

# 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.

*J Am Soc Nephrol* 28: 1340–1349, 2017. doi: <https://doi.org/10.1681/ASN.2016101139>

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

Published online ahead of print. Publication date available at [www.jasn.org](http://www.jasn.org).

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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>

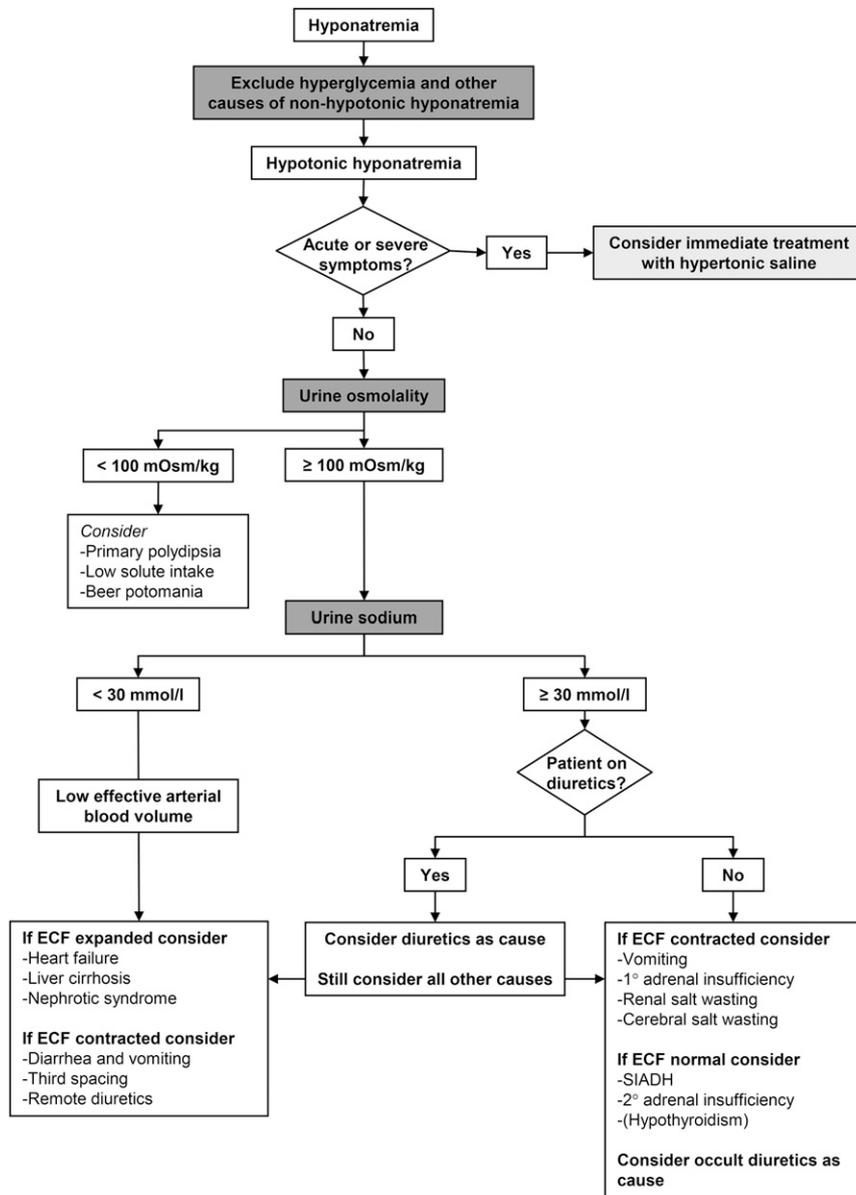
Recommendations Assessment Development and Evaluation scoring system. Both guideline committees were interdisciplinary, and the European guideline was endorsed by the European societies of nephrology, endocrinology, and intensive care.<sup>6–8</sup> This brief review will compare the two guidelines to 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.

