CME INFORMATION

Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations

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Program Overview

Hyponatremia is the most common disorder of electrolytes encountered in clinical practice. Although many cases are mild and relatively asymptomatic, hyponatremia is nonetheless important clinically because of the potential for substantial morbidity and mortality. Despite knowledge of hyponatremia since the mid-20th century, this common disorder remains incompletely understood in many basic areas because of its association with a plethora of underlying disease states, and its causation by multiple etiologies with differing pathophysiological mechanisms. Optimal treatment strategies have not been well defined, both due to these reasons, and because of marked differences in symptomatology and clinical outcomes based on the acuteness or chronicity of the hyponatremia. The approval of the first vasopressin receptor antagonist (vaptan) in 2005 heralded the beginning of a new era in the management of hyponatremic disorders. Since then the field has evolved considerably, including new data on previously unrecognized morbidities and mortalities associated with hyponatremia, the approval of a second vaptan, and additional clinical experience with vaptans and other therapies for the treatment of patients with hyponatremia. In view of this, a panel of experts in hyponatremia was convened in 2012 to update the panel's earlier recommendations for the evaluation and treatment of hyponatremia.

Target Audience

This activity was designed to meet the needs of endocrinologists, hepatologists, nephrologists, gastroenterologists, cardiologists, internists, emergency room physicians, pharmacists, and any healthcare provider who is likely to encounter patients with hyponatremia.

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Educational Activity Goal

Given new developments in the field of hyponatremia and its management—along with high interest by the multitudes of clinicians who see hyponatremia in their practices and/or hospitals—the need is clear for current, evidence-based recommendations to fill the demonstrated educational and practice gaps of treating physicians. These evidence-based, expert-authored recommendations will reflect current scientific and treatment realities of hyponatremia management. By completing this activity physicians should be better educated concerning: (1) risks for morbidity and mortality associated with hyponatremia; (2) recognition, accurate diagnosis, and assessment of hyponatremia; and (3) strategies for managing the condition—in cooperation with other specialists—based on clinical signs, biochemical measurements, risk factors, symptoms, rate of onset, and underlying causative factors.

After completing this activity, learners should be able to:

- Identify and assess patients at risk for hyponatremia.
- Achieve timely and effective diagnosis and management of patients with hyponatremia, taking into account the effects of underlying comorbid conditions and diuretic usage.
- Carefully monitor and control the rate of correction of serum sodium levels in patients with chronic hyponatremia to avoid permanent and potentially fatal neurologic complications.
- Balance the potential interactions of one treatment with another to achieve optimal resolution of both the hyponatremia and the underlying disease(s).

Core Competencies for Quality Patient Care

This educational activity primarily addresses Medical Knowledge core competency as defined by the Accreditation Council for Graduate Medical Education/American Board of Medical Specialties Competencies. Secondary competencies addressed by this activity include Patient Care and Procedural Skills, as well as Practice-Based Learning and Improvement.

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Physicians

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Steven Goldsmith, MD	***Grant/Research Support, Speakers' Bureau:*** Otsuka America Pharmaceutical, Inc. ***Consultant:*** Otsuka America Pharmaceutical, Inc.; Medtronic
Robert Schrier, MD	***Consultant:*** Otsuka America Pharmaceutical, Inc.; Janssen Pharmaceuticals, Inc.
Richard Sterns, MD	Has no real or apparent conflicts of interest to report
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Online URL: https://hyponatremiacme.amjmed.com

Mail: Educational Measures, 7373 S. Alton Way, Centennial, CO 80112

Fax: 303-339-2439 (No cover sheet is necessary)

The certificates will be e-mailed or mailed to the information provided on the evaluation.

Media

Journal supplement

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SUPPLEMENT

THE AMERICAN JOURNAL of MEDICINE®

Diagnosis, Evaluation, and Treatment of Hyponatremia: Expert Panel Recommendations

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ABSTRACT

Hyponatremia is a serious, but often overlooked, electrolyte imbalance that has been independently associated with a wide range of deleterious changes involving many different body systems. Untreated acute hyponatremia can cause substantial morbidity and mortality as a result of osmotically induced cerebral edema, and excessively rapid correction of chronic hyponatremia can cause severe neurologic impairment and death as a result of osmotic demyelination. The diverse etiologies and comorbidities associated with hyponatremia pose substantial challenges in managing this disorder. In 2007, a panel of experts in hyponatremia convened to develop the *Hyponatremia Treatment Guidelines 2007: Expert Panel Recommendations* that defined strategies for clinicians caring for patients with hyponatremia. In the 6 years since the publication of that document, the field has seen several notable developments, including new evidence on morbidities and complications associated with hyponatremia, the importance of treating mild to moderate hyponatremia, and the efficacy and safety of vasopressin receptor antagonist therapy for hyponatremic patients. Therefore, additional guidance was deemed necessary and a panel of hyponatremia experts (which included all of the original panel members) was convened to update the previous recommendations for optimal current management of this disorder. The updated expert panel recommendations in this document represent recommended approaches for multiple etiologies of hyponatremia that are based on both consensus opinions of experts in hyponatremia and the most recent published data in this field.
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Hyponatremia is the most common disorder of electrolytes encountered in clinical practice, occurring in 15%-30% of acutely or chronically hospitalized patients.[1] Although many cases are mild and relatively asymptomatic, hyponatremia is nonetheless important clinically because: 1) acute severe hyponatremia can cause substantial morbidity and mortality; 2) adverse outcomes, including mortality, are higher in hyponatremic patients with a wide range of underlying

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Authorship: All authors reviewed the data that were cited in the manuscript and wrote their respective sections of this manuscript.

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diseases; and 3) overly rapid correction of chronic hyponatremia can cause severe neurological deficits and death.

Despite knowledge of hyponatremia since the mid-20th century, this common disorder remains incompletely understood in many basic areas because of its association with a plethora of underlying disease states, its causation by multiple etiologies with differing pathophysiological mechanisms, and marked differences in symptomatology and clinical outcomes based on the acuteness or chronicity of the hyponatremia.[2] For these reasons, optimal treatment strategies have not been well defined.

The approval of the first vasopressin receptor antagonist (drugs in this class are also referred to as vaptans, for vasopressin antagonists), conivaptan (Astellas Pharma, U.S., Inc., Northbrook, IL), for clinical use by the US Food and Drug Administration (FDA) in 2005 heralded the beginning of a new era in the management of hyponatremic disorders. However, proper and effective use of these and other therapies requires careful thought and guidance. In 2005, a consensus panel of experts in hyponatremia was convened to review existing therapies for hyponatremia and to evaluate the situations where aquaretic agents should be considered as alternatives or supplements to accepted current therapies; the initial review by this group was published in 2007.[3] Since then, new data on previously unrecognized morbidities and mortalities associated with hyponatremia have emerged, additional clinical experience with vaptans and other therapies for patients with hyponatremia has accumulated, and the FDA and the European Medicines Agency (EMA) approved a second vaptan, tolvaptan (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan).[4] In view of these developments, a similar panel of experts in hyponatremia, including all of the participants of the initial panel, was convened in 2012 to update the earlier recommendations for the evaluation and treatment of hyponatremia.

METHODS

Search Strategy

The PubMed database was electronically searched from January 1, 2006 through December 31, 2012. Additional studies were obtained from reference libraries of the panel members and from publication reference lists. Searches were limited to English-language studies on humans using the search terms hyponatremia and: hypervolemia, euvolemia, hypovolemia, heart failure, liver cirrhosis, syndrome of inappropriate ADH (antidiuretic hormone secretion), chemically induced, congenital, ethnology, etiology, genetics, diagnosis, radiography, radionuclide, imaging, and ultrasonography. For each topic section, study selection was performed by an assigned reviewer.

Consensus

Topic summaries and recommendations were reached through consideration of the strength and quality of available evidence (eg, trial, type of trial vs. case report, number of trial subjects). Both negative and positive studies were considered. When the literature did not support recommendations based solely on evidence, recommendations reflect consensus opinion reached by the expert panel through roundtable discussion and multiple draft reviews. For topics for which consensus was not reached, divergent opinions are noted. The quality of the data available to support each recommendation was noted and taken into account for the final recommendations. Several steps were taken to ensure that objectivity was maintained throughout the various steps of manuscript preparation. First, the Tufts University Continuing Medical Education course director (C.K.), who has no potential conflicts of interest, was specifically tasked with identification and avoidance of bias and with ensuring the objectivity of the manuscript. Second, a separate external review for objectivity was conducted by the Tufts University Office of Continuing Medical Education.

Level of Evidence

Each panel member critically evaluated relevant literature to inform recommendations for each topic. The authors acknowledge the paucity of available randomized controlled trials with clinical outcome measures to support evidence-based recommendations for most available therapies. As such, the use of a quality-of-evidence scoring system to grade the strength of supporting data for each recommendation was not feasible. The panel recognizes the need for expert guidance in hyponatremia management in the absence of such literature, and the need for future studies to evaluate management strategies not currently supported by evidence from high-quality randomized controlled trials.

CLINICAL SIGNIFICANCE OF HYPONATREMIA

The rationale for these expert recommendations for the safe and effective treatment of hyponatremia is the clinical significance of this disorder. A wealth of evidence exists that fully justifies hyponatremia as an important clinical treatment target. However, perhaps the most convincing rationale for these recommendations is the need for a better understanding of the potential consequences of not effectively treating hyponatremia in the many patients with this disorder, both hospitalized and outpatients.

Incidence and Prevalence

Hypo-osmolality is one of the most common disorders of fluid and electrolyte balance encountered in hospitalized patients. The incidence and prevalence of hypo-osmolar disorders depend on the nature of the patient population being studied, as well as on the laboratory methods and diagnostic criteria used to ascertain hyponatremia. Most investigators have used the serum sodium concentration ($[Na^+]$) to determine the clinical incidence of

hypo-osmolality. When hyponatremia is defined as a serum [Na^+] below 135 mmol/L (sodium is univalent, so 1 mmol/L = 1 mEq/L), incidences as high as 15%-30% have been observed in studies of both acutely[5] and chronically[6] hospitalized patients. Similarly high incidences have been reported in patients with specific disease states, including patients with heart failure (HF) and cirrhosis; reports from recent trials and registries suggest that hyponatremia is seen in up to 27% of patients admitted with acute HF,[7-10] and that up to 50% of patients with cirrhosis and ascites are found to be hyponatremic.[11] A more recent study that analyzed adverse outcomes in a large number of hospitalized hyponatremic patients proposed revising the definition of hyponatremia to serum [Na^+] <138 mmol/L, because this marked the level at which the association with increased mortality reached statistical significance (see the subsequent section: *Association of Hyponatremia with Adverse Outcomes*); using this definition, 38% of patients in the hospital system experienced hyponatremia at some time during hospitalization.[12] However, incidences decrease to the range of 1%-4% when only patients with serum [Na^+] below 130-131 mmol/L are included,[6,13] which may represent a more appropriate level to define the occurrence of clinically significant cases of this disorder. Even with these more stringent criteria, incidences from 7%-53% have been reported in institutionalized geriatric patients.[14] Reports of many studies have noted a high proportion of iatrogenic or hospital-acquired hyponatremia, accounting for as many as 40%-75% of patients studied.[13]

Association of Hyponatremia with Adverse Outcomes

The association of hyponatremia with increased morbidity and mortality of hospitalized patients across a wide variety of disorders has long been recognized. The most prominent example of this relationship is the high mortality rate in patients with acute hyponatremia due to osmotically induced brain edema (see the subsequent section: *Hyponatremic Encephalopathy*).

Another well-known example is the independent association of hyponatremia with increased mortality in HF patients, both in hospitalized patients[7,9,10,15] and in the outpatient setting.[8] These relationships persist despite the widespread use of neurohormonal blocking therapies that might have been expected to reduce the incidence of hyponatremia or to mitigate its impact on survival, because in the past, hyponatremia had been viewed as largely a surrogate for overall neurohormonal activation, particularly of the renin angiotensin system.[16]

Similar analyses of patients with liver disease have demonstrated strong associations with adverse outcomes. Hyponatremia in patients with cirrhosis is a major predictor of hepatorenal syndrome,[17] hepatic encephalopathy,[18] and death.[19] In a recent study of 523 patients with cirrhosis and ascites, a multivariate analysis using the 36-item Short Form Health Survey developed for the Medical Outcome Study demonstrated that hyponatremia was a strong predictor of impaired mental and physical scores.[20] Hyponatremia has been shown to be an independent predictor of worse outcomes in patients awaiting liver transplantation[21] and in those who have undergone the surgery.[22,23]

Hyponatremia has been associated with worse clinical outcomes across the entire range of inpatient care, from the general hospital population to those treated in the intensive care unit (ICU). In a study of 4123 patients aged 65 years or older who were admitted to a community hospital, 3.5% had clinically significant hyponatremia (serum [Na^+] <130 mmol/L) at admission. When compared with normonatremic patients, those with hyponatremia were twice as likely to die during their hospital stay (relative risk [RR] 1.95; P <.05).[24] In another study of 2188 patients admitted to a medical ICU over a 5-year period, 13.7% had hyponatremia. The overall rate of in-hospital mortality among all ICU patients was high at 37.7%. However, severe hyponatremia (serum [Na^+] <125 mmol/L) more than doubled the risk of in-hospital mortality (RR 2.10; P <.001).[25] The largest study of adult hospitalizations included 53,236 patient admissions to an academic medical center over a 7-year period and showed that both community-acquired and hospital-acquired hyponatremia were associated with significantly increased adjusted odds ratios (ORs) for in-hospital mortality, discharge to a short- or long-term care facility, and increase in length of stay. The strength of the associations tended to increase with hyponatremia severity, although other analyses suggest that mortality may not progressively increase as the serum [Na^+] falls to very low levels.[26] Remarkably, the association between admission serum [Na^+] and predicted inpatient mortality reached significance at levels of serum [Na^+] <138 mmol/L.[12] In addition to the general hospital population, recent studies have found that preoperative hyponatremia was an independent marker for multiple perioperative complications, including 30-day morbidity and mortality.[27] In virtually every disease state examined to date, the presence of hyponatremia has been found to be an independent risk factor for increased mortality.[1]

Even in patients adjudged to be "asymptomatic" by virtue of a normal neurological examination, accumulating evidence suggests that chronic hyponatremia can be responsible for unapparent adverse effects. In one study, patients with hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (n = 16, serum [Na^+] = 124-130 mmol/L) demonstrated a significant gait instability that resolved with correction of the serum [Na^+] into the normal range.[28] The functional significance of the gait instability was illustrated in a case-control study of 122 patients with a variety of levels of hyponatremia, all judged to be "asymptomatic" at the time of their visit to an emergency department. Researchers found that 21% of the hyponatremic patients presented to the emergency department because of a recent fall, when compared with only 5% of the controls; this difference was highly significant and remained so after multivariable

adjustment.[28] This study provides clear documentation of an increased incidence of falls in so-called asymptomatic hyponatremic patients.

The clinical significance of the gait instability and fall data were further evaluated in a study that compared 553 patients with fractures to an equal number of matched controls. Hyponatremia was found in 13% of the patients presenting with fractures, when compared with only 4% of the controls.[29] Similar findings were reported in studies of 364 elderly patients with large-bone fractures in New York,[30] in 1408 female patients with early chronic renal failure in Ireland[31] (**Figure 1**), and in 5208 elderly patients followed for 12 years in the Rotterdam Longitudinal Aging Study.[32] More recently, published studies have shown that hyponatremia is associated with increased bone loss in experimental animals and with a significantly increased OR for osteoporosis of the femoral neck (OR 2.87; $P < .003$) in humans over the age of 50 years in the Third National Health and Nutrition Examination Survey (NHANES III) database.[33] Taken together, these data provide strong evidence that chronic hyponatremia, which would previously have been considered inconsequential, may increase the risk of falls and fractures in the elderly, occurrences that are associated with significant morbidity and mortality.

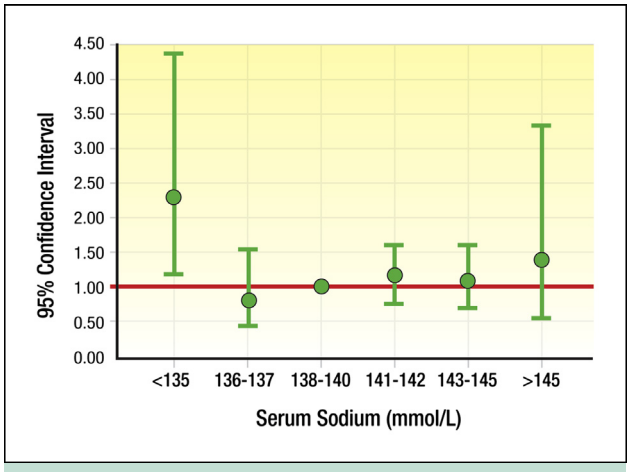

Figure 1 Risk of bone fracture in relation to serum [Na^+] in patients with chronic kidney disease. Odds ratio (95% confidence interval) of fracture occurrence by serum [Na^+] category, adjusting simultaneously for age (years), T-score, chronic kidney disease stage, osteoporotic risk factors (amenorrhea, low dietary calcium intake, high alcohol intake, maintenance steroids, ever having smoked, family history of osteoporosis, and history of liver disease), and osteoporosis therapy (use of calcium, vitamin D, antiresorptive therapy, and hormonal replacement therapy). Reproduced with the permission of the American Society of Nephrology, from Kinsella S, Moran S, Sullivan MO, et al. *Clin J Am Soc Nephrol.* 2010;5:275-280; permission conveyed through Copyright Clearance Center, Inc.[31]

Economic Burden of Hyponatremia

Given the high prevalence of hyponatremia, it is not surprising that the economic burden of hyponatremia is substantial, with estimated direct costs of treating hyponatremia in the US ranging from $1.6 to $3.6 billion annually.[34] Analyses of patients in large hospitalization databases in the US have indicated that hyponatremia is associated with a 7.6% increase in hospital length of stay, an 8.9% increase in hospital costs, and a 9% increase in ICU costs, as well as increased risk of ICU admission and 30-day hospital readmission for hyponatremia.[35] Similar results were obtained for analyses of various subgroups of hyponatremic patients with specific diseases, including HF,[36] cirrhosis,[37] and malignant brain tumors.[38] Similar data are available from outside the US.[39] These data inevitably raise the question about whether more effective treatment of hyponatremia can reduce the increased costs associated with the disorder. Economic cost-offset analyses of results from the Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT-1 and SALT-2)[4] and the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST)[40] tolvaptan clinical trials have suggested that the observed reductions in length of stay from these trials were associated with substantial estimated mean hospital cost reductions in patients with SIADH[41] and HF.[42] Whether these limited results are generalizable to larger populations remains to be determined.

