d, 4–6 mmol/L per d (high risk of ODS) Limits: 10–12 mmol/L per d, 8 mmol/L per d (high risk of ODS)	No minimum  Limit: 10 mmol/L per d
Management of overcorrection	Baseline $S_{Na} \geq 120$ mmol/L: probably unnecessary Baseline $S_{Na} < 120$ mmol/L: start relowering with electrolyte-free water or desmopressin after correction exceeds 6–8 mmol/L per d	Start once limit is exceeded  Consult an expert to discuss infusion containing electrolyte-free water (10 ml/kg) with or without 2 $\mu$ g desmopressin iv

<sup>a</sup>“Do not recommend” when  $S_{Na} < 130$  mmol/L, “recommend against” when  $S_{Na} < 125$  mmol/L.

<sup>b</sup>In liver cirrhosis, restrict to patients where potential benefit outweighs risk of worsened liver function.<sup>9</sup>

discriminatory power. A relevant question is whether a combination of diagnostic parameters might improve management.

## GENERAL APPROACH TO TREATMENT

A cutoff of 48 hours is usually used to differentiate acute from chronic hyponatremia (Table 1).<sup>7</sup> This classification is useful because acute and chronic hyponatremia may be complicated by different neurologic conditions. Acute hyponatremia can cause cerebral edema when cells have insufficient time to adapt to the hypotonic extracellular environment. In chronic hyponatremia brain cell adaptation has occurred and, in this setting, an acute increase in extracellular tonicity induced by treatment can cause osmotic demyelination syndrome (ODS).<sup>60,61</sup>

Therefore, for each patient with profound hyponatremia ( $S_{Na} < 125$  mmol/L), it is useful to consider whether cerebral edema or ODS should be suspected.<sup>62,63</sup> This automatically leads to the often heated debate on optimal correction rates in hyponatremia.<sup>64</sup> Both guidelines reached consensus that the limit (not the goal) should be around 10 mmol/L per day for both acute and chronic hyponatremia (Table 2).<sup>7,9</sup> Of note, the United States guideline recommends a lower limit of 8 mmol/L per day if there is a high risk of ODS (e.g., in patients with hypokalemia, alcoholism, malnutrition, or liver disease).<sup>9</sup> In response to these recommendations, Adrogué and Madias proposed even more conservative limits of 6–8 mmol/L per day regardless of duration or symptoms.<sup>11</sup> Although we agree that this is likely to be both sufficient and safe, the data to support this are still limited. It is of interest to see how over the years the recommended correction rates

have gradually become more conservative (with recommended correction rates as high as 20 mmol/L per day around 1990).<sup>65</sup> A subject directly related to correction rates is overcorrection. Both guidelines recommend frequent monitoring of  $S_{Na}$  during the active correction phase (i.e., all treatments except fluid restriction). An aspect that was overlooked by both guidelines is that the measurement of  $S_{Na}$  may not offer the precision required for this monitoring. Tormey *et al.* calculated the so-called “reference change value” for  $S_{Na}$  using a common analyzer and demonstrated that only changes in  $S_{Na} \geq 4$  mmol/L were certain to be real.<sup>12</sup> If overcorrection is detected, both guidelines used different criteria for when to relower  $S_{Na}$ : when initial  $S_{Na}$  was  $< 120$  mmol/L (United States guideline) or when limits are exceeded (European guideline, Table 2). Both guidelines recommend hypotonic fluids or desmopressin for relowering  $S_{Na}$ . A combination of

hypotonic fluids and desmopressin may be required for treating overcorrection in hypovolemic hyponatremia, because a persistent water diuresis may ensue after correction of hypovolemia.<sup>66</sup> Experimental data indicate improved outcomes with reinduction of hyponatremia after rapid overcorrection.<sup>67</sup> Another point that merits discussion is the consistent association of hyponatremia with worse outcomes.<sup>63,68</sup> This may indicate that hyponatremia has adverse effects beyond the classic neurologic symptoms.<sup>69,70</sup> However, in the absence of randomized intervention studies indicating that correction of hyponatremia improves outcomes, it remains unclear whether these associations are causal.<sup>5</sup>

### TREATMENT OF ACUTE HYPONATREMIA

Several settings predispose to acute hyponatremia, especially if combined with increased free water intake.<sup>71</sup> Among others, these include the postoperative period, exercise, and the use of 3,4-methylenedioxymethamphetamine (“Ecstasy”), haloperidol, thiazide diuretics, desmopressin, oxytocin, or intravenous cyclophosphamide.<sup>71–74</sup> A specific situation is the use of irrigants (glycine, sorbitol, mannitol) during transurethral or hysteroscopic procedures. Although absorption of the irrigants glycine and sorbitol may cause hypotonic hyponatremia, the degree of hypotonicity and therefore the risk of cerebral edema depends on the type of irrigant and the time course in osmolar shifts.<sup>75,76</sup> In contrast, mannitol causes hypertonic hyponatremia without a risk for cerebral edema. In daily practice, the distinction between acute and chronic hyponatremia is difficult, because the time in which hyponatremia developed is usually unknown. The United States and European guidelines approached this challenge differently. The United States guideline adhered to acute versus chronic hyponatremia, but did subdivide acute hyponatremia on the basis of the presence of severe or