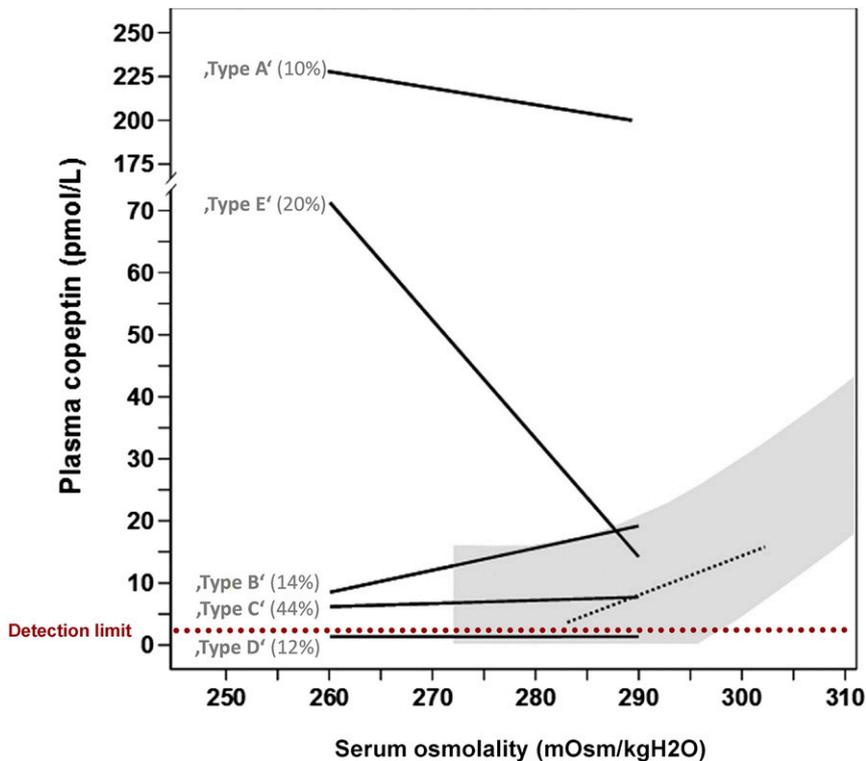
hyponatremia (although it was unclear if and to which extent each cause contributed).<sup>27</sup> In addition to a trial of volume repletion, an alternative approach to mixed pathogenesis would be to combine hypertonic saline with desmopressin.<sup>28,29</sup> Although the literature on this approach 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.

## ACKNOWLEDGMENTS

E.J.H. is supported by the Dutch Kidney Foundation (KSP-14OK19).

## DISCLOSURES

None.

## REFERENCES

1. Adrogué HJ, Madias NE: The challenge of hyponatremia. *J Am Soc Nephrol* 23: 1140–1148, 2012
2. Greenberg A, Verbalis JG, Amin AN, Burst VR, Chiodo JA 3rd, Chiong JR, Dasta JF, Friend KE, Hauptman PJ, Peri A, Sigal SH: Current treatment practice and outcomes. Report of the hyponatremia registry. *Kidney Int* 88: 167–177, 2015