ROLE OF VASOPRESSIN IN HYPONATREMIA

Most hyponatremic states are characterized by inappropriately elevated plasma levels of arginine vasopressin (AVP).[43] AVP secretion is normally stimulated by increased plasma osmolality via activation of osmoreceptors located in the anterior hypothalamus and by decreased blood volume or pressure via activation of high- and low-pressure baroreceptors located in the carotid sinus, aortic arch, cardiac atria, and pulmonary venous system. When osmolality falls below a genetically determined osmotic threshold, plasma AVP levels become undetectable and renal excretion of solute-free water (aquaresis) results to prevent decreases in plasma osmolality. Failure to suppress AVP secretion at osmolalities below the osmotic threshold results in water retention and hyponatremia if the intake of hypotonic fluids is sufficient. In SIADH, AVP release is not fully suppressed despite hypo-osmolality due to a variety of causes, including ectopic production of AVP by some tumors. The persistence of AVP release due to nonosmotic hemodynamic stimuli is also predominantly responsible for water retention and hyponatremia with hypovolemia, as well as in edema-forming disorders such as HF and cirrhosis.[44] Regardless of the stimulus, once it is secreted, AVP binds to the AVP V2 receptor subtype (V2R) in the kidney collecting ducts and activates the signal transduction cascade resulting in antidiuresis (**Figure 2**). Because of the critical role of AVP in abnormal water retention, all hyponatremic patients with inappropriately elevated plasma

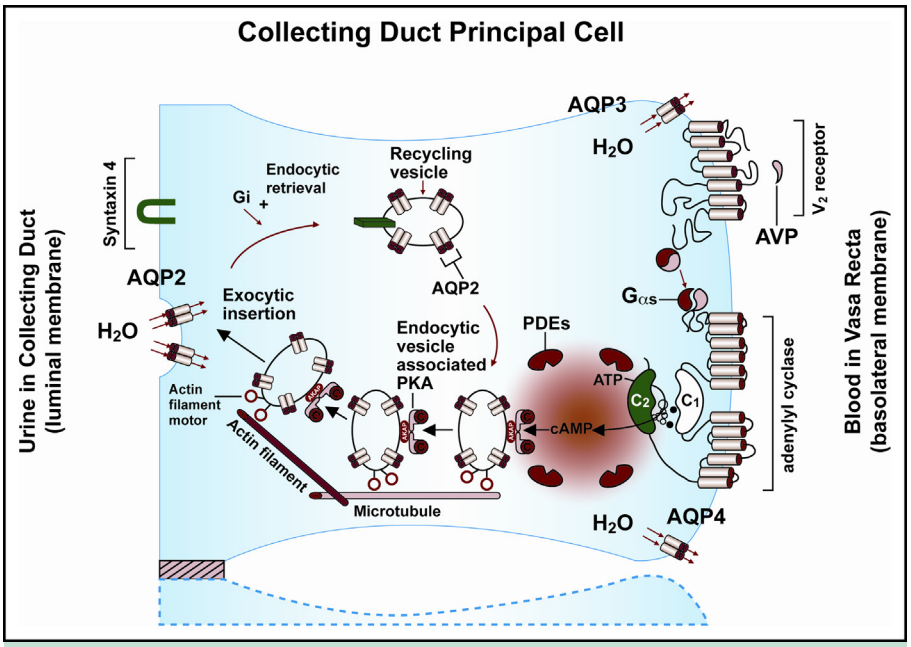

Figure 2 Mechanism of renal water reabsorption induced by arginine vasopressin (AVP) activation of the V_2 receptor on renal collecting duct principal cells. AVP binds to the G-protein-linked V_2 receptor on the basolateral membrane. G-protein-coupled receptor signaling consists of three steps: a hepta-helical receptor that detects a ligand (in this case, AVP) in the extracellular milieu, a G-protein ($G_{\alpha s}$) that dissociates into subunits bound to GTP and βγ subunits after interaction with the ligand-bound receptor, and an effector (adenylyl cyclase) that interacts with the dissociated G-protein subunits to generate second messengers. AVP activates adenylyl cyclase, increasing the intracellular concentration of cyclic adenosine monophosphate (cAMP). Protein kinase-A (PKA) is the target of the generated cAMP. The binding of cAMP to the regulatory subunits of PKA induces a conformational change, causing these subunits to dissociate from the catalytic subunits. These activated subunits (C) are anchored to an aquaporin-2 (AQP2)-containing endocytic vesicle via an A-kinase anchoring protein (AKAP). The local concentration and distribution of the cAMP gradient is limited by phosphodiesterases (PDE). Phosphorylation of the AQP2 water channels in the endocytic vesicles leads to movement of the vesicles toward the luminal membrane via microtubules and actin filaments with eventual fusion into the luminal membrane, thereby increasing the water permeability of this membrane. Water (H_2O) is then reabsorbed from the urine in the collecting duct into the principal cells along osmotic gradients. When AVP is not bound to the V_2 receptor, AQP2 water channels are retrieved by an endocytic process, and water permeability returns to its original low rate. AQP3 and AQP4 water channels are expressed constitutively at the basolateral membrane and allow intracellular water to exit into the blood of the vasa recta. In the presence of medullary hyperosmolality, water therefore moves across the principal cell and returns into the circulation. This process results in urinary concentration, or antidiuresis. In the presence of nonosmotic AVP stimulation, water is retained and hyponatremia can occur.
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AVP levels relative to osmolality are potential candidates for treatment with agents that block activation of the AVP-mediated antidiuretic effects in the kidneys. Exceptions include patients with hypovolemic hyponatremia who are more safely treated with solute and volume repletion and patients with hyponatremias in which AVP is not an etiologic factor, including acute water intoxication and renal failure; therapies for all hyponatremic disorders will be discussed in the appropriate sections based on the etiology of the hyponatremia.

CLASSIFICATION AND DIFFERENTIAL DIAGNOSIS OF HYPONATREMIA

The presence of significant hypo-osmolality indicates excess water relative to solute in the extracellular fluid (ECF)

compartment. Because water moves freely between the ECF and the intracellular fluid (ICF) compartments, an excess of total body water relative to total body solute is present as well.

Differentiation of Hypotonic Hyponatremia from Other Causes of Hyponatremia

The osmolality of body fluid normally is maintained within narrow limits by osmotically regulated AVP secretion and thirst. Although basal plasma osmolality can vary among individuals, the range in the general population under conditions of normal hydration is between 280 and 295 mOsm/kg H_2O. However, total osmolality is not always equivalent to *effective osmolality*, often termed plasma *tonicity*. Only solutes that are impermeable to the cell membrane and remain relatively compartmentalized within the ECF are "effective" solutes, because these are capable of creating osmotic gradients across cell membranes and thereby effect osmotic movement of water between the ICF and the ECF compartments. As such, the concentration of effective solutes in plasma should be used to determine whether clinically significant hypo-osmolality is present. Sodium and its accompanying anions are the major effective plasma solutes, so hyponatremia and hypo-osmolality are usually synonymous. However, there are 2 situations where hyponatremia and hypo-osmolality are discordant; these are important to recognize clinically because they represent situations where hyponatremia does not need to be treated.

Pseudohyponatremia. Marked elevations of either lipids or proteins in plasma can cause artifactual decreases in serum [Na^+] because of the larger relative proportion of plasma volume that is occupied by the excess lipids or proteins. Because the increased protein or lipid will not appreciably change the total number of solute particles in solution, the directly measured plasma osmolality will be normal in such cases and, therefore, the patient will be isotonic rather than hypotonic[45] (**Table 1**).

Isotonic or Hypertonic Hyponatremia. Hyponatremia with normal or even increased osmolality occurs when effective solutes other than sodium are present in the plasma. The initial hyperosmolality produced by the additional solute causes an osmotic shift of water from the ICF to the ECF compartment that, in turn, produces a dilutional decrease in the serum [Na^+]. Hyperglycemia is the most common example of this phenomenon. Depending on the severity of hyperglycemia and the duration and magnitude of the accompanying glucose-induced osmotic diuresis, such patients may actually be hypertonic despite hyponatremia (**Table 1**). In this setting, osmolality is best assessed by measuring plasma osmolality directly or by correcting the measured serum [Na^+] for the glucose elevation.[46] When the plasma contains significant amounts of unmeasured solutes, such as mannitol, radiographic contrast agents, or glycine from surgical irrigant solutions, plasma osmolality cannot be calculated accurately and must be ascertained by direct measurement.[47]

Pathogenesis of Hypotonic Hyponatremia

Because water moves freely between the ICF and ECF, osmolality will always be equivalent in both of these fluid compartments. As the bulk of body solute is comprised of electrolytes—namely, the exchangeable Na^+ (Na_E^+) in the ECF, the exchangeable K^+ (K_E^+) in the ICF, and associated anions—osmolality is largely a function of these parameters and can be expressed as:

$$OSM_{ECF} = OSM_{ICF} = \left(\frac{\text{ECF solute} + \text{ICF solute}}{\text{body water}}\right) = \left(\frac{2 \text{ x } Na_E^+ + 2 \text{ x } K_E^+ + \text{nonelectrolyte solute}}{\text{body water}}\right)$$

By this definition, the presence of plasma hypo-osmolality, and therefore hypotonic hyponatremia, indicates a relative excess of water to solute in the ECF. This can be produced either by excess body water, which results in a *dilution* of the remaining body solute, or by *depletion* of body solute (either Na^+ or K^+) relative to body water.[2] This classification is an oversimplification, because most hypo-osmolar states involve components of both solute depletion and water retention. Nonetheless, it is conceptually useful for understanding the mechanisms underlying the pathogenesis of hypo-osmolality, and it serves as a basis for selecting appropriate therapies of hyponatremic disorders.

CLASSIFICATION AND DIAGNOSIS OF HYPOTONIC HYPONATREMIAS

A definitive diagnosis of the underlying etiology of hyponatremia is not always possible at the time of initial presentation. In most cases, however, a diagnostic approach based on clinical assessment of the patient's ECF volume

Table 1 Classification of Hyponatremia by Plasma Tonicity

	Serum Sodium Concentration (mmol/L)	Plasma Osmolality (mOsm/kg H_2O)	Typical Causes
Hypotonic	<135	Low (<280)	SIADH; heart failure; cirrhosis
Isotonic	<135	Normal (280-295)	Hyperglycemia; pseudohyponatremia (hyperlipidemia, hyperproteinemia)
Hypertonic	<135	High (>295)	Severe hyperglycemia with dehydration; mannitol

H_2O = water; kg = kilogram; L = liter; mmol = millimole; mOsm = milliosmole; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

status and urine electrolyte excretion permits sufficient categorization of the underlying etiology to allow initiation of therapy and direct further diagnostic evaluation. The following sections will describe the diagnostic criteria, common etiologies, and pathophysiologies of the 3 major classifications of hypotonic hyponatremia based on the patient's ECF volume status: hypovolemic hyponatremia, euvolemic hyponatremia, and hypervolemic hyponatremia. It should be emphasized that these statements represent consensus-based clinical recommendations, not dogmatic diagnostic pathways; clinical acumen must always inform and temper their application. Nonetheless, studies have clearly documented that inappropriate diagnosis of hyponatremia often leads to illogical therapies and worse clinical outcomes.[48] Furthermore, following a simple algorithm for diagnosing and treating hyponatremia led to significantly improved management outcomes.[49] Thus, the importance of appropriate classification and diagnosis of hypotonic hyponatremia should not be underestimated. In some cases, the ECF volume status may be ambiguous, making it difficult to classify hyponatremia using standard criteria of ECF volume assessment; in other cases, multiple etiologies are present. Nonetheless, application of a standard approach to diagnosis and therapy with regular reassessment of responses to therapy will generally lead to improved outcomes.

Hypovolemic Hyponatremia

The presence of clinically detectable decreased ECF volume is usually indicative of solute depletion. Hyponatremia with volume depletion (hypovolemia) can arise in a variety of settings. Because intravascular volume cannot be easily measured directly, volume depletion is diagnosed clinically from the history, physical examination, and laboratory results. Patients with clinical symptoms or signs of volume depletion (eg, vomiting and diarrhea, orthostatic decreases in blood pressure and increases in pulse rate, dry mucus membranes, and decreased skin turgor) should be considered to be hypovolemic, unless there are alternative explanations for these findings. When available, direct hemodynamic measurements can provide corroboration of the clinical impression. Elevations of blood urea nitrogen (BUN), creatinine, the BUN-creatinine ratio, and uric acid level are helpful laboratory clues to the presence of volume depletion. However, these findings are neither sensitive nor specific and can be affected by other factors (eg, dietary protein intake, use of glucocorticoids). Measuring the urine sodium excretion is usually more helpful. The spot urine $[Na^+]$ should be <20 to 30 mmol/L in patients with hypovolemic hyponatremia, unless the kidney is the site of sodium loss.[50-52] Higher urine $[Na^+]$ cutoffs and the measurement of fractional excretion of uric acid in patients taking diuretics have also been suggested to be useful when trying to exclude hypovolemia.[52,53] When the clinical assessment is equivocal, a trial of volume expansion can be helpful in establishing the diagnosis and will be therapeutic if volume depletion is the cause of the hyponatremia. After a 0.5- to 1-L infusion of isotonic (0.9%) NaCl, patients with hypovolemic hyponatremia will begin to correct their hyponatremia without developing signs of volume overload. Conversely, in patients with SIADH, the urine $[Na^+]$ will increase but the serum $[Na^+]$ will remain unchanged or fall as the administered water is retained and the sodium load excreted in a smaller volume of concentrated urine.[54]

Euvolemic Hyponatremia

Many different hypo-osmolar disorders can potentially present clinically with a normal ECF volume or euvolemia. This occurs in large part because two-thirds of body water is intracellular. Only one-third of retained water will reside in the ECF, and it is difficult to detect modest changes in ECF volume status by routine clinical assessment. Most patients with hyponatremia are clinically euvolemic because of the high prevalence of SIADH. Euvolemia is generally diagnosed clinically from the history, physical examination, and laboratory results. Patients without clinical signs of volume depletion (eg, orthostatic decreases in blood pressure, decreased skin turgor, increases in pulse rate, dry mucus membranes) or volume expansion (eg, subcutaneous edema, ascites) should be considered to be euvolemic absent other evidence suggesting an abnormal ECF volume status. Supportive laboratory results include a normal or low BUN and a low serum uric acid level.[55] However, measuring the urine $[Na^+]$ is most helpful in this regard. A spot urine $[Na^+]$ should be ≥ 20 to 30 mmol/L in most patients with euvolemic hyponatremia, unless they have become secondarily sodium depleted. However, 2 important caveats should be considered when interpreting the urine $[Na^+]$: 1) reduced salt intake due to a low-salt diet or anorexia may lower the urine $[Na^+]$ in patients with SIADH, and 2) the urine $[Na^+]$ may be elevated by diuretic therapy. When the clinical assessment of ECF volume is equivocal, or the urine $[Na^+]$ is <20 to 30 mmol/L, a trial of volume expansion with isotonic saline can be helpful to ascertain the correct diagnosis (see the subsequent section: *Therapy of Hyponatremias, Hypovolemic Hyponatremia*).

Hypervolemic Hyponatremia

The presence of a clinically detectable increased ECF volume generally reflects hypervolemia from some degree of body Na^+ excess. In such patients, hypo-osmolality results from an even greater expansion of body water caused by a reduction in water excretion that is secondary to either or both an excess of AVP secretion or imbalances in intrarenal factors that limit the maximal excretion of free water. Hyponatremia with ECF volume excess can arise in a variety of diseases. Because intravascular volume cannot be easily measured directly, volume excess is a clinical diagnosis made from the history, physical examination, and laboratory results. Patients with signs of volume overload (eg, subcutaneous edema, ascites, pulmonary edema) should be considered to be

hypervolemic, unless there are alternative explanations for these findings. When available, hemodynamic measurements can corroborate the clinical impression. Elevation of plasma levels of brain natriuretic peptide provides useful laboratory support for the presence of volume overload. The urine [Na^+] or fractional sodium excretion are usually low (spot urine [Na^+] <20-30 mmol/L) in patients with hypervolemic hyponatremia due to activation of the renin-angiotensin-aldosterone system with secondary renal sodium conservation despite the whole-body volume overload.

ETIOLOGIES AND PATHOPHYSIOLOGIES OF HYPOTONIC HYPONATREMIAS

Hypovolemic Hyponatremia

Hypovolemic hyponatremia results from loss of body sodium or potassium with secondary water retention. The solute losses may be classified as of renal or extrarenal origin. The pathophysiologies underlying the major disorders associated with hypovolemic hyponatremia are described below.

