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.


Published online ahead of print. Publication date available at www.jasn.org.

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**Table 1. Classifications of hyponatremia**

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

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

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.6–8 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.10–13

**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.9 The initial differentiation in hypotonic and nonhypotonic hyponatremia is important, because management is different.14 Nonhypotonic hyponatremia is usually caused by hyperglycemia, but may also be caused by the administration of mannitol or hypertonic radiocontrast.7 In these settings, management is usually conservative, although a decrease in extracellular tonicity may occur during treatment.15 Nonhypotonic hyponatremia can also be caused by pseudohyponatremia, a laboratory artifact that may occur with high concentrations of triglycerides, cholesterol, or protein.16 The United States guideline subsequently divided hypotonic hyponatremia into hypovolemic, euveolemic, and hypervolemic hyponatremia.9 Although this represents the most traditional and commonly used approach to hypotonic hyponatremia, it deserves scrutiny. Hypovolemic and euveolemic hyponatremia are notoriously difficult to differentiate on the basis of physical examination,17 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%).18,19 Previously, we showed that clinicians often misclassify hyponatremia when using algorithms that start with clinical assessment of volume status.20 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.21 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.7,22 In addition, advanced CKD usually impairs water excretion, complicating the evaluation of the role of vasopressin in water balance.23 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.18 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.14,24 In addition, $S_{Na}$ has been shown to improve upon saline infusion in patients with SIAD with $U_{Osm} < 500$ mOsm/kg.25 Conversely, isotonic saline may sometimes worsen hyponatremia, a phenomenon called “desalination.”26 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.10 Indeed, we previously showed that patients often have two to three possible causes for
hyponatremia (although it was unclear if and to which extent each cause contributed).

In addition to a trial of volume repletion, an alternative approach to mixed pathogenesis would be to combine hypertonic saline with desmopressin. Although the literature on this approach is limited, it offers a rational approach to prevent a rapid rise in SNa that may occur once hypovolemia has been corrected. Fenske et al. found that FEUA.12% had the highest sensitivity and specificity to diagnose SIAD with or without diuretic use. 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 FEUA>12% had the best sensitivity and specificity for SIAD. In absolute terms, however, the performance of FEUA was still moderate, and UNa>30 mmol/L and FEUrea>55% had better sensitivity and specificity for SIAD, respectively. We frequently analyze FEUA in patients with hyponatremia, but mainly use it as supporting information. FEUA is high in both SIAD and cerebral salt wasting, but normalizes in SIAD only during treatment. 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.

Figure 1. Diagnostic algorithm for hyponatremia. Based on the European guideline. ECF, extracellular fluid.

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. Because hypotonicity normally suppresses vasopressin, the reasons for nonosmotic vasopressin release should be considered. “Inappropriate” 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 saliuresis, this is not the case. Instead, the pathogenesis appears to be a combination of polydipsia and impaired urea-mediated water excretion. “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). In addition, hypocortisolism increases vasopressin release, because corticotropin-releasing hormone normally suppresses vasopressin. Although rare, secondary and even primary adrenal insufficiency may mimic SIAD and can be missed without appropriate testing. Although the kidney usually limits the degree of hyponatremia in SIAD (“vasopressin escape”), it can also cause anti diuresis independent of vasopressin. A specific example is gain-of-function mutations of the vasopressin type 2 receptor causing hereditary hyponatremia (“nephrogenic SIAD”). Despite the pathogenetic role of vasopressin in hyponatremia, plasma vasopressin is rarely measured in clinical practice. This has
two reasons. First, U\textsubscript{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.49 These limitations, however, have largely been resolved by the development of an assay for copeptin.50