mild-to-moderate symptoms (Table 2).<sup>9</sup> The European guideline based its recommendations primarily on the presence and severity of symptoms rather than on duration.<sup>7</sup> Both guidelines recommend hypertonic saline (typically 3% NaCl) for acute or symptomatic hyponatremia.<sup>7,9</sup> Hypertonic saline is an effective and potentially life-saving treatment for cerebral edema due to hyponatremia, as the high extracellular sodium concentration immediately removes water from the intracellular space. In patients with hypervolemic hyponatremia, hypertonic saline may be combined with loop diuretics.<sup>9</sup> The required volume of hypertonic saline to reach a predefined increase in  $S_{Na}$  can be estimated using the Adrogé–Madias or Barsoum–Levine formulae.<sup>77,78</sup> Although predictions with these formulae are fairly accurate,<sup>66</sup> a switch toward giving hypertonic saline as fixed bolus has occurred in recent years.<sup>79</sup> No studies have systematically tested this approach, but there are a number of appealing aspects. First, especially in patients with cerebral edema, it is desirable to achieve a rapid partial correction in  $S_{Na}$ . Second, a fixed bolus omits the need for calculations in a patient with an acute problem, limiting potential calculation errors. Third, bolus therapy limits the risk of overcorrection, which does occur commonly with a continuous infusion of hypertonic saline.<sup>80</sup> On the basis of these considerations, both guidelines recommend bolus therapy, albeit with slightly different specifications (Table 2).<sup>7,9</sup> Recently, Ayus and colleagues reported their experience using a different protocol (500 ml 3% NaCl over 6 hours) in 64 patients with hyponatremic encephalopathy ( $S_{Na} < 130$  mmol/L and neurologic symptoms).<sup>81</sup> On average, this protocol increased  $S_{Na}$  with 12 and 14 mmol/L in the first 24–48 hours, and improved symptoms without evidence of ODS.<sup>81</sup> However, the severity of hyponatremia ( $S_{Na}$  frequently  $< 110$  mmol/L) and the duration of symptoms suggest that some of these patients had chronic hyponatremia. If so, these correction rates would exceed currently recommended limits (Table 2).

### TREATMENT OF CHRONIC HYPONATREMIA

Except for hypovolemic hyponatremia, the treatment of chronic hyponatremia relies on reducing free water intake and/or increasing renal free water excretion (Table 2). Fluid restriction ( $< 1$  L/d) is often the cornerstone of the therapy for chronic hyponatremia.<sup>24</sup> The urine to serum electrolyte ratio ( $[U_{Na} + \text{urine potassium concentration}] / S_{Na}$ ) indicates if the patient is in an antidiuretic or aquaretic phase, and can also help estimate the degree of fluid restriction required to increase  $S_{Na}$ .<sup>3,11,24,82</sup> For patients with a ratio  $> 1$  (indicating concentrated urine),  $< 500$  ml fluid/d is recommended, which is difficult to adhere to. Winzeler *et al.* recently showed that in patients with SIAD fluid restriction is effective in 59% of patients.<sup>83</sup> Predictors of nonresponse were a  $U_{Na} \geq 130$  mmol/L and  $U_{Osm} \geq 500$  mOsm/kg.<sup>83</sup> This implies that in patients with chronic hyponatremia pharmacologic therapy is often required to increase renal free water excretion. This can be achieved by treatment with loop diuretics, urea, vasopressin receptor antagonists (“vaptans”), or demeclocycline. The two guidelines diverge in their recommendations regarding pharmacologic therapy for SIAD and hypervolemic hyponatremia (Table 2). This was the case especially for vaptans, which will therefore be discussed in more detail below.

#### Vaptans

Vaptans block vasopressin type 2 receptors in collecting duct principal cells and therefore induce aquaresis (for comprehensive review, see Berl,<sup>84</sup> Hoorn and Zietse,<sup>85</sup> Leirich *et al.*,<sup>86</sup> Rozen-Zvi *et al.*,<sup>87</sup> and Greenberg and Verbalis<sup>88</sup>). Several vaptans were developed, including tolvaptan, satavaptan, lixivaptan, and conivaptan (which also targets vasopressin type 1a receptors). On the basis of their mechanism of action, vaptans are a logical and targeted therapy for hyponatremic patients with excess vasopressin. Indeed, several large clinical trials have shown that vaptans are clearly effective in increasing  $S_{Na}$  in patients with