3. Sterns RH: Disorders of plasma sodium—causes, consequences, and correction. *N Engl J Med* 372: 55–65, 2015
4. Winzeler B, Jeanloz N, Nigro N, Suter-Widmer I, Schuetz P, Arici B, Bally M, Blum C, Bock A, Huber A, Mueller B, Christ-Crain M: Long-term outcome of profound hyponatremia: A prospective 12 months follow-up study. *Eur J Endocrinol* 175: 499–507, 2016
5. Chawla A, Sterns RH, Nigwekar SU, Cappuccio JD: Mortality and serum sodium: Do patients die from or with hyponatremia? *Clin J Am Soc Nephrol* 6: 960–965, 2011
6. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E; Hyponatraemia Guideline Development Group: Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol* 170: G1–G47, 2014
7. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E; Hyponatraemia Guideline Development Group: Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant* 29[Suppl 2]: 11–i39, 2014
8. Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E: Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Intensive Care Med* 40: 320–331, 2014
9. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ: Diagnosis, evaluation, and treatment of hyponatremia: Expert panel recommendations. *Am J Med* 126[Suppl 1]: S1–S42, 2013
10. Gross P: Panel recommendations on hyponatremia. *Am J Med* 127: e29, 2014
11. Adrogué HJ, Madias NE: Diagnosis and treatment of hyponatremia. *Am J Kidney Dis* 64: 681–684, 2014
12. Tormey WP, Carney M, Cuesta M, Sreenan S: Reference change values for sodium are ignored by the American and European treatment guidelines for hyponatremia. *Clin Chem* 61: 1430–1432, 2015
13. Avila M: The clinical practice guideline on diagnosis and treatment of hyponatraemia: A response from Otsuka Pharmaceutical Europe Ltd. *Eur J Endocrinol* 171: L1–L3, 2014
14. Cohen DM, Ellison DH: Evaluating hyponatremia. *JAMA* 313: 1260–1261, 2015
15. Hoorn EJ, Carlotti AP, Costa LA, MacMahon B, Bohn G, Zietse R, Halperin ML, Bohn D: Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. *J Pediatr* 150: 467–473, 2007
16. Turchin A, Seifter JL, Seely EW: Clinical problem-solving. Mind the gap. *N Engl J Med* 349: 1465–1469, 2003
17. McGee S, Abernethy WB 3rd, Simel DL: The rational clinical examination. Is this patient hypovolemic? *JAMA* 281: 1022–1029, 1999
18. Musch W, Thimpoint J, Vandervelde D, Verhaeverbeke I, Berghmans T, Decaux G: Combined fractional excretion of sodium and urea better predicts response to saline in hyponatremia than do usual clinical and biochemical parameters. *Am J Med* 99: 348–355, 1995
19. Chung HM, Kluge R, Schrier RW, Anderson RJ: Clinical assessment of extracellular fluid volume in hyponatremia. *Am J Med* 83: 905–908, 1987
20. Hoorn EJ, Halperin ML, Zietse R: Diagnostic approach to a patient with hyponatraemia: Traditional versus physiology-based options. *QJM* 98: 529–540, 2005
21. Fenske W, Maier SK, Blechschmidt A, Allolio B, Störk S: Utility and limitations of the traditional diagnostic approach to hyponatremia: A diagnostic study. *Am J Med* 123: 652–657, 2010
22. Hoorn EJ, Hotho D, Hassing RJ, Zietse R: Unexplained hyponatremia: Seek and you will find. *Nephron, Physiol* 118: 66–71, 2011
23. Roussel R, Fezeu L, Marre M, Velho G, Fumeron F, Jungers P, Lantieri O, Balkau B, Bouby N, Bankir L, Bichet DG: Comparison between copeptin and vasopressin in a population from the community and in people with chronic kidney disease. *J Clin Endocrinol Metab* 99: 4656–4663, 2014