Gastrointestinal Disease. Gastric contents and stool are hypotonic. Protracted vomiting or diarrhea without replacement of fluid would, therefore, be expected to lead to volume depletion and hypernatremia. However, if patients ingest fluid and food low in sodium content (eg, "tea and toast") in conjunction with a baroreceptor-mediated stimulus to AVP secretion, hyponatremia will result instead. Most often, the diagnosis can readily be made from the history and physical examination. Signs and symptoms of volume depletion should be present. The urine [Na^+] will be low with volume depletion due to diarrhea but may be elevated with ongoing vomiting, because bicarbonaturia obligates excretion of an accompanying cation. In this instance, the urine [Cl^-], which is a more reliable indicator of volume depletion with vomiting, should be low.

Exercise-associated Hyponatremia. Hyponatremia after vigorous endurance exercise such as marathons, ultramarathons, and triathlons is well described.[56] Exercise-associated hyponatremia (EAH) originally was considered to be a form of volume-depletion-related hyponatremia resulting from loss of sodium and chloride in sweat during exercise. However, current evidence indicates that excessive water retention in the face of increased AVP secretion is responsible for most cases of EAH;[57] thus, this disorder is covered in the section on *Euvolemic Hyponatremia*.

Diuretic Therapy. Hyponatremia is a well-documented complication of diuretic use, and the diagnosis should be evident from the clinical setting. Because the sodium loss is renal, elevated urine [Na^+] is expected if diuretic use is ongoing. Thiazides are the predominant cause of diuretic-induced hyponatremia. Presumably, this is because they impair the diluting capacity of the distal tubule without affecting urinary concentration. In addition, they have been observed to upregulate aquaporin 2 (AQP2) abundance in some settings, an effect that would also increase water retention.[58] In a literature review, 73% of cases of diuretic-induced hyponatremia were caused by thiazides alone, 20% were caused by thiazides in combination with antikaliuretic agents, and 8% were caused by furosemide.[59] Because furosemide acts at the ascending limb of the loop of Henle, where it blocks sodium reabsorption and interferes with the renal concentrating mechanism, it is not surprising that furosemide is an infrequent cause of hyponatremia. Interestingly, all of the patients in this study with furosemide-associated hyponatremia also had HF, itself a cause of hyponatremia. This finding has led to the suggestion that furosemide may be associated with hyponatremia but is not causative.[60] On the other hand, furosemide has been reported to increase AVP secretion in patients with HF, even in the presence of angiotensin-converting enzyme inhibition, so it is possible that furosemide might result in further stimuli for inappropriate water reabsorption that, despite the intrarenal effects of the drug, may lead to worsened hyponatremia.

Furosemide-associated hyponatremia tends to develop after many months of therapy.[59] Reports of time of onset of thiazide-induced hyponatremia are more variable. In an earlier series, 31% of cases occurred within 5 days of commencement of therapy and an additional 31% within 14 days,[59] but more recent studies have not confirmed these results. In a series of 223 consecutive cases with serum [Na^+] <130 mmol/L, the median duration of thiazide usage was 118 days (25-757 days).[61] In an epidemiologic study, the median duration of thiazide use was 1.75 years.[62] Patients with thiazide-induced hyponatremia are typically elderly women. In one study, the mean age was 76.4 $\pm$ 9.6 years; 90% of those affected were $\geq$65 years of age, and 70% were women.[63] Although most patients with diuretic-induced hyponatremia are women, whether utilization patterns, female sex, or lower body weight confers increased risk is uncertain.[64] Furthermore, the reported risk factors are observed inconsistently. In a recent population-based study an increased risk of hyponatremia was observed with lower body mass index, but the odds ratio for development of hyponatremia was higher in males.[65] Evidence for volume depletion in thiazide-induced hyponatremia may be subtle. In the series mentioned above, only 24% of patients were judged to be clinically volume depleted despite having severe hyponatremia with a mean serum [Na^+] of 116 mmol/L (range, 98-128 mmol/L).[61]

Patients with a previous episode of thiazide-induced hyponatremia demonstrate increased susceptibility to a recurrence. When compared with both elderly and young controls, patients with a prior history had lower basal urine osmolality and demonstrated a greater fall in serum [Na^+] after rechallenge with a single dose of diuretics. Interestingly, although both control groups lost weight after receiving the diuretic, the patients who developed hyponatremia gained weight.[66] Serum uric acid levels, which

typically increase with volume depletion, were lower in patients with thiazide-induced hyponatremia when compared with normonatremic patients taking thiazides.[64] Taken together with the frequent lack of clinical evidence for volume depletion, these data suggest a role for abnormal thirst and water intake in individuals who develop thiazide-induced hyponatremia.

The urine [Na^+] concentration will be increased as an effect of diuretic administration; a level >30-50 mmol/L cannot be taken as evidence of euvolemia in a patient receiving a diuretic. Despite the point made previously about serum uric acid in thiazide-induced hyponatremia, a recent study reported that an increased fractional excretion of uric acid may be a more reliable indicator of the presence of euvolemia and SIADH in patients receiving diuretics.[52] However, we believe that the diagnosis of SIADH should be made with caution in a patient who is receiving a diuretic, particularly a thiazide. If the clinical suspicion exists that a patient receiving a diuretic actually has SIADH, reevaluation after cessation of the diuretic and a saline challenge is required.

Cerebral Salt Wasting. Cerebral salt washing (CSW) is a syndrome that has been described following subarachnoid hemorrhage, head injury, or neurosurgical procedures, as well as in other settings. The initiating event is loss of sodium and chloride in the urine, which results in a decrease in intravascular volume, leading to water retention and hyponatremia because of a baroreceptor-mediated stimulus to AVP secretion. The sodium resorptive defect has been attributed to a proximal tubular defect that is accompanied by increased uric acid and urea excretion, features that may make the use of BUN and uric acid levels unreliable for distinguishing between SIADH and CSW.[67] The incidence of CSW is unknown, but it is generally agreed to be uncommon. In a series of 187 consecutive cases of hyponatremia in neurosurgical patients, only 3.7% had CSW and 2.7% had CSW with SIADH.[68]

Differentiation of CSW from SIADH hinges upon establishing that a period of urinary sodium loss and volume depletion preceded the development of hyponatremia. Because infusion of isotonic saline into a patient with euvolemia and SIADH results in a rapid excretion of the sodium and fluid load to maintain balance, a high urine [Na^+] and urine flow rate alone do not establish that CSW is present. Physicians should review vital signs, weight, hematocrit, and input/output records to determine what the patient's volume status and net fluid balance were just before and during the development of hyponatremia. Current physical findings and hemodynamic measures should also be taken into account. Often, patients suspected to have CSW actually have SIADH, with high sodium and urine outputs driven by high sodium and fluid inputs. A cautious reduction in fluid replacement in such patients will distinguish them from individuals with CSW; only patients with the latter diagnosis will develop signs of volume depletion as fluid replacement is tapered.

Mineralocorticoid Deficiency. Patients with isolated glucocorticoid deficiency from adrenocorticotropic hormone (ACTH) suppression or deficiency do not have mineralocorticoid deficiency, so they do not have inappropriate renal sodium wasting or hyperkalemia. In these patients, hyponatremia results from a failure to fully suppress AVP release in response to hypo-osmolality. Such patients are euvolemic (see the subsequent section: *Euvolemic Hyponatremia, Glucocorticoid Deficiency*). The most common form of isolated mineralocorticoid deficiency, hyporeninemic hypoaldosteronism (type IV renal tubular acidosis), is associated with volume expansion and does not result in significant hyponatremia. In contrast, in patients with mineralocorticoid deficiency from primary adrenal insufficiency caused by adrenal destruction or hereditary enzyme deficiencies, renal sodium wasting leads to hypovolemia and a secondary volume stimulus to AVP release. Ingestion of water or administration of hypotonic fluids may lead to water retention and hyponatremia, as with volume depletion from other causes. Volume depletion with high urine [Na^+] and accompanying hyperkalemia should raise suspicion of mineralocorticoid deficiency; low urine [K^+] can provide additional confirmation. However, the absence of hyperkalemia does not exclude consideration of adrenal insufficiency, especially in children with volume depletion. In 18 children with proven mineralocorticoid deficiency, hyponatremia was observed in 88% but hyperkalemia in only 50%.[69] If combined mineralocorticoid and glucocorticoid deficiency from adrenal destruction is suspected, corticosteroids should be administered promptly even as diagnostic confirmation by measurement of aldosterone and ACTH levels, and cortisol response to cosyntropin (ACTH) stimulation, is undertaken.

Euvolemic Hyponatremia

Euvolemic hyponatremia always occurs as a result of a relative or absolute excess of body water. Although the excess body water can accumulate secondarily to overdrinking, the capability of the kidneys to excrete a large volume of electrolyte-free water makes excessive water ingestion as a sole cause of euvolemic hyponatremia very uncommon. The overwhelming majority of cases arise as a result of reduced renal electrolyte-free water excretion due to the antidiuretic actions of AVP at the kidney V2R. Very rarely, hyponatremia may be caused by non-AVP-mediated mechanisms. The major disorders associated with euvolemic hyponatremia are described below.

SIADH. SIADH is the most common cause of euvolemic hyponatremia, and is associated with many different disorders that can be divided into several major etiologic groups.[2] The criteria necessary for its diagnosis were originally defined by Bartter and Schwartz in 1967[70] and remain essentially unchanged (**Table 2**). These criteria have attained widespread clinical acceptance, but a number of interpretive considerations apply. First, to diagnose SIADH

Table 2 Criteria for Diagnosing SIADH

Decreased effective osmolality of the extracellular fluid (P_{osm} <275 mOsmol/kg H_2O).
Inappropriate urinary concentration (U_{osm} >100 mOsmol/kg H_2O with normal renal function) at some level of plasma hypo-osmolality.
Clinical euvolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites).
Elevated urinary sodium excretion (>20-30 mmol/L) while on normal salt and water intake.
Absence of other potential causes of euvolemic hypo-osmolality: severe hypothyroidism, hypocortisolism (glucocorticoid insufficiency).
Normal renal function and absence of diuretic use, particularly thiazide diuretics.

H_2O = water; kg = kilogram; mmol = millimole; mOsmol = milliosmole; P_{osm} = plasma osmolality; SIADH = syndrome of inappropriate antidiuretic hormone secretion; U_{osm} = urine osmolality.

it is not necessary for urine osmolality to exceed plasma osmolality. In the setting of hypo-osmolality, AVP secretion should be physiologically suppressed to promote an aquaresis; the urine should, therefore, be maximally dilute (ie, urine osmolality $\leq$100 mOsm/kg H_2O in adults). A urine osmolality >100 mOsm/kg, therefore, reflects inappropriate antidiuresis and is compatible with the diagnosis of SIADH. In SIADH due to a reset osmostat, urine osmolality need not be inappropriately elevated at all levels of plasma osmolality, but simply at some level under 275 mOsm/kg H_2O, as AVP secretion can be suppressed at lower levels of plasma osmolality, resulting in maximal urinary dilution.[71] Clinical euvolemia must be present to diagnose SIADH; this diagnosis cannot be made in a hypovolemic or edematous patient. This does not mean that patients with SIADH cannot become hypovolemic for other reasons; but, in such cases, the diagnosis of SIADH cannot be made until the patient is rendered euvolemic. Urine sodium excretion helps distinguish hypo-osmolality caused by a decreased effective arterial blood volume, in which case renal sodium conservation occurs, from dilutional disorders, in which renal sodium excretion is normal or increased due to ECF volume expansion. Elevated urine [Na^+] is not specific to SIADH and is also seen in renal causes of solute depletion such as diuretic use or mineralocorticoid deficiency. Conversely, if patients with SIADH become hypovolemic or solute depleted—for instance, during sodium and water restriction—urine [Na^+] may fall. Therefore, although the measurement of urine [Na^+] is central to the diagnosis of SIADH, elevated levels are neither pathognomonic nor essential. The final criterion emphasizes that SIADH remains a diagnosis of exclusion, and the absence of other potential causes of hypo-osmolality must always be verified, as discussed below. Of note, measurement of plasma AVP has never been a criterion for diagnosing SIADH because: 1) AVP levels are variably elevated in patients with SIADH, sometimes near assay detection limits; 2) AVP is difficult to measure accurately because it circulates at such low plasma levels and because sampling handling, storing, and assaying are difficult; and 3) AVP levels are elevated in all classifications of hyponatremia—hypovolemic, euvolemic, and hypervolemic—and thus would not help to differentiate among these diagnostically. In addition to the classical criteria of Bartter and Schwartz,[70] additional parameters have been suggested as valuable in the differential diagnosis of SIADH from other causes of hyponatremia. Copeptin is a large fragment of the AVP prohormone that is more stable than AVP and easier to assay. One group has suggested that the measurement of the ratio of copeptin to urine [Na^+] reliably distinguishes between hypovolemic hyponatremia and SIADH;[72] the same group has also advocated that the finding of increased fractional uric acid excretion is highly predictive of SIADH, even in patients on diuretic therapy.[52] However, neither of these measurements is widespread in clinical practice.

Nephrogenic Syndrome of Inappropriate Antidiuresis. Recent studies of children with hyponatremia have discovered 2 genetic mutations of the V2R leading to its constitutive activation and antidiuresis in the absence of AVP-V2R ligand binding.[73] These patients met all the classic criteria for a diagnosis of SIADH, except that the plasma AVP levels were found to be below detection limits by radioimmunoassay. At least 1 kindred has been described in which several individuals bearing this mutation did not manifest clinically recognized hyponatremia until late into adulthood.[74] The true incidence of these and similar V2R mutations, as well as how often they are responsible for the pattern of euvolemic hyponatremia with low or unmeasurable plasma AVP levels found in approximately 10% of patients with SIADH,[75] remains to be determined. However, based on the low number of reported cases to date, nephrogenic syndrome of inappropriate antidiuresis (NSIAD) appears to be rare as a cause of hyponatremia.

Glucocorticoid Deficiency. Isolated glucocorticoid deficiency occurs in association with pituitary disorders that impair normal ACTH secretion, leading to secondary adrenal insufficiency. The cortisol deficiency leads to failure to suppress AVP; thus, the biochemical abnormalities in isolated glucocorticoid deficiency more closely resemble SIADH rather than classical Addison's disease. Aldosterone secretion, which is under primary control of the renin-angiotensin system, remains intact; therefore, patients with hypopituitarism generally do not develop ECF volume contraction. The clinical observation that anterior pituitary insufficiency ameliorates, and sometimes even completely masks, the polyuria of patients with coexistent central diabetes insipidus[76] has led to a longstanding appreciation of the importance of glucocorticoids in water excretion.

Hyponatremia occurs frequently in ACTH-deficient patients without diabetes insipidus,[77] and diabetes insipidus may not become manifest until glucocorticoid therapy is started and enables normal electrolyte-free water excretion.

Although an apparent hypovolemia-mediated stimulus to AVP secretion is lacking, nonosmotic AVP secretion has nonetheless been strongly implicated in the impaired water excretion of glucocorticoid insufficiency, possibly secondary to associated hypotension. Elevated plasma AVP levels have clearly been documented in animals and patients[78] with hypopituitarism. That these elevated AVP levels were causally related to impaired water excretion was proven by studies using an AVP-V2R antagonist, which demonstrated near normalization of urinary dilution in adrenalectomized mineralocorticoid-replaced rats.[79] Therefore, the hyponatremia of glucocorticoid insufficiency is due to a combination of impaired electrolyte-free water excretion in the absence of normal glucocorticoid activity in the kidney, as well as the antidiuretic action of nonosmotically stimulated AVP secretion.

Glucocorticoid deficiency is primarily identified in hyponatremia by a high level of clinical suspicion, along with formal measurement of plasma cortisol concentrations. Ideally, this would be in response to dynamic stimulation with synthetic ACTH, which is a simple screening test. In situations where acute ACTH/cortisol deficiency develops and causes hyponatremia—for instance, following brain trauma or subarachnoid hemorrhage—adrenal atrophy will not have occurred, and the cortisol response to cosyntropin may give a false reassurance that cortisol dynamics are normal. Diagnosis is more difficult in this situation, as tests of the entire hypothalamic-pituitary-adrenal axis (such as the insulin tolerance test) may be contraindicated because of the risk of seizures. Simply measuring a 9 AM cortisol can provide useful empirical evidence; a level below 10 μg/dL (300 nmol/L) is unphysiological in an acutely ill patient and can serve as an indication for glucocorticoid therapy in conditions such as neurosurgical hyponatremia, where acute ACTH deficiency is a reasonable possibility.[68]

Hypothyroidism. Hyponatremia secondary to hypothyroidism is so rare that some investigators have questioned whether hypothyroidism is in fact causally related to hyponatremia.[80] If hyponatremia occurs in patients with an elevated thyroid-stimulating hormone, the assumption should not be made that hypothyroidism is the cause of the low serum [Na^+], as impaired water excretion leading to hyponatremia is seen only in patients with more severe hypothyroidism who typically are elderly and meet criteria for myxedema coma.[81] Hyponatremia may result from either primary or secondary hypothyroidism, although when hyponatremia accompanies hypopituitarism it is usually a manifestation of secondary glucocorticoid deficiency rather than hypothyroidism.