**COPEPTIN**

Enzymatic cleavage of the vasopressin prohormone produces not only vasopressin, but also neurophysin and copeptin (also called C-terminal proarginine vasopressin).51 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 hypovolemic hyponatremia than in patients with SIAD.52 This was demonstrated previously\textsuperscript{35} 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.53,54 Because hypovolemic hyponatremia is characterized by high plasma copeptin and low U\textsubscript{Na}, the plasma copeptin to U\textsubscript{Na} ratio may be especially useful to differentiate it from SIAD. Although the study by Fenske et al. did indeed demonstrate this,\textsuperscript{52} the specificity of copeptin/U\textsubscript{Na} for SIAD in a more recent and larger study was less high.\textsuperscript{51} An interesting approach was the use of plasma copeptin to differentiate SIAD subtypes.\textsuperscript{55} 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.\textsuperscript{31,52} 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\textsubscript{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).\textsuperscript{56,57} Physiologically, apelin and vasopressin are regulated in opposite directions by volemic and osmotic stimuli.\textsuperscript{56} Apelin not only inhibits vasopressin release centrally, but also counteracts the antidiuretic effect in the kidney.\textsuperscript{58} However, in patients with hyponatremia due to SIAD or heart failure, plasma apelin was insufficiently suppressed, possibly contributing to antidiuresis in these settings.\textsuperscript{56} 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).\textsuperscript{57} High MR-proANP in hypovolemic hyponatremia is counterintuitive, but may be explained by lower GFR secondary to volume depletion.\textsuperscript{59} 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

**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.\textsuperscript{55} and figure modified from Fenske et al.\textsuperscript{116} with permission.
Table 2. Comparison of the United States and European guidelines

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

aDo not recommend when $S_{Na} < 130$ mmol/L. “recommend against” when $S_{Na} < 125$ mmol/L.
bIn liver cirrhosis, restrict to patients where potential benefit outweighs risk of worsened liver function.

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). 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). 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. This automatically leads to the often heated debate on optimal correction rates in hyponatremia. 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). 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). In response to these recommendations, Adrogue and Madias proposed even more conservative limits of 6–8 mmol/L per day regardless of duration or symptoms. 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). 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. 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.66 Ex-
perimental data indicate improved
outcomes with reinduction of hypona-
tremia after rapid overcorrection.67
Another point that merits discussion
is the consistent association of hypona-
tremia with worse outcomes.63,68 This
may indicate that hyponatremia has
adverse effects beyond the classic neu-
rologic symptoms.69,70 However, in the
absence of randomized intervention
studies indicating that correction of
hyponatremia improves outcomes, it re-
 mains unclear whether these associations
are causal.5

TREATMENT OF ACUTE
HYPONATREMIA

Several settings predispose to acute hy-
ponatremia, especially if combined with
increased free water intake.71 Among
others, these include the postoperative
period, exercise, and the use of 3,4-
methylenedioxymethamphetamine
("Ecstasy"), haloperidol, thiazide di-
uretics, desmopressin, oxytocin, or in-
travenous cyclophosphamide.71–74 A
specific situation is the use of irrigants
(glycine, sorbitol, mannitol) during
transurethral or hysteroscopic proce-
dures. Although absorption of the irri-
gants 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 osmo-
lar shifts.75,76 In contrast, mannitol cau-
ses hypertonic hyponatremia without a
risk for cerebral edema. In daily practice,
the distinction between acute and
chronic hyponatremia is difficult, be-
cause 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).9 The European guideline based its
recommendations primarily on the
presence and severity of symptoms
rather than on duration.7 Both guide-
lines recommend hypertonic saline
(typically 3% NaCl) for acute or symp-
tomatic hyponatremia.7,9 Hypertonic
saline is an effective and potentially
life-saving treatment for cerebral edema
due to hyponatremia, as the high extra-
cellular sodium concentration immedi-
ately removes water from the intracellular
space. In patients with hypervolemic hy-
ponatremia, hypertonic saline may be
combined with loop diuretics.9 The
required volume of hypertonic saline to
reach a predefined increase in SNa can
be estimated using the Adrogue–Madias
or Barsoum–Levine formulae.77,78 Al-
 though predictions with these formulae
are fairly accurate,66 a switch toward
giving hypertonic saline as fixed bolus
has occurred in recent years.79 No studi es
have systematically tested this ap-
proach, but there are a number of
appealing aspects. First, especially in pa-
tients with cerebral edema, it is desirable
to achieve a rapid partial correction in
SNa. Second, a fixed bolus omits the need
for calculations in a patient with an
acute problem, limiting potential calcu-
lation errors. Third, bolus therapy limits
the risk of overcorrection, which does
occur commonly with a continuous in-
fusion of hypertonic saline.80 On the
basis of these considerations, both
guidelines recommend bolus therapy,
albeit with slightly different specifica-
tions (Table 2).7,9 Recently, Ayus and
colleagues reported their experience
using a different protocol (500 ml 3%
NaCl over 6 hours) in 64 patients with
hyponatremic encephalopathy (SNa<130
mmol/L and neurologic symptoms).81 On
average, this protocol increased SNa with
12 and 14 mmol/L in the first 24–48
hours, and improved symptoms without
evidence of ODS.81 However, the severity
of hyponatremia (SNa frequently
<110
mmol/L) and the duration of symptoms
suggest that some of these patients had
chronic hyponatremia. If so, these correc-
tion rates would exceed currently recom-
ended 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 excre-
tion (Table 2). Fluid restriction (<1 L/d)
is often the cornerstone of the therapy
for chronic hyponatremia.24 The urine
to serum electrolyte ratio ([UNa + urine
potassium concentration]/SNa) indi-
cates if the patient is in an antidiuretic
or aquaretic phase, and can also help
estimate the degree of fluid restriction
required to increase SNa.11,24,82 For
patients with a ratio>1 (indicating con-
centrated urine), <500 ml fluid/d is rec-
ommended, which is difficult to adhere
to. Winzeler et al. recently showed that
in patients with SIAD fluid restriction is
effective in 59% of patients.83 Predictors
of nonresponse were a UNa ≥130 mmol/L
and UNa/Osm ≥500 mOsm/kg.83 This
implies that in patients with chronic hypo-
natremia pharmacologic therapy is
often required to increase renal free wa-
ter excretion. This can be achieved by
treatment with loop diuretics, urea, vasopres-
sin receptor antagonists ("vaptans"),
or demeclocycline. The two guidelines
diverge in their recommendations re-
garding pharmacologic therapy for
SIAD and hypervolemic hyponatremia
(Table 2). This was the case especially
for vaptans, which will therefore be dis-
cussed in more detail below.