hyponatremia due to SIAD, heart failure, or liver cirrhosis.<sup>89,90</sup> Both guidelines agree that there is no place for vaptans in patients with acute or severely symptomatic hyponatremia, for which hypertonic saline is the treatment of choice.<sup>7,9</sup> Still, it has been difficult to position vaptans in the therapeutic arsenal of chronic hyponatremia.<sup>11,84,91,92</sup> The United States guideline lists vaptans as one of the pharmacologic options, if fluid restriction has failed (Table 2).<sup>9</sup> The European guideline did not recommend vaptans in moderate hyponatremia.<sup>7</sup> The reason to do so was the absence of evidence for improved hard outcomes with correction of  $S_{Na}$ . Meanwhile, one meta-analysis has suggested improved survival with correction of hyponatremia,<sup>93</sup> although bias is difficult to exclude because no randomized controlled trials are available. Furthermore, there is evidence for potential harm of vaptans, including overcorrection, and liver toxicity.<sup>7,87,94–96</sup> Because ODS has mainly been reported after overcorrection of profound hyponatremia, the European guideline recommended against vaptans in this setting.<sup>7</sup> Recently, Tzoulis *et al.* reported “real-life experience” with tolvaptan in 61 patients with resistant hyponatremia due to SIAD.<sup>97</sup> The average rise in  $S_{Na}$  after 24 hours was  $9.0 \pm 3.9$  mmol/L. Excessive correction of hyponatremia ( $>12$  mmol/L per day) was observed in 23% of patients (all with profound hyponatremia), although none of them developed signs of ODS.<sup>97</sup> ODS was reported in one patient with heart failure in whom 15 mg tolvaptan caused  $S_{Na}$  to increase from 126 to 142 mmol/L in the first day and to further increase to 187 mmol/L in subsequent days.<sup>94</sup> On the other hand, improvement of symptoms has been shown with the use of vaptans. This includes improvements in some neurocognitive symptoms,<sup>98</sup> performance status in cancer patients,<sup>99</sup> dyspnea in patients with heart failure,<sup>100</sup> and ascites in patients with liver cirrhosis.<sup>101</sup> Therefore, in our view, an unresolved question with regard to the use of vaptans remains, of whether symptomatic improvement outweighs the risk of overcorrection, even if ODS is rare.

## Urea

Both guidelines suggest an interesting alternative to vaptans for chronic hyponatremia due to SIAD, namely urea.<sup>102</sup> Urea induces an osmotic diuresis, thereby increasing renal free water excretion. Decaux and colleagues pioneered the use of urea in the 1980s for SIAD, but also for other forms of hyponatremia.<sup>103–109</sup> More recently, in 12 patients with SIAD, Soupart *et al.* compared the treatment with satavaptan to urea (both treatment periods 1 year).<sup>110</sup> Interestingly, both therapies had a similar efficacy and side-effect profile. Although urea does not prevent overcorrection, it may reduce the risk of the associated brain damage. In a rat model of experimental SIAD, Gankam Kenge *et al.* compared the neurologic outcomes after overcorrection (approximately 30 mmol/L per day) with hypertonic saline, lixivaptan, or urea.<sup>111</sup> Quite strikingly, neurologic scores and survival were better in the animals treated with urea. Histologic analysis showed that, in comparison to the two other treatments, urea reduced demyelination, microglial activation, and changes in the blood-brain barrier, and increased astrocyte viability.<sup>111</sup> Although one should be careful to extrapolate these findings to humans, this may explain why patients with ESRD and hyponatremia do not develop ODS after treatment with hemodialysis.<sup>112</sup> One specific disadvantage of urea used to be its palatability. This problem has been solved by developing a formulation in which urea is combined with sodium bicarbonate, citric acid, and sucrose (see European guideline for prescription<sup>7</sup>) and by the development of a commercially available urea powder drink mix (Ure-Na by Nephcentric).

## SUMMARY AND CONCLUSIONS

Our impression is that the development of the United States and European guidelines has helped to standardize and improve the management of hyponatremia. The two guidelines are more often in agreement than in disagreement. The discrepancies are likely related to the interpretation of the limited evidence and the methodology used to draft the guidelines.<sup>113</sup> Nagler *et al.*

evaluated all available international guidelines on hyponatremia and analyzed how well they met the Appraisal of Guidelines for Research and Evaluation criteria.<sup>114</sup> They identified considerable variation in methodologic rigor in the development of guidelines, potentially explaining inconsistencies in recommendations.<sup>114</sup> Because hyponatremia is a heterogeneous disorder rather than a clear-cut disease, not all patients can be covered by guidelines. That said, which evidence does the field need for the coming years? First, it would be useful to evaluate if a combination of the traditional and newer diagnostic tests would improve not only diagnosis but also outcomes. Second, the approach of giving a bolus of hypertonic saline should be studied to address the optimal volume, whether this should be on the basis of (ideal) body weight, and how often it should be repeated to reach the desired increase in  $S_{Na}$ .<sup>115</sup> Third, the role of vaptans in the treatment of chronic hyponatremia remains a logical focus. For example, it would be important to analyze whether the copeptin-based subtypes of SIAD respond differently to vaptans (Figure 2). Finally, studies analyzing the effect of a vaptan in comparison with another active treatment (rather than placebo) on patient-relevant outcomes (rather than  $S_{Na}$ ) are warranted.

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## DISCLOSURES

None.

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