The major cause of impaired water excretion in hypothyroidism appears to be an alteration in renal perfusion and a reduced glomerular filtration rate (GFR) secondary to the systemic effects of thyroid hormone deficiency on cardiac output and peripheral vascular resistance.[82] In uncomplicated hypothyroidism, there appears to be little elevation of plasma AVP levels. However, as the hypothyroidism becomes more severe, the effective arterial blood volume can decrease sufficiently to stimulate AVP secretion via baroreceptor mechanisms. Additionally, the impaired cardiac function that often occurs with advanced myxedema can lead to an elevation in plasma AVP levels. Whether hyponatremia develops at any stage of disease progression depends on the relative balance between water intake and excretory capacity; because maximal solute-free water clearance decreases as these defects become more pronounced, the incidence of hyponatremia increases as the severity of the underlying hypothyroidism worsens.

EAH. Detailed balance studies performed during the recovery from an ultramarathon race show that runners with EAH excreted a large volume of dilute urine in contrast to normonatremic finishers who excreted a small volume of highly concentrated urine; both groups had equivalent sodium losses as reflected by positive sodium balances during recovery.[83] The decrease in serum [Na^+] after endurance exercise is directly proportional to the increase in body weight, and the athletes with EAH tended to gain weight during the exercise.[84] In marathon runners, low body mass index, race time exceeding 4 hours, consumption of fluids every mile, following advice to "drink as much as possible" during the race, and greater frequency of urination during the race have all been associated with EAH. In some studies, female sex and the use of nonsteroidal anti-inflammatory drugs were also risk factors.[56] Thus, while athletes with normonatremia and hypernatremia are often dehydrated, most runners with EAH are overhydrated as a result of excessive, and perhaps ill-advised, water ingestion over an extended race time during which water excretion is limited by nonosmotically stimulated AVP secretion.[57,85,86]

Low Solute Intake. Some cases of euvolemic hyponatremia do not fit particularly well into either a euvolemic or hypovolemic category. Among these is the hyponatremia that sometimes occurs in patients who ingest large volumes of beer with little food intake for prolonged periods (beer potomania). Even though the volume of fluid ingested may not seem sufficiently excessive to overwhelm renal-diluting mechanisms, in these cases, solute-free water excretion is limited by very low urine solute excretion as a result of the low solute content of beer, because $\geq$50 mOsmol of urinary solute excretion are required to excrete each liter of maximally dilute urine. Because of this, water retention and hyponatremia will result when fluid intake exceeds the maximum volume of urine that can be excreted based on the available urine solute.[87] Similar cases have been reported in patients on very-low-protein diets[88] or who restrict themselves to "tea and toast" diets; both these diet types are also low in solute content. Because urine osmolality is typically

very low in such patients, there is no significant role for AVP in producing the hyponatremia.

Primary Polydipsia. Excessive water intake itself is rarely of sufficient magnitude to produce hyponatremia in the presence of normal renal function. However, it is often a significant contributing factor to hyponatremia in patients with polydipsia, particularly those with underlying defects in electrolyte-free water excretion. The most dramatic cases of primary polydipsia are seen in psychiatric patients, particularly those with acute psychosis secondary to schizophrenia.[89] Studies of psychiatric patients with polydipsia have shown a marked diurnal variation in serum [Na^+] (eg, from 141 mmol/L at 7:00 AM to 130 mmol/L at 4:00 PM), suggesting that many such patients drink excessively during the daytime but then correct themselves via a water diuresis at night.[90] This and other considerations have led to defining this disorder as the psychosis-intermittent hyponatremia-polydipsia syndrome. Polydipsia has been observed in up to 20% of psychiatric inpatients, with incidences of intermittent hyponatremia ranging from 5%-10%.[91] Hyponatremic patients have often been prescribed medications, such as selective serotonin-reuptake inhibitors or phenothiazines, which can contribute to SIADH. Other conditions, such as central nervous system (CNS) sarcoidosis[92] and craniopharyngioma,[93] can also be associated with increased thirst and fluid ingestion. Consequently, polydipsic patients should be evaluated with a computed tomography or magnetic resonance imaging scan of the brain before concluding that excessive water intake is due to a psychological cause.

Sometimes excessive water intake alone will be sufficient to overwhelm renal excretory capacity and produce severe hyponatremia. Although the water excretion rate of normal adults can exceed 20 L/day (d), maximum hourly rates rarely exceed 800-1000 mL/hour (h). Studies of water loading in nonexercising athletes have indicated a similar peak urine excretion rate of 778 $\pm$ 39 mL/h.[94] Because many psychiatric patients drink predominantly during the day or during intense drinking binges, they can transiently achieve symptomatic levels of hyponatremia with total daily volumes of water intake $<$20 L if ingestion is sufficiently rapid. This likely accounts for many of the cases in which such patients present with maximally dilute urine, accounting for as many as 50% of patients in some studies, and correct quickly via a solute-free water diuresis.[95] However, other cases have been found to meet the criteria for SIADH, suggesting nonosmotically stimulated AVP secretion; some of these cases are drug induced. As might be expected, in the face of much higher than normal water intakes, virtually any impairment of urinary dilution and water excretion can lead to positive water balance and thereby produce hypo-osmolality. Thus, hyponatremia has been reported in patients with polydipsia who are taking thiazide diuretics or drugs known to be associated with SIADH. Acute psychosis itself can also cause AVP secretion, which often appears to take the form of a reset osmostat.[96] Although no single mechanism can completely explain the occurrence of hyponatremia in psychiatric patients with polydipsia, the combination of higher-than-normal water intakes plus even modest elevations of plasma AVP levels from a variety of potential causes likely accounts for a substantial portion of such cases.

Hypervolemic Hyponatremia

Disorders associated with hypervolemic hyponatremia all manifest edema formation due to renal sodium and water retention. All cases involve impairments of renal ability to excrete water maximally, principally due to AVP effects at the V2R. The pathophysiologies responsible for the major disorders associated with hypervolemic hyponatremia are described below.

HF. The renal regulation of sodium and water excretion in HF involves multiple factors. Under normal circumstances, several atrial−renal reflexes modulate renal sodium and water excretion. An increase in left atrial pressure suppresses the release of AVP and causes a water diuresis, also called the Gauer-Henry reflex. This reflex has not been demonstrated convincingly in humans to be independent of the impact of atrial pressure on atrial natriuretic factor secretion. An increase in transmural atrial pressure is known to increase atrial natriuretic factor secretion, which directly leads to an increase in sodium and water excretion. A decrease in renal adrenergic tone is another reflex that normally occurs with an increase in left atrial pressure. In the presence of HF, atrial pressure is increased, but these reflexes are blunted.[97,98] There is, however, an increase in the ventricular synthesis and release of brain natriuretic peptide, which, in theory, may attenuate the sodium and water retention associated with HF.[99]

High-pressure baroreceptors are present in the left ventricle, carotid body, aortic arch, and juxtaglomerular apparatus. Normally, tonic inhibition of adrenergic stimulation is present via the vagus and glossopharyngeal nerves from the arterial baroreceptors in the carotids and aortic arch. With decreased stretch on these receptors, as occurs in HF, the central inhibition is removed so that there is an increase in adrenergic activity, renin secretion, and AVP release.[100] A central effect of angiotensin or adrenergic activity may also be involved in the nonosmotic release of AVP in HF patients.[101]

Although the nonosmotic release of AVP is the dominant factor leading to water retention and hyponatremia in HF,[102] intrarenal events also attenuate maximal solute-free water excretion in patients with HF. With severe renal vasoconstriction in HF, a decrease in GFR occurs and peritubular Starling forces are altered in a direction to enhance tubular sodium and water reabsorption.[103,104] In addition to their effect on renal vascular tone, both adrenergic stimulation and angiotensin II activate receptors on the proximal tubular epithelium and increase sodium and water reabsorption by the kidneys.[105]

Normally, only 20% of glomerular filtrate reaches the distal diluting segment of the nephron, which begins at the

water-impermeable thick ascending limb of the loop of Henle. Thus, a GFR of 100 mL/min theoretically leads to a daily filtrate of 144 L, with 20% (ie, 28 L) reaching the distal diluting segment.[44] With normal renal function and maximal AVP suppression, the renal capacity to excrete solute-free water is, therefore, enormous. Because most HF patients become hyponatremic with only 2-3 L/d of fluid intake, the nonosmotic release of AVP, rather than intrarenal hemodynamic abnormalities, is likely to be the dominant factor in the pathogenesis of hyponatremia in HF. Studies with AVP antagonists demonstrating a prompt correction in the serum [Na^+] in patients with HF support this notion (see the subsequent section: *Vasopressin Receptor Antagonists*).

Cirrhosis. Hyponatremia occurs commonly in patients with advanced cirrhosis, but rarely in the absence of ascites.[106] The pathophysiology of hyponatremia in cirrhosis is associated with portal hypertension and a resultant arterial vasodilation of the splanchnic circulation.[107] Among several putative mediators, the most compelling evidence implicates endothelial or inducible nitric oxide synthase with increased nitric oxide.[108] As a result of the vasodilation, arterial stretch receptors in the carotids and aortic arch are unloaded with a resultant decrease in the CNS tonic inhibition of sympathetic efferent outflow. This arterial underfilling results in activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, as well as the nonosmotic secretion of AVP. The net effect of this neurohumoral activation is renal vasoconstriction with attenuation of systemic vasodilation and sodium and water retention, resulting in hyponatremia.[109]

Although the decrease in GFR and increased tubular fluid reabsorption diminish the kidneys' maximal capacity to excrete solute-free water in patients with cirrhosis, the major mediator of the hyponatremia appears to be nonosmotic AVP stimulation.[51] Plasma AVP concentration has been shown to be increased in patients with cirrhosis in the presence of hyponatremia/hypo-osmolality that in normal subjects would cause suppression to undetectable levels.[110] Moreover, as with HF, V2R antagonists have been shown to correct the hyponatremia in patients with cirrhosis[4] (see the subsequent section: *Vasopressin Receptor Antagonists*).

Acute Kidney Injury, Chronic Kidney Disease, and Nephrotic Syndrome. Even with complete suppression of AVP release, hyponatremia may occur in acute kidney injury as a result of the diminished GFR. In oliguric or nonoliguric acute kidney injury, the urine output is relatively fixed, and water intake in excess of urine output and insensible losses will cause hyponatremia. Patients with advanced chronic kidney disease (CKD) are also more prone to develop hyponatremia than individuals with normal kidney function for the same reason. A study of 655,493 patients with CKD and a mean estimated GFR of 50.2 $\pm$ 14.1 mL/min/1.73 m^2 demonstrated a 13.6% prevalence of hyponatremia at baseline; 26% of patients had $\geq$1 episode of hyponatremia during a 5.5-year follow-up.[111] The decreased serum [Na^+] in these patients with CKD correlated with increased mortality independent of comorbid conditions. Whether nonosmotic stimulation of AVP is involved in patients with CKD who have hyponatremia is not known, but certainly the decreased GFR must contribute. In patients with end-stage renal disease who are on dialysis, it has been shown that predialysis hyponatremia was present in 29.3% of patients and correlated with increased mortality.[112] This relationship was independent of the mode of hemodialysis, ultrafiltration volume, HF, or volume overload.

Hyponatremia with nephrotic syndrome has been less frequently reported, perhaps because many of these patients have normal kidney function. Moreover, volume overload in patients with nephrotic syndrome may suppress AVP secretion.[113] However, when serum albumin concentration falls below 2 g/dL, intravascular hypovolemia may cause nonosmotic stimulation of AVP secretion and lead to hyponatremia.

RATE OF CORRECTION OF HYPONATREMIA

No data suggest that the etiology of the hyponatremia or the method used to correct hyponatremia influence susceptibility to complications from overly rapid correction. Consequently, the rate of correction of hyponatremia must be taken into account before deciding the most appropriate therapy for any hyponatremic patient.

Brain Adaptation to Hyponatremia

To understand the scientific rationale supporting guidelines for correcting hyponatremia, and why the consequences and treatment of acute and chronic hyponatremia differ, it is essential to appreciate how the brain adapts to hyponatremia and the time course over which this process occurs.

Acute versus Chronic Hyponatremia. Treatment regimens for hyponatremia should always respect the pathophysiology of the disease. Because intracellular and extracellular osmolality must be equal, cells either swell with water or extrude solutes when the serum [Na^+] is low.[114,115] Given the confines of the skull, cell swelling is most important in the brain. When hyponatremia develops quickly over several hours, the ability of the brain to adapt is exceeded, and cerebral edema may result. Thus, patients with acute (<48 hours) hyponatremia may present with alarming neurological findings, and they sometimes die of brain herniation.[116] In chronic hyponatremia, brain cells extrude organic solutes from their cytoplasm, allowing intracellular osmolality to equal plasma osmolality without a large increase in cell water.[117] Therefore, when hyponatremia develops over several days, brain swelling is minimized so that patients with chronic ($\geq$48 hours) hyponatremia have more modest symptoms and almost never die of brain herniation.[118]

Hyponatremic Encephalopathy. Cerebral edema from water intoxication was first recognized in the 1920s. The

first fatality from acute postoperative hyponatremia was reported in 1936, and an account of the first successful treatment was published by the same author 2 years later, in which a woman was rescued from her moribund condition by the bolus infusion of 130 mL of 5% saline (NaCl), enough to increase the serum [Na^+] by about 4 mmol/L.[119] Over the ensuing decades, few refinements were made to this approach. To avoid confusion with 5% dextrose in water, 5% NaCl has been largely replaced with 3% NaCl. In 2005, a consensus conference convened to develop treatment guidelines for acute water intoxication from EAH in competitive runners advocated treatment with a 100-mL bolus of 3% NaCl, enough to increase the serum [Na^+] approximately 2 mmol/L.[86] A small, quick increase in the serum [Na^+] (2-4 mmol/L) is effective in treating acute hyponatremia because reducing brain swelling even slightly will substantially decrease intracerebral pressure.[120]

Osmotic Demyelination. The adaptation that permits survival in chronic hyponatremia also makes the brain vulnerable to injury from overzealous therapy. When hyponatremia is corrected too rapidly, the brain's ability to recapture lost organic osmolytes can be outpaced, leading to osmotic demyelination.[121,122] Complications of rapid correction of chronic hyponatremia were first recognized in the 1970s. Clinical observations in patients with central pontine and extrapontine myelinolysis led to experimental studies showing that the human disorder could be reproduced in chronically hyponatremic dogs, rabbits, and rats. Animals with severe, uncorrected chronic hyponatremia do not develop brain lesions, which confirms that myelinolysis is a complication of the rapid correction of hyponatremia and not the electrolyte disturbance itself. Similarly, demyelination can occur occasionally in patients who develop acute hypernatremia, and it can be induced by rapid induction of severe hypernatremia in normonatremic animals.[123,124]

The neurological complications of chronic hyponatremia present in a stereotypical biphasic pattern that has been called the osmotic demyelination syndrome (ODS).[121] Patients initially improve neurologically with correction of hyponatremia, but then, one to several days later, new, progressive, and sometimes permanent neurological deficits emerge. Most patients with ODS survive, and those with persistent deficits can be diagnosed with magnetic resonance imaging.[125] Several lines of evidence have linked the pathogenesis of myelinolysis to the slow reuptake of organic osmolytes by the brain, which can predispose to disruption of the blood−brain barrier and influx of immune-competent proteins.[126] In experimental models, brain regions that are slowest to recover osmolytes are the most severely affected by myelinolysis.[127] Uremia protects against myelinolysis, and brain osmolytes are recovered more rapidly during correction of hyponatremia in uremic animals than in nonuremic animals.[128] Finally, infusion of myo-inositol—a major osmolyte lost in the adaptation to hyponatremia—protects against mortality and myelinolysis from rapid correction of hyponatremia in rats.[129]

The risk of ODS varies, depending on several factors. It is highly unlikely to occur in patients who have been hyponatremic for <24 hours or in patients whose serum [Na^+] is ≥120 mmol/L, unless other factors are present that place the patient at high risk or the serum [Na^+] rises above normal ranges.

Current Recommendations for Rate of Correction of Hyponatremia

Acute Hyponatremia. Brain herniation, the most dreaded complication of hyponatremia, is seen almost exclusively in patients with acute hyponatremia (usually <24 hours) or in patients with intracranial pathology.[130-132] In postoperative patients and in patients with self-induced water intoxication associated with endurance exercise, psychiatric diseases (eg, acute psychosis, schizophrenia), or use of drugs such as "ecstasy" (methylenedioxy-N-methamphetamine or MDMA), nonspecific symptoms like headache, nausea, vomiting, or confusion can rapidly progress to seizures, respiratory arrest, and ultimately, death, or to a permanent vegetative state as a complication of severe cerebral edema.[133] Hypoxia from noncardiogenic pulmonary edema or hypoventilation may exacerbate brain swelling caused by the low serum [Na^+].[134,135] Seizures can complicate both severe chronic hyponatremia and acute hyponatremia. Although usually self-limited, hyponatremic seizures may be refractory to anticonvulsants.

A review of the limited available literature concluded that a 4- to 6-mmol/L increase in serum [Na^+] is sufficient to reverse the most serious manifestations of acute hyponatremia.[132] Similarly, published experience with hypertonic saline to treat cerebral edema in patients who are normonatremic and have neurosurgical conditions has shown that a 5-mmol/L increase in serum [Na^+] promptly reverses clinical signs of herniation and reduces intracranial pressure by nearly 50% within an hour.[136] Therefore, although data are limited, we agree with a regimen advocated by a consensus conference on symptomatic hyponatremia in marathon runners—a 100-mL bolus of 3% saline infused over 10 minutes to be given in the field for severe symptoms and repeated twice if needed.[86,137] Experience with this regimen in a small number of runners to date has been favorable.[138]

After this initial correction, the purpose of which is to correct cerebral edema, treat or prevent hyponatremic seizures, and improve level of consciousness, the serum [Na^+] can be allowed to correct to normal quickly in patients with self-induced water intoxication who have been hyponatremic for only several hours. This will typically occur spontaneously if AVP secretion is suppressed, which results in the excretion of a large volume of dilute urine in the absence of further water ingestion.