24. Ellison DH, Berl T: Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 356: 2064–2072, 2007
25. Musch W, Decaux G: Treating the syndrome of inappropriate ADH secretion with isotonic saline. *QJM* 91: 749–753, 1998
26. Steele A, Gowrishankar M, Abrahamson S, Mazer CD, Feldman RD, Halperin ML: Postoperative hyponatremia despite near-isotonic saline infusion: A phenomenon of desalination. *Ann Intern Med* 126: 20–25, 1997
27. Hoorn EJ, Lindemans J, Zietse R: Development of severe hyponatraemia in hospitalized patients: Treatment-related risk factors and inadequate management. *Nephrol Dial Transplant* 21: 70–76, 2006
28. Sood L, Sterns RH, Hix JK, Silver SM, Chen L: Hypertonic saline and desmopressin: A simple strategy for safe correction of severe hyponatremia. *Am J Kidney Dis* 61: 571–578, 2013
29. Perianayagam A, Sterns RH, Silver SM, Grieff M, Mayo R, Hix J, Kouides R: DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. *Clin J Am Soc Nephrol* 3: 331–336, 2008
30. Fenske W, Störk S, Koschker AC, Blechschmidt A, Lorenz D, Wortmann S, Allolio B: Value of fractional uric acid excretion in differential diagnosis of hyponatremic patients on diuretics. *J Clin Endocrinol Metab* 93: 2991–2997, 2008
31. Nigro N, Winzeler B, Suter-Widmer I, Schuetz P, Arici B, Bally M, Blum CA, Nickel CH, Bingisser R, Bock A, Huber A, Müller B, Christ-Crain M: Evaluation of copeptin and commonly used laboratory parameters for the differential diagnosis of profound hyponatraemia in hospitalized patients: ‘The Co-MED Study’ [published online ahead of print September 22, 2016]. *Clin Endocrinol (Oxf)* 10.1111/cen.13243
32. Maesaka JK, Imbriano LJ, Ali NM, Ilamathi E: Is it cerebral or renal salt wasting? *Kidney Int* 76: 934–938, 2009
33. Sherlock M, O’Sullivan E, Agha A, Behan LA, Owens D, Finucane F, Rawluk D, Tormey W, Thompson CJ: Incidence and pathophysiology of severe hyponatraemia in neurosurgical patients. *Postgrad Med J* 85: 171–175, 2009
34. Singh S, Bohn D, Carlotti AP, Cusimano M, Rutka JT, Halperin ML: Cerebral salt wasting: Truths, fallacies, theories, and challenges. *Crit Care Med* 30: 2575–2579, 2002
35. Anderson RJ, Chung HM, Kluge R, Schrier RW: Hyponatremia: A prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med* 102: 164–168, 1985
36. Hoorn EJ, Zietse R: Hyponatremia revisited: Translating physiology to practice. *Nephron, Physiol* 108: 46–59, 2008
37. Friedman E, Shadel M, Halkin H, Farfel Z: Thiazide-induced hyponatremia. Reproducibility by single dose rechallenge and an analysis of pathogenesis. *Ann Intern Med* 110: 24–30, 1989
38. Frenkel NJ, Vogt L, De Rooij SE, Trimpert C, Levi MM, Deen PM, van den Born BJ: Thiazide-induced hyponatraemia is associated with increased water intake and impaired urea-mediated water excretion at low plasma antidiuretic hormone and urine aquaporin-2. *J Hypertens* 33: 627–633, 2015
39. Robertson GL: Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. *Am J Med* 119[Suppl 1]: S36–S42, 2006
40. Hoorn EJ, Monserez DA, Fenton RA, Overvest I, Apperloo AJ, Zietse R, Hardillo JA: Olfactory neuroblastoma with hyponatremia. *J Clin Oncol* 33: e88–e92, 2015
41. Yamada K, Tamura Y, Yoshida S: Effect of administration of corticotropin-releasing hormone and glucocorticoid on arginine vasopressin response to osmotic stimulus in