Vaptans
Vaptans block vasopressin type 2 recep-
tors in collecting duct principal cells
and therefore induce aquarexia (for com-
prehensive review, see Berl,84 Hoorn and
Zietse,85 Lehrl et al.,86 Rozen-Zvi
et al.,87 and Greenberg and Verbalis88).
Several vaptans were developed, includ-
ing tolvaptan, satavaptan, lixivaptan,
and conivaptan (which also targets vasopres-
sin type 1a receptors). On the basis
of their mechanism of action, vaptans
are a logical and targeted therapy for
hyponatremic patients with excess vasopres-
sin. Indeed, several large clinical trials
have shown that vaptans are clearly effec-
tive in increasing SNa in patients with
hyponatremia due to SIAD, heart failure, or liver cirrhosis. 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. Still, it has been difficult to position vaptans in the therapeutic arsenal of chronic hyponatremia. The United States guideline lists vaptans as one of the pharmacologic options, if fluid restriction has failed (Table 2). The European guideline did not recommend vaptans in moderate hyponatremia. The reason to do so was the absence of evidence for improved hard outcomes with correction of SNa. Meanwhile, one meta-analysis has suggested improved survival with correction of hyponatremia, 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. Because ODS has mainly been reported after overcorrection of profound hyponatremia, the European guideline recommended against vaptans in this setting. Recently, Tzoulis et al. reported “real-life experience” with tolvaptan in 61 patients with resistant hyponatremia due to SIAD. The average rise in SNa after 24 hours was 9.0 ± 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. ODS was reported in one patient with heart failure in whom 15 mg tolvaptan caused SNa to increase from 126 to 142 mmol/L in the first day and to further increase to 187 mmol/L in subsequent days. On the other hand, improvement of symptoms has been shown with the use of vaptans. This includes improvements in some neurocognitive symptoms, performance status in cancer patients, dyspnea in patients with heart failure, and ascites in patients with liver cirrhosis. 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. 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. More recently, in 12 patients with SIAD, Soupart et al. compared the treatment with satavaptan to urea (both treatment periods 1 year). 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. 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. 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. 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) 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. 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. They identified considerable variation in methodologic rigor in the development of guidelines, potentially explaining inconsistencies in recommendations. 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 SNa. 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 SNa) are warranted.

**ACKNOWLEDGMENTS**

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

**DISCLOSURES**

None.

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