Chronic Hyponatremia. Six cohort studies[118,122,125,139-141] and 3 reviews of the literature by 3 different authors[59,121,142] have concluded that, in patients with chronic hyponatremia,

Expert Panel Recommendation: Treatment of Symptomatic Acute Hyponatremia

- Indications:
  - Self-induced acute water intoxication (eg, psychiatric diseases such as acute psychosis or schizophrenia, endurance exercise, "ecstasy" use);
  - Known duration of hyponatremia <24-48 hours (eg, postoperative);
  - Intracranial pathology or increased intracranial pressure;
  - Seizures or coma, regardless of known chronicity.
- Goal:
  - Urgent correction by 4-6 mmol/L to prevent brain herniation and neurological damage from cerebral ischemia.
- Recommended Treatment:
  - For severe symptoms, 100 mL of 3% NaCl infused intravenously over 10 minutes × 3 as needed;
  - For mild to moderate symptoms with a low risk of herniation, 3% NaCl infused at 0.5-2 mL/kg/h;
  - The rate of correction need not be restricted in patients with true acute hyponatremia, nor is relowering of excessive corrections indicated (**Figure 3**); however, if there is any uncertainty as to whether the hyponatremia is chronic versus acute, then the limits for correction of chronic hyponatremia should be followed (see section: *Current Recommendations for Rate of Correction of Hyponatremia*).

neurological sequelae are associated with more rapid rates of correction.

Although there are differences in terminology (eg, osmotic demyelination, pontine and extrapontine myelinolysis, cerebral demyelinating lesions), virtually all investigators now agree that overly rapid correction of hyponatremia risks iatrogenic brain damage.[130,143,144] A variety of guidelines derived from small numbers of patients have provided varying estimates of correction rates that should not be exceeded. Therapeutic limits have been expressed in terms of mmol/L/h, mmol/L/24 h, and mmol/L/48 h. For the past 25 years, there has been universal agreement that correction by >25 mmol/L within 48 hours is excessive;[145] but more recently, many authors have argued that the therapeutic limit is still set too high. Rates expressed in mmol/L/h have led to considerable confusion in the literature. In most studies linking the rate of correction of hyponatremia to outcomes, the hourly rate of correction was computed by dividing the total increase in the serum [Na^+] by the time it took to increase the [Na^+] from its initial value to a final value. Using this average rate can lead to misleading conclusions, particularly if the treatment is extended over many days and in patients with a very low starting serum [Na^+]. If an end point of 130 mmol/L is used to compute the rate—as it was for one frequently cited analysis[146]—one might conclude erroneously that patients with neurological sequelae had not been corrected rapidly, despite treatment with hypertonic saline and correction by >25 mmol/L during a 48-hour interval.

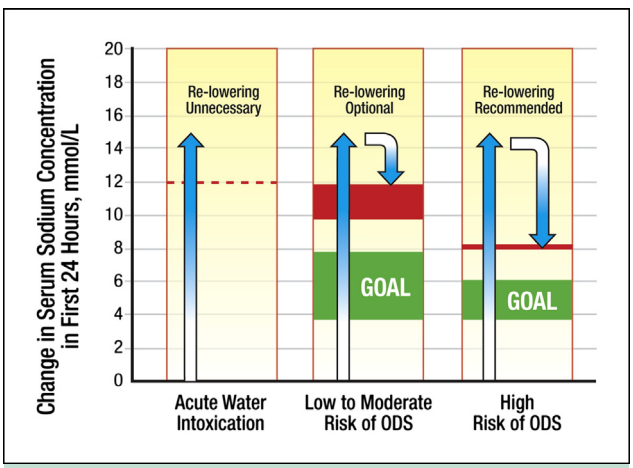

Figure 3 Recommendations for relowering of serum sodium concentration ([Na^+]) to goals (green) for patients presenting with serum [Na^+] <120 mmol/L who exceed the recommended limits of correction (red) in the first 24 hours. Abbreviations: L = liter; mmol = millimole; ODS = osmotic demyelination syndrome.

Current published estimates of the recommended 2-day limit are actually quite similar—18 mmol/L versus 15-20 mmol/L within 48 hours.[130,131,137] However, a 2-day limit can also be confusing. These limits are sometimes expressed as applying to the first 2 days of therapy, ignoring the possibility that initial therapy in the first day might be delayed or ineffective and might be followed by a large increase in serum [Na^+] on subsequent days. It is unlikely that the adverse neurological events caused by a large osmotic insult will be lessened by such a delay. In fact, if the duration of severe hyponatremia were prolonged before a large increase in serum [Na^+], chronicity would be expected to enhance the brain's vulnerability to injury.[129,147] A 2-day increment is also difficult to implement in practice because clinicians instinctively base their treatments on changes that have occurred since the previous day.

A 1-day increase of 12 mmol/L/d was initially proposed based on a literature review and observational studies of outcomes in patients with severe hyponatremia.[121] The same limit was recently validated in a single-center observational study of 255 patients with serum [Na^+] ≤120 mmol/L.[141] Four patients with typical ODS were identified, all presenting initially with serum [Na^+] <105 mmol/L with hypokalemia and all corrected by >12 mmol/L/d; no neurological sequelae were observed among 118 patients (85%) corrected by ≤12 mmol/L/d. Other evidence, however, suggests that this 1-day limit may be too high, particularly for patients with severe malnutrition, alcoholism, or advanced liver disease who may be especially susceptible to osmotic demyelination.[148] Although not rigorously proven to increase the susceptibility to ODS, alcoholism, hypokalemia, malnutrition, and liver disease are

present in a high percentage of patients who develop the syndrome after correction of hyponatremia. Unlike the rate of increase in serum [Na^+], neither the precise level of the serum [K^+] nor the degree of alcoholism, liver disease, or malnutrition that alter the brain's tolerance to an osmotic stress has been (or perhaps can be) defined. Clinicians should be extra cautious about raising the serum [Na^+] when it is known or suspected that a patient harbors these risk factors to any significant degree. A prospective cohort study of 184 consecutive patients with serum [Na^+] $\leq$120 mmol/L confirmed that sequelae were associated with more rapid correction; but, of the 9 patients with sequelae whose serum [Na^+] was measured during the first 24 hours of correction, 3 had been corrected by 12 mmol/L, 2 by 11 mmol/L, and 1 by 10 mmol/L.[139] Similarly, case reports and case series of patients with ODS have included a few patients corrected by <12 mmol/L/d. However, this finding can be misleading; for example, in a series of 6 patients with ODS after hyponatremia treatment, a first-day increase by 7 and 10 mmol/L in 2 cases was followed by a 14- and 18-mmol/L increase, respectively, on the second day.[123]

Drawing a distinction between 1-day and 2-day correction limits is premised on the assumption that a larger increase in serum [Na^+] is necessary on the first day of therapy to prevent complications of untreated severe hyponatremia. As discussed earlier, a 6-mmol/L increase in serum [Na^+] appears to be adequate to treat the most severe manifestations of acute hyponatremia. Although there is some evidence that correction by <3 to 4 mmol/L/24 h may be associated with excess mortality in patients with acute or postoperative hyponatremia,[149,150] there is no evidence that correction by >6 mmol/L/24 h improves outcomes in acute or chronic hyponatremia. In a recent single-center study of 168 patients with serum [Na^+] $\leq$120 mmol, correction rates in the 64% of patients with neurological symptoms and in the 36% without symptoms did not differ in the first 24 hours (5 mmol/L vs. 6 mmol/L), the second 24 hours (6 mmol/L vs. 5 mmol/L), or the third 24 hours (3 mmol/L vs. 3 mmol/L), and these slow rates of correction were not associated with adverse outcomes.[151]

Concerns about rare reports of post-therapeutic neurological complications after correction once thought to be safe, and reports of favorable outcomes after conservative therapy have led some authors to suggest that the maximum correction limit be set at 6-8 mmol/L for any 24-hour period.[143] Although this is a reasonable goal for most patients, in practice it is unlikely to be achievable as a limit in most centers. However, as discussed below, when this 1-day goal is exceeded, efforts to attenuate or stop further correction on the subsequent day can be implemented to avoid exceeding the 2-day limit.

Complications of therapy often occur in patients whose hyponatremia autocorrects unexpectedly during the course of treatment.[131,132,152,153] Patients with hyponatremia caused by volume depletion, cortisol deficiency, desmopressin, or thiazides are particularly vulnerable. In these disorders, once the cause of hyponatremia is eliminated by volume repletion, cortisol replacement, or discontinuation of desmopressin or thiazides, an aquaresis emerges. Without a nonosmotic stimulus for AVP secretion, patients who are hyponatremic excrete maximally dilute urine, which can increase the serum [Na^+] by more than 2 mmol/L/h. Potentially life-threatening overcorrection may result in as little as 12 hours. Given the risk of overshooting the recommended maximal increases, it is best to aim for a correction (the correction *goal*) that falls well short of rates associated with harm (the correction *limit*) and to monitor the serum [Na^+] and the urine volume frequently.

Because a 6-mmol/L increase appears to be sufficient for patients with the most severe manifestations of hyponatremia, we believe that the goal of therapy (ie, the desired increase in serum [Na^+]) in chronic hyponatremia should be 4-8 mmol/L/d for those at low risk of ODS, with an even lower goal of 4-6 mmol/L/d if the risk of ODS is high (**Figure 3**, **Table 3**). For patients with severe symptoms, the first day's increase can be accomplished during the first 6 hours of therapy, with subsequent increases postponed until the next day. The strategy has been described as an easy-to-remember "rule of sixes," using the abbreviation *sx's* for symptoms: "six a day makes sense for safety; so six in six hours for severe sx's and stop."[154]

Managing Excessive Correction of Chronic Hyponatremia. If the correction exceeds therapeutic limits (ie, rates associated with potential harm), the approach will depend on the relative risk of developing ODS. Patients who have been hyponatremic for only a few hours due to self-induced water intoxication related to psychosis or endurance exercise often develop a spontaneous water diuresis that rapidly brings their serum [Na^+] back to normal. Although this autocorrection may exceed commonly accepted limits of 10-12 mmol/L/d or 18 mmol/L within 48 hours in these cases, the risk of osmotic demyelination is low,[95] and efforts to prevent or reverse overcorrection are unnecessary (**Figure 3**).

The longer the duration of hyponatremia and the lower the serum [Na^+], the greater the concern for injury due to overcorrection of hyponatremia. Except for patients with

Table 3 Factors That Place Patients at High Risk of Developing the Osmotic Demyelination Syndrome with Correction of Chronic Hyponatremia

High Risk of Osmotic Demyelination Syndrome

- Serum sodium concentration $\leq$105 mmol/L
- Hypokalemia*
- Alcoholism*
- Malnutrition*
- Advanced liver disease*

L = liter; mmol = millimole.

*Unlike the rate of increase in serum sodium concentration, neither the precise level of the serum potassium concentration nor the degree of alcoholism, malnutrition, or liver disease that alters the brain's tolerance to an acute osmotic stress have been rigorously defined.

Expert Panel Recommendation: Avoiding Osmotic Demyelination Syndrome (ODS) in Patients with Chronic Hyponatremia

- Population at risk: hyponatremia with serum [Na^+] ≤120 mmol/L of >48 hours' duration; for example, outpatients drinking conventional volumes of water or treated with thiazides and hospital-acquired hyponatremia with a known duration of >48 hours.
- Increased vigilance in patients at heightened risk of ODS (see **Table 3**).
- Goal:
  - Minimum correction of serum [Na^+] by 4-8 mmol/L per day, with a lower goal of 4-6 mmol/L per day if the risk of ODS is high.
- Limits not to exceed:
  - For high risk of ODS: 8 mmol/L in any 24-hour period;
  - For normal risk of ODS: 10-12 mmol/L in any 24-hour period; 18 mmol/L in any 48-hour period.

self-induced water intoxication, careful monitoring and therapeutic interventions to prevent and reverse overcorrection are indicated for patients with a serum [Na^+] ≤120 mmol/L, particularly those with comorbidities that increase the risk of osmotic demyelination (**Table 3**, **Figure 3**). Serum [Na^+] measurements at 4- to 6-hour intervals and monitoring of urine volume are advisable until mildly hyponatremic levels of ≥125 mmol/L have been reached. In high-risk patients, correction by more than 8 mmol/L/d should be actively avoided; whereas in patients without major risk factors for osmotic demyelination, correction by 8-12 mmol/L in the first day of therapy is greater than necessary but is unlikely to cause harm as long as the 2-day increment does not exceed 18 mmol/L. If the day's increase has exceeded 8 mmol/L, active therapies to raise the serum [Na^+] any further should be avoided for the next 24 hours.

To prevent overcorrection, ongoing measures to increase the serum [Na^+] (eg, saline or vaptan therapy) should be temporarily withheld once the targeted daily increase has been achieved. For the rest of the day, further correction from urinary free water losses should be prevented either by replacing losses with 5% dextrose in water or oral water or by terminating further urinary losses by administering 2-4 μg of desmopressin parenterally (**Figure 3**). Alternatively, rather than waiting for an unwelcome aquaresis in patients with potentially reversible causes of hyponatremia, one group has advocated preemptive administration of desmopressin every 6-8 hours in combination with a slow infusion of 3% saline titrated to achieve a 6-mmol/L/d increase in serum [Na^+]. This strategy creates a state of iatrogenic SIADH and permits a controlled increase in the serum [Na^+] with a low risk of inadvertent overcorrection; desmopressin is stopped once the serum [Na^+] has been raised to 128 mmol/L.[155]

Desmopressin is not a reliable therapeutic option for patients corrected with vaptans, but urinary water losses usually stop after the drug is metabolized. Correction by >12 mmol/L/d is uncommon with vaptan therapy, and no cases of osmotic demyelination have been reported after vaptan therapy alone (without concurrent saline therapy). Nonetheless, it is prudent to withhold the next day's dose after a large increase in serum [Na^+], with resumption of the same dose or a lower dose in subsequent days.

If overcorrection occurs, therapeutic re-lowering of the serum [Na^+] can be considered, but it has not been validated in controlled trials. Re-lowering of the serum [Na^+] prevents osmotic demyelination in experimental animals[156] and has been shown to be well tolerated in a small series of patients.[152] It can be achieved by administering 2-4 μg of desmopressin in combination with repeated 3-mL/kg infusions of 5% dextrose in water administered over 1 hour—measuring the serum [Na^+] after each infusion to determine the need for more 5% dextrose in water—until the serum [Na^+] has been returned to a level below the therapeutic limit for the patient. In the absence of risk factors for osmotic demyelination, a limit of 10-12 mmol/L in any 24-hour period or 18 mmol/L in any 48-hour period appears to be appropriate; in high-risk patients (**Table 3**), correction by >8 mmol/L in any 24-hour period may be justification for therapeutic re-lowering (**Figure 3**). Studies in experimental animals have also shown benefit from administration of high doses of glucocorticoids to stabilize and prevent osmotic disruption of the blood−brain barrier, but efficacy of this approach has not been verified in human patients.[157]

Expert Panel Recommendation: Managing Excessive Correction of Chronic Hyponatremia

- Starting serum [Na^+] ≥120 mmol/L: Intervention probably unnecessary.
- Starting serum [Na^+] <120 mmol/L:
  - Replace water losses or administer desmopressin after correction by 6-8 mmol/L during the first 24 hours of therapy;
  - Withhold the next dose of vaptan if the correction is >8 mmol/L;
  - Consider therapeutic re-lowering of serum [Na^+] if correction exceeds therapeutic limits;
  - Consider administration of high-dose glucocorticoids (eg, dexamethasone, 4 mg every 6 hours) for 24-48 hours following the excessive correction.
- Re-lowering serum [Na^+]:
  - Administer desmopressin to prevent further water losses: 2-4 μg every 8 hours parenterally;
  - Replace water orally or as 5% dextrose in water intravenously: 3 mL/kg/h;
  - Recheck serum [Na^+] hourly and continue therapy infusion until serum [Na^+] is reduced to goal (**Figure 3**).

VASOPRESSIN RECEPTOR ANTAGONISTS (VAPTANS)

Vaptans have long been anticipated as a more effective method to treat hyponatremia by virtue of their unique effect to selectively increase solute-free water excretion by the kidneys.[158] The recent approval by the FDA of 2 such agents, conivaptan and tolvaptan, for clinical use and the application of a third drug, lixivaptan, mark the beginning of a new era in the management of hyponatremic disorders. Intelligent use of vaptans for FDA-approved indications will need to be based on existing knowledge of the pathophysiology of hyponatremia and a physiologic understanding of how these agents work gleaned from the results of clinical trials and accumulated experience with clinical use.

Vasopressin Receptors

AVP receptors (AVPR) are G-protein-coupled receptors. The 3 known subtypes differ in localization and in signal transduction mechanisms.[159] The AVP V1a (V1aR) and V1b (V1bR) receptors are G_q-coupled receptors that activate phospholipase C and increase cytosolic free calcium; the physiological effects caused by activation depend primarily on the localization of the receptors and include vasoconstriction, platelet aggregation, ionotropic stimulation, and myocardial protein synthesis (all V1aR) and pituitary ACTH secretion (V1bR). V2Rs are found on the principal cells of the renal collecting tubules and the vascular endothelium, where they mediate the antidiuretic effects of AVP and stimulate release of von Willebrand factor and factor 8, respectively. V2R-mediated vasodilatation has also been described at high concentrations of AVP. Binding of AVP to its V2R activates the G_s-coupled adenylyl cyclase system, thereby increasing intracellular levels of cyclic adenosine monophosphate. In the kidney, this activates protein kinase A, which then phosphorylates preformed AQP2 water channels localized in intracellular vesicles. Phosphorylation stimulates trafficking of the vesicles to the apical membrane, followed by insertion of AQP2 into the membrane[160] (**Figure 2**). Activation of this signal transduction cascade is necessary to render the collecting duct permeable to water. AQP2 membrane insertion and transcription, and hence, apical membrane water permeability, is reduced when AVP is absent or chronically suppressed.