- normal subjects and patients with hypocorticotropinism without overt diabetes insipidus. *J Clin Endocrinol Metab* 69: 396–401, 1989
42. Cuesta M, Garrahy A, Slattery D, Gupta S, Hannon AM, Forde H, McGurken K, Sherlock M, Tormey W, Thompson CJ: The contribution of undiagnosed adrenal insufficiency to euvoalaemic hyponatraemia: Results of a large prospective single-centre study. *Clin Endocrinol (Oxf)* 85: 836–844, 2016
  43. Smith JC, Siddique H, Corral RJ: Misinterpretation of serum cortisol in a patient with hyponatraemia. *BMJ* 328: 215–216, 2004
  44. van der Hoek J, Hoorn EJ, de Jong GM, Janssens EN, de Herder WW: Severe hyponatremia with high urine sodium and osmolality. *Clin Chem* 55: 1905–1908, 2009
  45. Ecelbarger CA, Nielsen S, Olson BR, Murase T, Baker EA, Knepper MA, Verbalis JG: Role of renal aquaporins in escape from vasopressin-induced antidiuresis in rat. *J Clin Invest* 99: 1852–1863, 1997
  46. de Bragança AC, Moyses ZP, Magaldi AJ: Carbamazepine can induce kidney water absorption by increasing aquaporin 2 expression. *Nephrol Dial Transplant* 25: 3840–3845, 2010
  47. Moyses ZP, Nakandakari FK, Magaldi AJ: Fluoxetine effect on kidney water reabsorption. *Nephrol Dial Transplant* 23: 1173–1178, 2008
  48. Feldman BJ, Rosenthal SM, Vargas GA, Fenwick RG, Huang EA, Matsuda-Abdini M, Lustig RH, Mathias RS, Portale AA, Miller WL, Gitelman SE: Nephrogenic syndrome of inappropriate antidiuresis. *N Engl J Med* 352: 1884–1890, 2005
  49. Moses AM, Clayton B: Impairment of osmotically stimulated AVP release in patients with primary polydipsia. *Am J Physiol* 265: R1247–R1252, 1993
  50. Morgenthaler NG, Struck J, Alonso C, Bergmann A: Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. *Clin Chem* 52: 112–119, 2006
  51. Christ-Crain M, Fenske W: Copeptin in the diagnosis of vasopressin-dependent disorders of fluid homeostasis. *Nat Rev Endocrinol* 12: 168–176, 2016
  52. Fenske W, Störk S, Blechschmidt A, Maier SG, Morgenthaler NG, Allolio B: Copeptin in the differential diagnosis of hyponatremia. *J Clin Endocrinol Metab* 94: 123–129, 2009
  53. Robertson GL, Athar S: The interaction of blood osmolality and blood volume in regulating plasma vasopressin in man. *J Clin Endocrinol Metab* 42: 613–620, 1976
  54. Zhang Z, Bourque CW: Amplification of transducer gain by angiotensin II-mediated enhancement of cortical actin density in osmosensory neurons. *J Neurosci* 28: 9536–9544, 2008
  55. Fenske WK, Christ-Crain M, Hörning A, Simet J, Szinnai G, Fassnacht M, Rutishauser J, Bichet DG, Störk S, Allolio B: A copeptin-based classification of the osmoregulatory defects in the syndrome of inappropriate antidiuresis. *J Am Soc Nephrol* 25: 2376–2383, 2014
  56. Blanchard A, Steichen O, De Mota N, Curis E, Gauci C, Frank M, Wuerzner G, Kamenicky P, Passeron A, Azizi M, Llorens-Cortes C: An abnormal apelin/vasopressin balance may contribute to water retention in patients with the syndrome of inappropriate antidiuretic hormone (SIADH) and heart failure. *J Clin Endocrinol Metab* 98: 2084–2089, 2013
  57. Nigro N, Winzler B, Suter-Widmer I, Schuetz P, Arici B, Bally M, Blum CA, Nickel CH, Bingisser R, Bock A, Rentsch Savoca K, Huber A, Müller B, Christ-Crain M: Mid-regional pro-atrial natriuretic peptide and the assessment of voalaemic status and differential diagnosis of profound hyponatraemia. *J Intern Med* 278: 29–37, 2015
  58. Hus-Citharel A, Bodineau L, Frugière A, Joubert F, Bouby N, Llorens-Cortes C: Apelin counteracts vasopressin-induced water reabsorption via cross talk between apelin and vasopressin receptor signaling pathways in the rat collecting duct. *Endocrinology* 155: 4483–4493, 2014