Mechanism of Action

Binding of the antagonists to V2R blocks activation of the receptor by endogenous AVP. The increased urine output produced by the V2R antagonists is quantitatively equivalent to that of diuretics such as furosemide; qualitatively it is different in that only water excretion results and excretion of urinary solutes is not augmented.[161] Thus, V2R antagonists produce solute-sparing water excretion in contrast to classic diuretic agents that block distal tubule sodium transporters, leading to simultaneous electrolyte and water losses. For this reason, the renal effects produced by V2R antagonists have been termed *aquaretic* to distinguish them from the renal effects produced by classical diuretic agents, which are natriuretic and kaliuretic as well. This is not simply a semantic issue, because appreciating these important differences in renal effects is crucial for the intelligent clinical use of AVP receptor antagonists. For example, the negative water balance induced by aquaretic agents has less adverse effect on neurohormonal activation and renal function than comparable degrees of urine output induced by loop diuretic agents, because only one third of the negative water balance induced by aquaretics derives from the ECF, whereas two thirds comes from intracellular water.[162]

Vaptans in Clinical Use and Development

Four nonpeptide agents have been studied in clinical trials (**Table 4**). Conivaptan is a combined V1aR and V2R antagonist, while all of the others are selective V2R antagonists.

Conivaptan is FDA approved for euvolemic and hypervolemic hyponatremia in hospitalized patients. It is available only as an intravenous preparation and is given as a 20-mg loading dose over 30 minutes, followed by a continuous infusion of 20 or 40 mg/d.[163] Generally, the 20-mg

Table 4 AVP Receptor Antagonists Evaluated in Clinical Trials

	Conivaptan	Lixivaptan	Satavaptan	Tolvaptan
Compound	YM-087	VPA-985	SR-121463	OPC-41061
Receptor	V1a/V2	V2	V2	V2
Route of administration	IV	Oral	Oral	Oral
Urine volume	↑	↑	↑	↑
Urine osmolality	↓	↓	↓	↓
Sodium excretion/24 hours	↔	↔ at low dose ↑ at high dose	↔	↔
Company developing agent	Astellas Pharma US, Inc.	Cornerstone	Sanofi-Aventis	Otsuka America Pharmaceutical, Inc.
Status	FDA-approved	Phase 3 studies completed	Development suspended	FDA- and EMA-approved

↑ = increased; ↓ = decreased; ↔ = no change; AVP = arginine vasopressin; EMA = European Medicines Agency; FDA = US Food and Drug Administration; IV = intravenous; V1a = vasopressin receptor 1a; V2 = vasopressin receptor 2.

continuous infusion is used for the first 24 hours to gauge the initial response. If the correction of serum [Na^+] is felt to be inadequate (eg, <5 mmol/L), then the infusion rate can be increased to 40 mg/d. Therapy is limited to a maximum duration of 4 days because of drug-interaction effects with other agents metabolized by the CYP3A4 hepatic isoenzyme. Importantly, for conivaptan and all other vaptans, it is critical that the serum [Na^+] concentration is measured frequently during the active phase of correction of the hyponatremia—a minimum of every 6-8 hours for conivaptan, but more frequently in patients with risk factors for osmotic demyelination (see previous section: *Rate of Correction*).[3] If the correction exceeds 8-12 mmol/L in the first 24 hours, the infusion should be stopped and the patient monitored closely. Consideration should be given to administering sufficient water, either orally or as intravenous 5% dextrose in water, to avoid a correction of >12 mmol/L/d. The maximum correction limit should be reduced to 8 mmol/L over the first 24 hours in patients with risk factors for osmotic demyelination, as stressed previously (**Table 3**). The most common side effects of conivaptan include headache, thirst, and hypokalemia.[164]

Tolvaptan, an oral V2R antagonist, is also FDA approved for the treatment of euvolemic and hypervolemic hyponatremia. In contrast to conivaptan, the availability of tolvaptan in tablet form allows both short- and long-term use.[4] Similar to conivaptan, tolvaptan treatment must be initiated in the hospital so that the rate of correction can be monitored carefully. In the US, patients with a serum [Na^+] <125 mmol/L are eligible for therapy with tolvaptan as primary therapy; if the serum [Na^+] is ≥125 mmol/L, tolvaptan therapy is only indicated if the patient has symptoms that could be attributable to the hyponatremia and the patient is resistant to attempts at fluid restriction.[165] In the European Union, tolvaptan is approved only for the treatment of euvolemic hyponatremia, but any symptomatic euvolemic patient is eligible for tolvaptan therapy regardless of the level of hyponatremia or response to previous fluid restriction. The starting dose of tolvaptan is 15 mg on the first day, and the dose can be titrated to 30 mg and 60 mg at 24-hour intervals if the serum [Na^+] remains <135 mmol/L or the increase in serum [Na^+] has been <5 mmol/L in the previous 24 hours. As with conivaptan, it is essential that the serum [Na^+] concentration is measured frequently during the active phase of correction of the hyponatremia at a minimum of every 6-8 hours, particularly in patients with risk factors for osmotic demyelination (**Table 3**). Goals and limits for safe correction of hyponatremia and methods to compensate for overly rapid corrections are the same as described previously for conivaptan. One additional factor that helps to avoid overly rapid correction with tolvaptan is the recommendation that fluid restriction not be used during the active phase of correction, thereby allowing the patient's thirst to compensate for an overly vigorous aquaresis. Common side effects of tolvaptan include dry mouth, thirst, increased urinary frequency, dizziness, nausea, and orthostatic hypotension.[4,165]

Vaptans are not indicated for treatment of hypovolemic hyponatremia, because simple volume expansion would be expected to abolish the nonosmotic stimulus to AVP secretion and lead to a prompt aquaresis. Furthermore, inducing increased renal fluid excretion via either a diuresis or an aquaresis can cause or worsen hypotension in such patients. This possibility has resulted in the labeling of these drugs as contraindicated for hypovolemic hyponatremia.[3] Importantly, clinically significant hypotension was not observed in either the conivaptan or tolvaptan clinical trials in euvolemic and hypervolemic hyponatremic patients. Although vaptans are not contraindicated with decreased renal function, these agents generally will not be effective if the serum creatinine is >2.5 mg/dL (see subsequent section: *Therapy of Hyponatremias, Hypervolemic Hyponatremia*).

The FDA recently issued a caution about hepatic injury that was noted in patients who received tolvaptan in a 3-year clinical trial examining the effect of tolvaptan on autosomal dominant polycystic kidney disease (ADPKD), the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO).[166] An external panel of liver experts found that 3 cases of reversible jaundice and increased transaminases in this trial were either probably or highly likely to be caused by tolvaptan. Additionally, 4.4% (42/958) of ADPKD patients on tolvaptan exhibited elevations of alanine aminotransferase test (ALT) results of >3× the upper limit of normal (ULN) compared with 1.0% (5/484) of patients on placebo. These findings indicate that tolvaptan has the potential to cause irreversible and potentially fatal liver injury. The doses used in the TEMPO study were up to twice the maximum dose approved for hyponatremia (ie, 120 mg/d vs. 60 mg/d). Furthermore, in clinical trials of tolvaptan at doses approved by the FDA for treatment of clinically significant euvolemic or hypervolemic hyponatremia, liver damage was not reported, including long-term trials of >30 days such as SALTWATER (a multicenter, open-label extension of SALT-1 and SALT-2) and EVEREST.[40,167] Based largely on the hepatic injury noted in the TEMPO trial, on April 30, 2013 the FDA recommended that: "[tolvaptan] treatment should be stopped if the patient develops signs of liver disease. Treatment duration should be limited to 30 days or less, and use should be avoided in patients with underlying liver disease, including cirrhosis."[168] The EMA has approved the use of tolvaptan for SIADH but not for hyponatremia due to heart failure or cirrhosis. Based on the TEMPO trial results, the EMA has also issued a warning about the possible occurrence of hepatic injury in patients treated with tolvaptan, but it did not recommend any restriction on the duration of treatment of SIADH patients with tolvaptan.[169] Accordingly, the authors believe that appropriate caution should be exercised in patients treated with tolvaptan for hyponatremia for extended periods (eg, >30 days), but this decision should be based upon the clinical judgment of the treating physician. Patients who are refractory to or unable to tolerate or obtain other therapies for hyponatremia, and in whom the benefit of tolvaptan

treatment outweighs the risks, remain candidates for long-term therapy with tolvaptan; but in such cases, liver function tests should be monitored carefully and serially (ie, every 3 months), and the drug discontinued in the event of significant changes in liver function tests (ie, 2× ULN of ALT). With rare exception, tolvaptan should not be used in patients with underlying liver disease given the difficulty of attributing causation to any observed deterioration of hepatic function. One such exception may be hyponatremic patients with end-stage liver disease awaiting imminent liver transplantation, who are at little risk of added hepatic injury and will benefit from correction of hyponatremia before surgery to decrease the risk of ODS postoperatively.[170]

THERAPY OF HYPONATREMIAS

Hypovolemic Hyponatremia

The first and key step in the successful treatment of hypovolemic hyponatremia is to establish that volume depletion is present. Once this is done, treatment is straightforward—with correction of the volume deficit, the relative water excess will correct itself via a water diuresis. Indeed, with severe hyponatremia due to volume depletion, the bulk of the treatment effort may be devoted to the prevention of an overly rapid increase in serum [Na^+] due to the ensuing spontaneous aquaresis. Monitoring urine volume and osmolality will permit detection of the aquaresis and allow clinicians to anticipate and avoid an unduly rapid rate of increase in serum [Na^+] (see previous section: *Managing Excessive Correction of Chronic Hyponatremia*).

When ECF volume depletion is obvious and potentially life threatening, resuscitation with isotonic fluid will likely have been begun empirically even before the results of routine laboratory tests have been returned. Volume expansion should be continued until blood pressure is restored and the patient has clinical euvolemia. Not infrequently, the initial volume estimate is equivocal, and both volume depletion and SIADH remain as diagnostic considerations. In that circumstance, a fluid challenge can be both diagnostic and therapeutic. With volume depletion, administering isotonic saline leads to an increase in both the serum and urine [Na^+] once intravascular volume has been restored. If SIADH is present, administering saline also results in an increase in urine [Na^+]. However, serum [Na^+] concentration may actually fall with isotonic saline administration as the administered sodium is excreted in a small volume of concentrated urine and the water is retained. Maximum urine-concentrating ability is insufficient to permit net water retention if hypertonic saline is used. In cases where there is even a remote possibility that the primary diagnosis is SIADH and either significant CNS symptoms from hyponatremia are present or the starting serum [Na^+] is $\leq$120 mmol/L, hypertonic saline (eg, 3% NaCl) should be used for the initial diagnostic volume challenge to avoid any risk of lowering the serum [Na^+] further.

Hypovolemic hyponatremia is nearly always chronic rather than acute, and the current limits for rate of correction of chronic hyponatremias should be carefully observed (see previous section: *Rate of Correction of Hyponatremia*). Current recommendations for treating hyponatremia in patients with specific disorders associated with hypovolemia are given below.

Gastrointestinal Disease. Hyponatremia associated with gastrointestinal fluid loss is seldom acute or severe enough in its own right to require hypertonic saline for urgent correction. Isotonic saline is the mainstay of treatment. Potassium chloride should be added if hypokalemia and metabolic alkalosis are present due to vomiting, and an isonatric mixture of NaCl and sodium bicarbonate can be used when metabolic acidosis is present because of diarrhea. Potassium is exchangeable with intracellular sodium, so supplementation to correct hypokalemia will raise serum [Na^+] to the same degree as sodium repletion. Potassium dosing should be taken into account in predicting the rate at which the serum [Na^+] increases in response to treatment. Specific therapy for the underlying disorder should be initiated, and antiemetic and antidiarrheal agents can be used as appropriate.

Diuretic Therapy. Thiazides produce hyponatremia by at least 3 separate mechanisms. They interfere with function of the distal tubule diluting site, produce volume depletion that stimulates nonosmotic AVP release, and deplete potassium leading to cellular uptake of sodium. As these disorders are reversed by withholding the diuretic and correcting sodium and potassium deficits, the serum [Na^+] may increase very rapidly in association with development of an aquaresis. ODS and an increased risk of death with rapid correction of

Expert Panel Recommendations: Hyponatremia from Gastrointestinal Losses

- Because urine [Na^+] may be high if vomiting leads to obligate urinary bicarbonate loss, urine chloride should be measured if vomiting is present to confirm the presence of solute and volume depletion.
- This is typically a chronic hyponatremia, so current limits for rate of correction of chronic hyponatremias should be observed (see *Current Recommendations for Rate of Correction of Hyponatremia*).
- After any urgent fluid resuscitation to stabilize blood pressure, tailor the repletion fluid to correct accompanying potassium or base deficits; use potassium-supplemented fluid or custom-formulated fluid incorporating sodium bicarbonate; remember that potassium administration will also increase the serum [Na^+].
- Monitor serum [Na^+] increase and urine volume frequently and urine osmolality as needed; switch to hypotonic fluid to retard the rate of correction once the correction approaches goal (**Figure 3**).

diuretic-induced hyponatremia are well described, so the precautions described elsewhere in this review regarding the maximal daily increase in serum [Na^+] should be followed scrupulously, and vigilance for emergence of autocorrection is essential (see previous section: *Current Recommendations for Rate of Correction of Hyponatremia*).

Initial treatment consists of withholding all diuretics and cautiously repleting the patient with isotonic fluid if CNS abnormalities are mild. Hypertonic saline is indicated to raise the serum [Na^+] by 4-8 mmol/L acutely when seizures or a significantly altered level of consciousness are present. However, furosemide should not be used with the hypertonic saline because of the risk of precipitating hypotension, and a minimum of hypertonic fluid should be administered in anticipation of the water diuresis that will ensue. Correction of hypokalemia presents a special problem. Sodium and potassium are exchangeable, as well as osmotically active. As the administered potassium enters cells to correct the intracellular deficit induced by kaliuretic diuretics like the thiazides, sodium exits and thereby raises the serum [Na^+] even without any change in external water balance and without any additional sodium administration. Orally or parenterally administered potassium will raise the serum [Na^+] to the same degree as administered sodium.[171] ODS due to potassium repletion in thiazide-induced hyponatremia has been reported.[172] Given the potential for rapid correction, encouraging oral fluid intake and administering hypotonic fluid by the enteral or parenteral route may be required to slow the rate of correction. This is one of the settings in which prophylactic administration of desmopressin may be useful.[152]

Whichever maneuver or combination of maneuvers is chosen to effect a controlled increase in serum [Na^+], frequent (every 6-8 hours, particularly when the serum [Na^+] is below 120 mmol/L) and vigilant measurement of serum [Na^+] to avoid and mitigate overcorrection is mandatory. Patients with thiazide-induced hyponatremia are at high risk for a recurrence of the disorder and should not be re-challenged with a thiazide.[66] There are no data on the risk of hyponatremia due to loop-acting agents in patients who previously developed thiazide-induced hyponatremia. If diuretic therapy is essential in such a patient, the serum [Na^+] should be measured within a few days after initiation of treatment and frequently within the first several weeks.

Expert Panel Recommendations: Diuretic-Induced Hyponatremia

- Diuretic-induced hyponatremia is always a chronic hyponatremia, so current limits for rate of correction of chronic hyponatremias should be observed (see *Current Recommendations for Rate of Correction of Hyponatremia*).
- Thiazides interfere with urinary dilution. Discontinuation of thiazides and correction of volume deficits may be followed by a rapid, spontaneous water diuresis that can raise serum [Na^+] very quickly; numerous cases of ODS have been reported after correction of severe thiazide-induced hyponatremia.
- Serially follow changes in urine osmolality together with urine volume to detect the development of an aquaresis with heightened risk of overly rapid correction.
- The focus of therapy for patients with serum [Na^+] $<$120 mmol/L is typically not on achieving adequate correction but on restraining the rate at which the [Na^+] increases.
- Frequent (every 6-8 hours) measurement of serum [Na^+] is advisable during the active correction phase until the serum [Na^+] has reached a stable value $>$125 mmol/L; once the serum [Na^+] has reached 125 mmol/L, the risk of hyponatremia-related CNS complications is low; if the starting serum [Na^+] $<$120 mmol/L, halting further correction for 1-2 days to allow slower equilibration should be considered.
- Sodium shifts out of cells in exchange for potassium as deficits of the latter are corrected after supplementation; administering potassium will raise the [Na^+] to an equivalent degree as administering sodium; therefore, potassium dosing should be taken into account in the hyponatremia treatment plan.
- Enteral water or 5% dextrose in water can be used to slow the correction if necessary; desmopressin is also useful to abrogate the water diuresis in cases where the aquaresis is pronounced (see *Rate of Correction of Hyponatremia*).

CSW. Because hypovolemia may exacerbate CNS injury, patients with CSW-related volume depletion should be resuscitated by administering isotonic saline until they become euvolemic or minimally expanded and then maintained in neutral sodium balance. Hypertonic saline should be used if impairment of the sensorium that is believed to be due to hyponatremia is present, but the correction should be no faster than recommended for other hyponatremic states. One frequently cited paper suggests combined use of isotonic saline and NaCl tablets, but this is not substantially different from using hypertonic saline.[173] The neurosurgical literature suggests that hyponatremia and fluid restriction increase the likelihood of cerebral infarction after subarachnoid hemorrhage.[174,175] These studies, however, did not assess concurrent risk factors or the severity of the injury required to induce the hyponatremia in the first place and did not establish that treating hyponatremia improved any outcome. Patients with CSW (if any) were not rigorously distinguished from those with SIADH. Nonetheless, it has been recommended that serum [Na^+] values $<$131 mmol/L be corrected, principally by using sodium supplementation with avoidance of fluid restriction.[175,176] Although evidence-based guidance is lacking, volume depletion, whether from CSW or another cause, cannot be beneficial after acute brain injury. It seems prudent to administer adequate sodium and fluid to maintain a normal

intravascular volume, as stated above. Isotonic saline, hypertonic saline, and supplemental oral NaCl have been advised, together with fludrocortisone in some instances.[176,177] Because the response to oral NaCl and fludrocortisone is unpredictable, we favor the use of hypertonic saline to correct hyponatremia (if its severity warrants) and isotonic saline for maintenance of intravascular volume.

Mineralocorticoid Deficiency. Volume repletion with isotonic saline will be required initially in patients with primary adrenal insufficiency. Fludrocortisone is used chronically for mineralocorticoid replacement, which will prevent hypovolemia-induced hyponatremia from recurring. Hyporeninemic hypoaldosteronism (type IV renal tubular acidosis) is characterized by volume expansion and is not a cause of hyponatremia; acquired mineralocorticoid deficiency severe enough to lead to volume depletion and hyponatremia occurs only with bilateral adrenal failure from adrenal destruction or adrenalectomy. As such, patients presenting with features of mineralocorticoid deficiency should be suspected to have glucocorticoid deficiency as well. The latter deficiency should be treated urgently with glucocorticoid at stress doses (eg, 50-100 mg of hydrocortisone given parenterally every 8 hours) while definitive testing results are awaited. Because stress doses of hydrocortisone also activate the mineralocorticoid receptors, replacement with fludrocortisone is not required until the patient is titrated to lower replacement doses of glucocorticoids (see subsequent section: *Therapy of Hyponatremias, Glucocorticoid Deficiency*).

Expert Panel Recommendations: Hyponatremia from CSW

- The overwhelming majority of patients in the neurosurgical setting with hyponatremia after subarachnoid hemorrhage, trauma, or surgery have SIADH, not CSW.
- Reduced BUN and uric acid values are features of both CSW and SIADH and cannot be used to distinguish between these disorders.
- Diagnosing CSW requires demonstration of a period of inappropriate renal sodium and fluid loss preceding the development of volume depletion and hyponatremia; a high urine output and urinary sodium content during sodium infusion alone are insufficient evidence because a patient with SIADH will excrete any administered sodium and fluid to maintain balance.
- To distinguish between SIADH and CSW, the response to a cautious reduction in fluid supplementation should be observed; CSW patients will develop signs of volume depletion, while SIADH patients will demonstrate reduced urine output while remaining euvolemic.
- Intravenous sodium supplementation is preferred for patients with unreliable oral intake; isonatric fluids suffice, once volume depletion has been corrected in CSW; a high-sodium diet or NaCl tablets may be useful in the rare patient with CSW who has satisfactory oral intake.

Euvolemic Hyponatremia

As with other forms of hyponatremia, the treatment of patients with euvolemic hyponatremia will vary greatly, depending on 3 main aspects of their presentation:

1. The treatment of the underlying condition that has precipitated the hyponatremia. In some circumstances, such as glucocorticoid deficiency, treatment of the underlying condition alone is all that is necessary. In other circumstances, such as SIADH due to acute pneumonia, hyponatremia is so transient and responsive to treatment of infection that specific therapy is usually unnecessary.
2. The presence of neurological symptoms. This is the key factor in guiding the nature and rapidity of treatment.
3. The speed at which onset of the hyponatremia occurred. To an extent, this overlaps with point 2, as most cases of acute hyponatremia (arbitrarily defined as $\leq$48 hours in duration) are usually symptomatic if the hyponatremia is severe ($\leq$120 mmol/L). These patients are at greatest risk from neurological complications from the hyponatremia itself and should be corrected to higher serum [Na^+] levels promptly. Conversely, patients with more chronic hyponatremia (>48 hours in duration) who have minimal neurological symptomatology are at little risk from complications of hyponatremia itself; however, they can develop osmotic demyelination following rapid correction and for this reason, the risk-benefit analysis of treatment favors much slower correction.

Most hyponatremic patients present with hyponatremia of indeterminate duration and with varying degrees of milder neurological symptomatology. This group presents the most challenging treatment decision, because hyponatremia will have been present sufficiently long enough to

Expert Panel Recommendations: Hyponatremia from Mineralocorticoid Deficiency

- This is typically a chronic hyponatremia, so current limits for rate of correction of chronic hyponatremias should be observed (see *Current Recommendations for Rate of Correction of Hyponatremia*).
- A spontaneous aquaresis with rapid correction of hyponatremia may occur once the volume deficit is replete; frequent monitoring of the serum [Na^+] is essential.
- Presumptive glucocorticoid deficiency should be confirmed by cosyntropin testing and treated with stress-dose hydrocortisone while results are pending.
- Fludrocortisone therapy should be initiated once a diagnosis is confirmed, unless the patient is receiving stress doses of hydrocortisone.

allow some degree of brain volume regulation but not enough to prevent some brain edema and neurological symptomatology.[2] Prompt treatment is generally recommended because of their symptoms, but with methods that allow a *controlled and limited correction* of the hyponatremia, using parameters discussed previously (see *Rate of Correction of Hyponatremia*).

With each hyponatremic patient, it is important to individualize the answer to the question of how quickly the plasma osmolality should be corrected. Current recommendations for treatment of hyponatremia in specific disorders associated with euvolemia are provided below (but also see subsequent section: *Potential Future Indications for Treatment of Hyponatremia* for how these recommendations may change).

SIADH. Acute symptomatic hyponatremia is best corrected with hypertonic (3%) saline given either via bolus or continuous intravenous infusion. Patients with euvolemic hypo-osmolality due to SIADH will not respond to isotonic saline, which in some cases will cause the hyponatremia to worsen. An initial infusion rate can be estimated by multiplying the patient's body weight in kg by the desired rate of increase in serum [Na^+] in mmol/L/h (eg, in a 70-kg patient, an infusion of 3% NaCl at 70 mL/h will increase serum [Na^+] by approximately 1 mmol/L/h, while infusing 35 mL/h will increase serum [Na^+] by approximately 0.5 mmol/L/h).[178] Furosemide (20-40 mg) should be used intravenously to treat volume overload, and it may be appropriate to initiate it prophylactically in patients at risk for developing HF. However, the estimated infusion rate is much less important than the rate of increase in serum [Na^+] that it produces. Many clinicians become obsessed with infusion rates when the focus of their attention should be on the changes in serum [Na^+] and whether they achieve therapeutic goals while adhering to correction limits to avoid neurological sequelae. In other words, after the initial corrective intravenous bolus, the subsequent rate of intravenous infusion should be serially adjusted based on measurements of serum [Na^+] to ensure an appropriate increase in serum [Na^+] that stays within the goals and limits of the correction (**Figure 3**). It logically follows that serum [Na^+] levels must be carefully monitored at frequent intervals during the active phases of treatment (generally, the first 24-48 hours) in order to adjust therapy so that the correction stays within the correction goals and below the correction limits. Regardless of the therapy or correction rate initially chosen, it cannot be emphasized too strongly that it is only necessary and appropriate to correct the serum [Na^+] acutely to a safe range, rather than completely to normal levels.

In some situations, patients may spontaneously correct their hyponatremia via an aquaresis. If the hyponatremia is acute (eg, self-induced water intoxication associated with psychiatric disease), such patients do not appear to be at risk for subsequent demyelination;[93,95] however, in cases where the serum [Na^+] increases quickly following spontaneous correction of a chronic hyponatremia (eg, cessation of desmopressin therapy or repletion of cortisol deficiency), intervention should be considered to limit the rate and magnitude of correction of serum [Na^+] using the same end points as for active corrections[2,169,178] (see previous section: *Managing Excessive Correction of Chronic Hyponatremia*).

Treatment of chronic hyponatremia entails choosing among several suboptimal therapies. Patients with the reset osmostat syndrome are an important exception; because the hyponatremia in such patients is not progressive but rather fluctuates around their reset level of serum [Na^+], no therapy is typically required. For most other cases of mild-to-moderate SIADH, fluid restriction represents the cheapest and least toxic therapy and has generally been the treatment of choice despite the almost complete lack of a supportive evidence base. Several points should be remembered when using this approach (**Table 5**):

1. All fluid intake, not only water, must be included in the restriction; this includes intravenous fluids used to administer therapies such as antibiotics, as well as parenteral and enteral nutritional supplements. It should be emphasized that the electrolyte content of sports beverages, in particular, is minimal; their consumption will contribute to perpetuation of hyponatremia as much as water does.
2. The degree of restriction required depends on urine output plus insensible fluid loss. Generally, discretionary (ie, nonfood) fluids should be limited to 500 mL/d below the average daily urine volume.[179]
3. Several days of restriction are usually necessary before a significant increase in plasma osmolality occurs.
4. Only fluid, not sodium or protein intake, should be restricted.

Because of the ongoing natriuresis, patients with chronic SIADH often have a negative total body sodium balance, and therefore, should be maintained on normal or relatively

Table 5 General Recommendations for Employment of Fluid Restriction and Predictors of the Increased Likelihood of Failure of Fluid Restriction

General recommendations:
- Restrict all intake that is consumed by drinking, not just water.
- Aim for a fluid restriction that is 500 mL/d below the 24-hour urine volume.
- Do not restrict sodium or protein intake unless indicated.

Predictors of the likely failure of fluid restriction:
- High urine osmolality (>500 mOsm/kg H_2O).
- Sum of the urine Na^+ and K^+ concentrations exceeds the serum Na^+ concentration.
- 24-hour urine volume <1500 mL/d.
- Increase in serum Na^+ concentration <2 mmol/L/d in 24-48 hours on a fluid restriction of ≤1 L/d.

D = day; H_2O = water; K = potassium; kg = kilogram; L = liter; mL = milliliter; mmol = millimole; mOsm = milliosmole; Na = sodium.

high NaCl intakes unless otherwise contraindicated. However, just as failure to correct a presumed hypovolemic hyponatremia with isotonic saline should lead one to consider the possibility of a euvolemic hyponatremia, so should the failure of significant fluid restriction after several days of confirmed negative fluid balance prompt reconsideration of other possible causes, including solute depletion and clinically unapparent hypovolemia. At the time that fluid restriction is first initiated, any drugs known to be associated with SIADH should be discontinued or changed.

Fluid restriction has traditionally been regarded as first-line therapy, despite the absence of an evidence-based rationale for its effectiveness. In the past, pharmacological intervention was reserved for refractory cases, where the degree of fluid restriction required to avoid hypo-osmolality is so severe that the patient is unable, or unwilling, to comply with restriction. In general, the higher the urine osmolality (indicating higher plasma AVP levels), the less likely that fluid restriction will be successful; in patients with urine osmolalities higher than 500 mOsm/kg H_2O, fluid restriction is so unlikely to achieve the goals for the increase in plasma sodium that alternative pharmacological treatments should be considered as first-line treatment (**Table 5**). In patients with SIADH secondary to tumors, successful treatment of the underlying malignant lesion often eliminates or reduces the inappropriate AVP secretion,[180] such that specific therapy to correct plasma sodium may be unnecessary. In cases of SIADH where the cause of hyponatremia persists, and where fluid restriction is ineffective, impractical, or unpalatable, pharmacological therapy should be considered. A number of options are available as described below.

Demeclocycline. The tetracycline derivative demeclocycline[181] causes a nephrogenic form of diabetes insipidus,[182] thereby decreasing urine concentration even in the presence of high plasma AVP levels. Appropriate doses of demeclocycline range from 600-1200 mg/d administered in divided doses. Treatment must be continued for several days to achieve maximal diuretic effects; consequently, one should wait 3-4 days before deciding to increase the dose. Demeclocycline can cause reversible azotemia and sometimes nephrotoxicity, especially in patients with cirrhosis.[183] Therefore, renal function should be monitored in patients treated with demeclocycline on a regular basis and the medication discontinued if increasing azotemia is noted. In addition, some patients develop a photosensitive skin rash.

Urea. Urea has been described as an alternative oral treatment for SIADH and other hyponatremic disorders. The mode of action is to correct hypo-osmolality not only by increasing solute-free water excretion, but also by decreasing urinary sodium excretion.[184] Doses of 15-60 g/d are generally effective; the dose can be titrated in increments of 15 g/d at weekly intervals as necessary to achieve normalization of the serum [Na^+]. It is advisable to dissolve the urea in orange juice or some other strongly flavored liquid to camouflage the taste. Even if completely normal water balance is not achieved, it is often possible to allow the patient to maintain a less strict regimen of fluid restriction while receiving urea. The disadvantages associated with the use of urea include poor palatability (though some clinicians feel that this has been exaggerated), the development of azotemia at higher doses, and the unavailability of a convenient or FDA-approved form of the agent. Data suggest that blood urea concentrations may double during treatment,[185] but it is important to remember that this does not represent renal impairment.

Reports of retrospective, uncontrolled studies suggest that the use of urea has been effective in treating SIADH in patients with hyponatremia due to subarachnoid hemorrhage and in critical care patients,[186] whereas case reports have documented success in infants with chronic SIADH[187] and NSIAD.[188] More recent evidence from a short study in a small cohort of SIADH patients has shown that urea has a comparable efficacy to tolvaptan in reversing hyponatremia due to chronic SIADH.[189] Because urea primarily corrects hyponatremia by producing a solute diuresis, these effects could theoretically be mimicked by increased dietary protein intake to increase renal water excretion. However, the amounts of protein required to achieve effects similar to urea would be impractical in most cases, and no evidence-based studies have demonstrated the efficacy of this approach. Nonetheless, hyponatremic patients should not be on a low-protein diet, because solute deficiency clearly limits free water excretion (see subsequent section: *Low Solute Intake*).

Vaptans. Plasma AVP levels are elevated in >95% of cases of SIADH,[190] so specific antagonists to the V2R provide the means with which to specifically target the pathophysiology of SIADH (see previous section: *Vasopressin Receptor Antagonists*). Several vaptans have now been studied in the treatment of euvolemic and hypervolemic states, of which 2, conivaptan and tolvaptan, are available for clinical use. Conivaptan is available for intravenous use in the US, with studies showing that it is both safe and effective in treating euvolemic and hypervolemic hyponatremia.[191-193] In contrast, tolvaptan is an oral V2R-specific antagonist. The effects of tolvaptan in patients with SIADH were explored in the SALT-1 and SALT-2 trials, conducted, respectively, in North America and Europe. The patient groups were heterogeneous in that they included individuals with hyponatremia due to cardiac failure and liver failure as well as SIADH. Using a randomized, placebo-controlled trial of tolvaptan versus placebo, the SALT studies showed a progressive increase in serum [Na^+] in patients treated with tolvaptan, when compared with those treated with placebo, without the requirement for water restriction. The greatest increase in serum [Na^+] occurred in patients with the lowest baseline serum [Na^+]. Although the rate at which the serum [Na^+] rose exceeded the maximum recommended correction rate in approximately 2% of cases, there were no instances of ODS. A subsequent subgroup analysis of the SIADH cohort showed that, in this group, tolvaptan had a

predictable effect to increase free water clearance and cause an elevation in serum [Na^+] without serious side effects.[194] By study design, the SALT studies included too few patients with plasma [Na^+] <120 mmol/L to demonstrate that the use of tolvaptan would be safe in the treatment of more severe hyponatremia. However, given the clear safety guidelines available for monitoring the rate of increase in plasma [Na^+] during treatment and the clear interventions if the recommended rate of increase is exceeded, it is not anticipated that the use of vaptans will be problematic in patients with lower serum [Na^+] who are monitored carefully.

Data from the SF-12 Mental Component Summary Scale readings in the combined SALT-1 and SALT-2 study groups showed that the mean score was significantly improved in the tolvaptan group from readings comparable to those derived from patients with depression too close to the normal adult mean at the end of treatment, indicating that the increase in serum [Na^+] observed during the study was symptomatically beneficial. A subsequent long-term follow-up study (the SALT studies only lasted 30 days) showed that oral tolvaptan retained both efficacy and safety over 4 years of study.[167]

Expert Panel Recommendations: Cautions for Using Vaptans to Treat Hyponatremia

- Exclude hypovolemic hyponatremia.
- Do not use in conjunction with other treatments for hyponatremia.
- Do not use immediately after cessation of other treatments for hyponatremia, particularly 3% NaCl.
- Monitor serum [Na^+] closely (every 6-8 hours) for the first 24-48 hours after initiating treatment.
- Maintain ad libitum fluid intake during the first 24-48 hours of treatment; hyponatremia can correct too quickly with coincidental fluid restriction; in patients with a defective or impaired thirst mechanism (eg, intubated or unconscious patients), provide sufficient fluid to prevent overly rapid correction due to unopposed aquaresis.
- Increase the frequency of serum [Na^+] monitoring and consider stopping the vaptan if there is a change or deterioration in the patient's condition (eg, NPO [nothing by mouth] status, intubation) that limits the ability to request, access, or ingest fluid.
- Severe, symptomatic hyponatremia should be treated with 3% NaCl, as this provides a quicker and more certain correction of serum [Na^+] than vaptans.
- Currently, there are insufficient data for use of vaptans in severe asymptomatic hyponatremia (ie, serum [Na^+] <120 mmol/L)—use vaptans with caution and with more frequent monitoring in these patients.
- If overcorrection occurs, consider re-lowering the serum [Na^+] to safe limits (see *Managing Excessive Correction of Chronic Hyponatremia*).