  59. Tzikas S, Keller T, Wild PS, Schulz A, Zwiener I, Zeller T, Schnabel RB, Sinning C, Lubos E, Kunde J, Münzel T, Lackner KJ, Blankenberg S: Midregional pro-atrial natriuretic peptide in the general population/ Insights from the Gutenberg Health Study. *Clin Chem Lab Med* 51: 1125–1133, 2013
  60. Sterns RH, Riggs JE, Schochet Jr. SS: Osmotic demyelination syndrome following correction of hyponatremia. *N Engl J Med* 314: 1535–1542, 1986
  61. Sterns RH, Silver SM: Brain volume regulation in response to hypo-osmolality and its correction. *Am J Med* 119[Suppl 1]: S12–S16, 2006
  62. Berl T: Treating hyponatremia: Damned if we do and damned if we don't. *Kidney Int* 37: 1006–1018, 1990
  63. Hoorn EJ, Zietse R: Hyponatremia and mortality: Moving beyond associations. *Am J Kidney Dis* 62: 139–149, 2013
  64. Berl T: Treating hyponatremia: What is all the controversy about? *Ann Intern Med* 113: 417–419, 1990
  65. Martin RJ: Central pontine and extrapontine myelinolysis: The osmotic demyelination syndromes. *J Neurol Neurosurg Psychiatry* 75[Suppl 3]: iii22–iii28, 2004
  66. Liamis G, Kalogirou M, Saugos V, Elisaf M: Therapeutic approach in patients with dysnatraemias. *Nephrol Dial Transplant* 21: 1564–1569, 2006
  67. Gankam Kengne F, Soupart A, Pochet R, Brion JP, Decaux G: Re-induction of hyponatremia after rapid overcorrection of hyponatremia reduces mortality in rats. *Kidney Int* 76: 614–621, 2009
  68. Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ: Electrolyte disorders in community subjects: Prevalence and risk factors. *Am J Med* 126: 256–263, 2013
  69. Hoorn EJ, Zietse R: Hyponatremia and mortality: How innocent is the bystander? *Clin J Am Soc Nephrol* 6: 951–953, 2011
  70. Schrier RW, Sharma S, Shchekochikhin D: Hyponatraemia: More than just a marker of disease severity? *Nat Rev Nephrol* 9: 37–50, 2013
  71. Hsu YJ, Chiu JS, Lu KC, Chau T, Lin SH: Biochemical and etiological characteristics of acute hyponatremia in the emergency department. *J Emerg Med* 29: 369–374, 2005
  72. Achinger SG, Arief AI, Kalantar-Zadeh K, Ayus JC: Desmopressin acetate (DDAVP)-associated hyponatremia and brain damage: A case series. *Nephrol Dial Transplant* 29: 2310–2315, 2014
  73. Moses AM, Miller M: Drug-induced dilutional hyponatremia. *N Engl J Med* 291: 1234–1239, 1974
  74. Liamis G, Milionis H, Elisaf M: A review of drug-induced hyponatremia. *Am J Kidney Dis* 52: 144–153, 2008
  75. Agarwal R, Emmett M: The post-urethral resection of prostate syndrome: Therapeutic proposals. *Am J Kidney Dis* 24: 108–111, 1994
  76. Ayus JC, Arief AI: Glycine-induced hypo-osmolar hyponatremia. *Arch Intern Med* 157: 223–226, 1997
  77. Adrogue HJ, Madias NE: Hyponatremia. *N Engl J Med* 342: 1581–1589, 2000
  78. Barsoum NR, Levine BS: Current prescriptions for the correction of hyponatraemia and hypernatraemia: Are they too simple? *Nephrol Dial Transplant* 17: 1176–1180, 2002
  79. Moritz ML, Ayus JC: 100 cc 3% sodium chloride bolus: A novel treatment for hyponatremic encephalopathy. *Metab Brain Dis* 25: 91–96, 2010
  80. Mohmand HK, Issa D, Ahmad Z, Cappuccio JD, Kouides RW, Sterns RH: Hypertonic saline for hyponatremia: Risk of inadvertent overcorrection. *Clin J Am Soc Nephrol* 2: 1110–1117, 2007
  81. Ayus JC, Caputo D, Bazerque F, Heguilen R, Gonzalez CD, Moritz ML: Treatment of hyponatremic encephalopathy with a 3% sodium chloride protocol: A case series. *Am J Kidney Dis* 65: 435–442, 2015
  82. Rose BD: New approach to disturbances in the plasma sodium concentration. *Am J Med* 81: 1033–1040, 1986
  83. Winzler B, Lengsfeld S, Nigro N, Suter-Widmer I, Schütz P, Arici B, Bally M, Blum C, Bock A, Huber A, Müller B, Christ-Crain M: Predictors of nonresponse to fluid restriction in hyponatraemia due to the syndrome of

- inappropriate antidiuresis. *J Intern Med* 280: 609–617, 2016
84. Berl T: Vasopressin antagonists. *N Engl J Med* 372: 2207–2216, 2015
  85. Hoom EJ, Zietse R: Vasopressin-receptor antagonists. *Future Cardiol* 6: 523–534, 2010
  86. Leirich RW, Ortiz-Melo DI, Patel MB, Greenberg A: Role of vaptans in the management of hyponatremia. *Am J Kidney Dis* 62: 364–376, 2013
  87. Rozen-Zvi B, Yahav D, Gheorghide M, Korzets A, Leibovici L, Gafer U: Vasopressin receptor antagonists for the treatment of hyponatremia: Systematic review and meta-analysis. *Am J Kidney Dis* 56: 325–337, 2010
  88. Greenberg A, Verbalis JG: Vasopressin receptor antagonists. *Kidney Int* 69: 2124–2130, 2006
  89. Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, Czerwiec FS; SALTWATER Investigators: Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol* 21: 705–712, 2010
  90. Schrier RW, Gross P, Gheorghide M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C; SALT Investigators: Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med* 355: 2099–2112, 2006
  91. Gross PA, Wagner A, Decaux G: Vaptans are not the mainstay of treatment in hyponatremia: Perhaps not yet. *Kidney Int* 80: 594–600, 2011
  92. Borne RT, Krantz MJ: Lixivaptan for hyponatremia—the numbers game. *JAMA* 308: 2345–2346, 2012
  93. Corona G, Giuliani C, Verbalis JG, Forti G, Maggi M, Peri A: Hyponatremia improvement is associated with a reduced risk of mortality: Evidence from a meta-analysis. *PLoS One* 10: e0124105, 2015
  94. Malhotra I, Gopinath S, Janga KC, Greenberg S, Sharma SK, Tarkovsky R: Unpredictable nature of tolvaptan in treatment of hypervolemic hyponatremia: Case review on role of vaptans. *Case Rep Endocrinol* 2014: 807054, 2014
  95. Sarges P, Steinberg JM, Lewis JH: Drug-induced liver injury: Highlights from a review of the 2015 literature. *Drug Saf* 39: 801–821, 2016
  96. Woodhead JL, Brock WJ, Roth SE, Shoaf SE, Brouwer KL, Church R, Grammatopoulos TN, Stiles L, Siler SQ, Howell BA, Mosedale M, Watkins PB, Shoda LK: Application of a mechanistic model to evaluate putative mechanisms of tolvaptan drug-induced liver injury and identify patient susceptibility factors [published online ahead of print September 21, 2016]. *Toxicol Sci* 10.1093/toxsci/kfw193
  97. Tzoulis P, Waung JA, Bagkeris E, Carr H, Khoo B, Cohen M, Bouloux PM: Real-life experience of tolvaptan use in the treatment of severe hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion. *Clin Endocrinol (Oxf)* 84: 620–626, 2016
  98. Verbalis JG, Ellison H, Hobart M, Krasa H, Ouyang J, Czerwiec FS; Investigation of the Neurocognitive Impact of Sodium Improvement in Geriatric Hyponatremia: Efficacy and Safety of Tolvaptan (INSIGHT) Investigators: Tolvaptan and neurocognitive function in mild to moderate chronic hyponatremia: A randomized trial (INSIGHT). *Am J Kidney Dis* 67: 893–901, 2016
  99. Petereit C, Zaba O, Teber I, Lüders H, Grohé C: A rapid and efficient way to manage hyponatremia in patients with SIADH and small cell lung cancer: Treatment with tolvaptan. *BMC Pulm Med* 13: 55, 2013
  100. Konstam MA, Gheorghide M, Burnett JC Jr., Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators: Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST outcome trial. *JAMA* 297: 1319–1331, 2007
  101. Yan L, Xie F, Lu J, Ni Q, Shi C, Tang C, Yang J: The treatment of vasopressin V2-receptor antagonists in cirrhosis patients with ascites: A meta-analysis of randomized controlled trials. *BMC Gastroenterol* 15: 65, 2015
  102. Sterns RH, Silver SM, Hix JK: Urea for hyponatremia? *Kidney Int* 87: 268–270, 2015
  103. Decaux G, Brimiouille S, Genette F, Mockel J: Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by urea. *Am J Med* 69: 99–106, 1980
  104. Decaux G, Soupart A: Urea treatment for exercise-associated hyponatremia. *Clin J Sport Med* 16: 276, author reply 276, 2006
  105. Decaux G, Andres C, Gankam Kengne F, Soupart A: Treatment of euvolemic hyponatremia in the intensive care unit by urea. *Crit Care* 14: R184, 2010
  106. Cauchie P, Vincken W, Decaux G: Urea treatment for water retention in hyponatremic congestive heart failure. *Int J Cardiol* 17: 102–104, 1987
  107. Verhoeven A, Musch W, Decaux G: Treatment of the polydipsia-hyponatremia syndrome with urea. *J Clin Psychiatry* 66: 1372–1375, 2005
  108. Decaux G, Unger J, Brimiouille S, Mockel J: Hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone. Rapid correction with urea, sodium chloride, and water restriction therapy. *JAMA* 247: 471–474, 1982
  109. Decaux G, Mols P, Cauchie P, Flamion B, Delwiche F: Treatment of hyponatremic cirrhosis with ascites resistant to diuretics by urea. *Nephron* 44: 337–343, 1986
  110. Soupart A, Coffernils M, Couturier B, Gankam-Kengne F, Decaux G: Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin J Am Soc Nephrol* 7: 742–747, 2012
  111. Gankam Kengne F, Couturier BS, Soupart A, Decaux G: Urea minimizes brain complications following rapid correction of chronic hyponatremia compared with vasopressin antagonist or hypertonic saline. *Kidney Int* 87: 323–331, 2015
  112. Oo TN, Smith CL, Swan SK: Does uremia protect against the demyelination associated with correction of hyponatremia during hemodialysis? A case report and literature review. *Semin Dial* 16: 68–71, 2003
  113. Van Biesen W, Vanholder R: Clinical practice guidelines on diagnosis and treatment of hyponatraemia: Response to letter from Otsuka Ltd. *Eur J Endocrinol* 171: L5–L6, 2014
  114. Nagler EV, Vanmassenhove J, van der Veer SN, Nistor I, Van Biesen W, Webster AC, Vanholder R: Diagnosis and treatment of hyponatremia: A systematic review of clinical practice guidelines and consensus statements. *BMC Med* 12: 1, 2014
  115. Spital A: Treatment of hyponatremic encephalopathy. *Am J Kidney Dis* 66: 540, 2015
  116. Fenske W, Sandner B, Christ-Crain M: A copeptin-based classification of the osmoregulatory defects in the syndrome of inappropriate antidiuresis. *Best Pract Res Clin Endocrinol Metab* 30: 219–233, 2016