The most likely role for vaptans in SIADH in the immediate future is in treating mild to moderate hyponatremia and asymptomatic severe hyponatremia. Because there is a paucity of data for patients with severely symptomatic hyponatremia, hypertonic saline remains the treatment of choice in this group until more evidence-based data are available. Although mild to moderate hyponatremia has traditionally been treated with fluid restriction as first-line therapy, the difficulty with treatment compliance among patients with SIADH (due to the downward resetting of the thirst threshold[195]) and clinical scenarios in which fluid restriction would be predicted to be suboptimal (**Table 5**) means that vaptans have the potential to replace water restriction as first-line treatment. The fact that both tolvaptan[4] and conivaptan[192] are effective without the need for fluid restriction means that patient acceptability will be superior to that of water restriction. The extent to which vaptans replace fluid restriction as first-line therapy will be predicated upon additional data about the cost—benefit ratio of these therapies, including hospital length of stay. In outpatients, the chronic use of tolvaptan is limited by its very high cost and the recent FDA, but not EMA, recommendation that it not be used for more than 30 days (see previous section: *Vasopressin Receptor Antagonists*). It is important to stress that vaptans should not be used in conjunction with, or immediately after, other treatments such as hypertonic saline, because of the risk of overcorrection of hyponatremia with increased risk of ODS in this scenario.

NSIAD. Because patients with activating mutations of the V2R present clinically with the characteristics of patients with SIADH, they should be treated as described in the previous section. To date, vaptans have not been effective in the few patients with NSIAD in whom they have been tried, but urea therapy has been found to be effective in young children with this disorder.[197]

Glucocorticoid Deficiency. If there is any suspicion that hyponatremia is the biochemical manifestation of either primary or secondary adrenal insufficiency, glucocorticoid replacement should be started immediately after withdrawal of blood to measure baseline plasma cortisol, or the completion of a rapid cosyntropin-stimulation test. Prompt water diuresis following initiation of glucocorticoid treatment strongly supports glucocorticoid deficiency, and hyponatremia nearly always responds well to steroid therapy alone. However, serum [Na^+] must be followed carefully after initiating glucocorticoid therapy, because the subsequent development of an aquaresis may result in a more rapid correction than desirable; anecdotal evidence exists that neurological sequelae may occur if the rate of increase in serum [Na^+] exceeds currently recommended limits. For this reason, it is important not to limit fluid intake when initiating steroid therapy. If the rate at which the serum [Na^+] increases is too rapid, consideration should be given to coadministration of desmopressin or intravenous 5%

Expert Panel Recommendations: Hyponatremia in Patients with SIADH

- Complete laboratory testing should be done to verify an accurate diagnosis of SIADH (**Table 2**), but initial therapy can be undertaken while awaiting some of the results.
- In most cases, this is a chronic hyponatremia, so current limits for rate of correction of chronic hyponatremias should be observed (see *Current Recommendations for Rate of Correction of Hyponatremia*).
- Isotonic (0.9%) NaCl infusion is not an effective therapy for hyponatremia resulting from SIADH and may worsen the hyponatremia if the renal electrolyte-free water clearance is negative (ie, urine $[Na^+] + [K^+] >$ serum $[Na^+]$).
- Fluid restriction is generally first-line therapy, but pharmacological therapies should be strongly considered if the patient's urinary parameters indicate low renal electrolyte-free water excretion or if the serum $[Na^+]$ is not corrected after 24-48 hours of attempted fluid restriction (**Table 5**).
- Frequent (every 4-6 hours) measurement of serum $[Na^+]$ is advisable during the active correction phase with a maneuver other than fluid restriction until the serum $[Na^+]$ has reached a stable value >125 mmol/L; once the serum $[Na^+]$ has reached 125 mmol/L, the risk of CNS complications of hyponatremia is low; if the starting serum $[Na^+] \leq 120$ mmol/L, halting further correction for 1-2 days to allow slower equilibration should be considered (see *Rate of Correction of Hyponatremia*).
- Patients treated with vaptans should not be on fluid restriction for the first 24-48 hours when active correction of serum $[Na^+]$ is occurring; the patient's thirst and increased fluid intake will act to brake the rate at which the serum $[Na^+]$ increases.
- Enteral water or 5% dextrose in water can be used to slow the correction if necessary; desmopressin may be tried to abrogate the water diuresis in cases where the aquaresis is pronounced, but there are no data to verify that this agent can compete effectively with pharmacological levels of vaptans at the V2R (see *Managing Excessive Correction of Chronic Hyponatremia*).
- Whether therapy for hyponatremia should be continued after discharge from the hospital depends on the etiology of the SIADH, as many causes of inpatient hyponatremia are transient and resolve with treatment of the underlying comorbidity (**Figure 4**);[196] affordability and the cost to the patient and health care system of long-term treatment with a vaptan, as well as the potential for liver damage, must be weighed against potential benefit (see *Vasopressin Receptor Antagonists*).

Etiology of SIADH	Likely duration of SIADH	Relative risk of chronic SIADH
Tumors producting vasopressin ectopically (small-cell lung carcinoma, head and neck carcinoma)	Indefinite	High
Drug-induced, with continuation of offending agent (carbamazepine, SSRI)	Duration of drug therapy	
Brain tumors	Indefinite	
Idiopathic (senile)	Indefinite	
Subarachnoid hemorrhage	1-4 weeks	
Stroke	1-2 weeks	
Inflammatory brain lesions	Dependent on response to therapy	Medium
Respiratory failure (chronic obstructive lung disease)	Dependent on response to therapy	
HIV infection	Dependent on response to therapy	
Traumatic brain injury	2-7 days to indefinite	
Drug-induced, with cessation of offending agent	Duration of drug therapy	
Pneumonia	2-5 days	
Nausea, pain, prolonged exercise	Variable depending on cause	
Post operative hyponatremia	2-3 days postoperatively	Low

Abbreviations: SIADH, syndrome of inappropriate antidiuretic hormone secretion; HIV, human immunodeficiency virus.

Figure 4 Estimated probability of the need for long-term treatment of hyponatremia depending on the underlying etiology of the syndrome of inappropriate antidiuretic hormone secretion. Abbreviations: HIV = human immunodeficiency virus; SIADH = syndrome of inappropriate antidiuretic hormone secretion; SSRI = selective serotonin-reuptake inhibitor. Adapted with permission from WB Saunders Elsevier, from Verbalis JG. Disorders of water balance. In Brenner and Rector's The Kidney, Vol 1, 9th ed, pp. 540-594, 2012.[196]

dextrose in water to prevent neurological sequelae (see previous section: *Managing Excessive Correction of Chronic Hyponatremia*). Much less commonly, several days of glucocorticoid therapy may be required to normalize the plasma osmolality. In such cases, primary treatment of

Expert Panel Recommendations: Hyponatremia in Patients with NSIAD

- The general guidelines for treatment of euvolemic hyponatremia should be followed (see *Expert Panel Recommendations, Hyponatremia in Patients with SIADH*).
- Suspicion for NSIAD should be raised when a patient meets all criteria for a diagnosis of SIADH (**Table 2**) without any apparent cause for the disorder or if there is a family history of hyponatremia; unmeasurable plasma AVP levels heighten suspicion, but confirmation of NSIAD requires sequencing of the V2R gene.
- Although use of vaptans has not been tested in large numbers of patients with NSIAD, available data suggest that most such patients are unresponsive to vaptans; urea therapy is a reasonable alternative in these cases.

Expert Panel Recommendations: Hyponatremia in Patients with Glucocorticoid Deficiency

- All patients with euvolemic hyponatremia should be evaluated for glucocorticoid deficiency before concluding they have SIADH.
- Although glucocorticoid deficiency can be ruled out in some patients with a random or early morning cortisol level $\geq$18 mg/dL, failure to achieve this level will require consideration of a cosyntropin stimulation test for a definitive diagnosis unless clinical judgment makes this possibility unlikely.
- The general guidelines for treating euvolemic hyponatremia should be followed (see *Expert Panel Recommendations: Hyponatremia in Patients with SIADH*).
- Unless the patient has severe symptoms of hyponatremic encephalopathy, primary treatment of the hyponatremia should consist of glucocorticoid replacement at either maintenance or stress doses, depending on the degree of intercurrent illness.
- Because glucocorticoid replacement can result in a spontaneous large aquaresis with rapid correction of serum [Na^+], both serum [Na^+] and urine volume should be followed carefully, particularly in patients with serum [Na^+] <120 mmol/L or with risk factors for ODS (**Table 3**).
- Enteral water or parenteral 5% dextrose in water can be used to slow the spontaneous correction if necessary; desmopressin is also useful to abrogate the water diuresis in cases where aquaresis is pronounced (see *Rate of Correction of Hyponatremia*).

Expert Panel Recommendations: Hyponatremia in Patients with Hypothyroidism

- Unless hypothyroidism is severe (ie, symptoms and signs of myxedema or thyroid-stimulating hormone >50 mIU/mL), other causes of hyponatremia should be sought rather than ascribing the hyponatremia to hypothyroidism.
- Unless the patient has symptoms of hyponatremic encephalopathy, primary treatment of hyponatremia should consist of thyroid hormone replacement at standard weight-based doses; several days may be needed to normalize the serum [Na^+].

hyponatremia may be indicated if significant neurological symptoms are present, but this is rarely the case.

Hypothyroidism. The primary therapy of hypothyroidism is thyroid hormone replacement. Because hyponatremia with hypothyroidism is infrequent and generally is mild in severity, modest fluid restriction is generally the only treatment necessary. However, because symptomatic hyponatremia is seen primarily in patients who have more severe hypothyroidism and altered mental status, primary treatment of hyponatremia may be indicated to ascertain whether the hyponatremia is contributing to the patient's neurological symptoms.

EAH. EAH can be severe and life threatening as a result of cerebral edema and noncardiogenic pulmonary edema.[83,134] Prevention is paramount. Guidelines for appropriate fluid ingestion during marathons are available.[86] In general, runners should drink primarily when thirsty, with an input $\leq$400-800 mL/h; the greater amount is for heavier, faster runners during high-temperature conditions, and the lesser amount for lighter, slower runners during low-temperature conditions. Hyponatremia occurring in the setting of endurance exercise is acute, and treatment of symptomatic hyponatremia should be rapid. Runners are frequently fatigued, light-headed, presyncopal, or dizzy at the conclusion of exercise; however, seizures, profoundly altered level of consciousness, ataxia, or focal neurological deficits should raise suspicion of severe hyponatremia and require emergent treatment. A proposed treatment algorithm recommends that a 100-mL bolus of 3% NaCl infused over 10 minutes be given in the field for severe symptoms and repeated twice if needed.[86,137] Although this regimen has not been validated in a large series, experience in a small number of runners has been favorable.[138] With significant CNS impairment, hypertonic saline should be started at once while the serum [Na^+] result is awaited. Bolus therapy can be continued every 30 minutes until the serum [Na^+] reaches 125 mmol/L or symptoms resolve. Nonspecific symptoms such as weakness, dizziness, or headache warrant measurement of serum electrolytes, but treatment with intravenous fluid should be started only if warranted by clinical signs of volume depletion, as discussed previously. Hypertonic saline should be started if the serum [Na^+] is $\leq$125 mmol/L, is optional with a serum [Na^+] between 126 and 130 mmol/L, and is generally not needed if the serum [Na^+] is >130 mmol/L.

Low Solute Intake. Hyponatremia from low solute intake is corrected by instituting proper nutrition, with increased content of solute both as electrolytes and protein.

Primary Polydipsia. Ideally, patients whose hyponatremia is caused primarily by polydipsia should have therapy directed at reducing fluid intake into normal range. Unfortunately, this can prove difficult to accomplish. Patients with a reset thirst threshold will be resistant to fluid restriction because of stimulation of brain thirst centers at lower plasma osmolalities.[198] In some cases, the use of alternative methods to ameliorate the sensation of thirst (eg, wetting the mouth with ice chips or using sour candies to increase salivary flow) can help to reduce fluid intake. Fluid ingestion in patients with psychogenic causes of polydipsia is driven by psychiatric factors that respond variably to

Expert Panel Recommendations: Hyponatremia in Patients with EAH

- Individuals who develop neurological symptoms during or following endurance exercise should be evaluated for EAH by measuring the serum [Na^+], preferably via point-of-care testing at the medical tent of sanctioned endurance events.
- Patients with EAH and clinical evidence of hypovolemia should be volume repleted using isotonic (0.9%) NaCl as for patients with other forms of hypovolemia (see *Therapy of Hyponatremias, Hypovolemic Hyponatremia*).
- Most patients with EAH will be water overloaded rather than hypovolemic, and general guidelines for treatment of euvolemic hyponatremia should be followed (see *Expert Panel Recommendations: Hyponatremia in Patients with SIADH*); because EAH is a transient form of SIADH, simply keeping the patient under observation with fluid restriction until a spontaneous aquaresis occurs will usually be sufficient to prevent worsening of the hyponatremia.
- In patients with severe neurological symptoms or a serum [Na^+] <125 mmol/L (or both), a 100-mL bolus of 3% NaCl should be infused over 10 minutes, and repeated twice at 30-minute intervals if needed; failure to improve neurological symptoms with this therapy requires transfer to a medical facility.
- Because EAH is virtually always an acute hyponatremia, limits for safe correction of chronic hyponatremias do not need to be followed (see *Managing Excessive Correction of Chronic Hyponatremia*, and **Figure 3**).

behavioral modification and pharmacological therapy. Several case reports have suggested the efficacy of the antipsychotic drug clozapine as a promising agent to reduce polydipsia and prevent recurrent hyponatremia in at least a subset of these patients;[199] this appears to be a specific property of this agent, because similar results have not been observed with other antipsychotic agents.[200] Acute intoxication with water is usually reversible simply by denying fluid intake; serum [Na^+] may increase very quickly to normal in this circumstance. If hyponatremia has developed quickly, the risk of neurological sequelae is usually small, but if there is any doubt about the chronicity of hyponatremia, overly rapid correction should be avoided.

Expert Panel Recommendations: Hyponatremia in Patients with Low Solute Intake

- Most cases of hyponatremia from low solute intake can be adequately corrected by instituting proper nutrition, with increased content of solute both as electrolytes and protein.
- In rare cases, patients with clinical evidence of hypovolemia should be volume repleted using isotonic (0.9%) NaCl, as for patients with other forms of hypovolemia (see *Therapy of Hyponatremias, Hypovolemic Hyponatremia*).

Hypervolemic Hyponatremia

For all diseases associated with edema formation, dietary sodium restriction and diuretic therapy are the mainstays of therapy. When hyponatremia occurs in patients with these diseases, fluid restriction to amounts less than insensible losses plus urine output is necessary to cause a negative solute-free water balance, but is often difficult to achieve. If hyponatremia is mild, loop diuretics may be effective in raising serum [Na^+] because they induce diuresis with urine typically hypotonic to plasma. Whether this can be effective over long periods of time is not known, especially because loop diuretics have been shown to stimulate AVP release.[201] As already discussed, it is not known whether hyponatremia is just a marker for disease severity in HF and cirrhosis or whether it contributes to poor outcomes. However, because hyponatremia may cause cognitive deficits,[202] limit the optimum use of other effective therapies such as loop diuretics, and at least in theory exacerbate myocardial or hepatic dysfunction by causing cellular edema, it is certainly possible that hyponatremia may be an active contributor to poor outcomes in patients with HF or cirrhosis. Recent studies of HF treatment using hypertonic saline infusions combined with high doses of loop diuretics, a somewhat counterintuitive strategy, have demonstrated improved outcomes when compared with diuretics alone. This could be, at least in part, due to increasing the serum [Na^+], although other mechanisms may also have contributed to this outcome.[203]

Antagonism of the V2R represents a viable approach to treating hyponatremia in most edema-forming states,

Expert Panel Recommendations: Hyponatremia in Patients with Primary Polydipsia

- Patients whose hyponatremia is caused primarily by polydipsia should have primary therapy directed at reducing fluid intake to normal.
- Pharmacological therapy has not been proven to be effective in such cases, and therapy should be focused on local measures to relieve mouth dryness.
- Acute intoxication with water is usually reversible simply by preventing fluid intake; the serum [Na^+] usually increases very quickly to normal in this circumstance. If hyponatremia has developed quickly, the risk of neurological sequelae is small; however, if there is any doubt about the chronicity of hyponatremia, overly rapid correction should be avoided (see *Managing Excessive Correction of Chronic Hyponatremia*, and **Figure 3**).

because excess AVP secretion is the most important pathophysiological factor involved in these conditions.[204] Conivaptan and tolvaptan both produce an aquaresis with concomitant increase in the serum [Na^+] in patients with hypervolemic hyponatremia.[4,164,205] Current recommendations for treating hyponatremia in patients with specific disorders that cause hypervolemia are given below.

HF. Conventional therapies for HF include sodium restriction, diuretic therapy, and neurohormonal blockade with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, aldosterone antagonists, and antagonists to the β-adrenergic receptors with or without concomitant α-adrenergic blockade. Hyponatremia remains a persistent problem in patients with HF despite the use of these therapies. Severely symptomatic hyponatremia is uncommon but can, in theory, be treated with hypertonic saline, provided adequate diuresis is established. However, the volume expansion associated with the use of hypertonic saline makes this, at best, a challenging option for all but emergent situations. The reports mentioned above describing the use of hypertonic saline combined with high doses of loop diuretics, even in the absence of significant hyponatremia, provide some evidence that this treatment may be safe and even effective.[203]

No data specifically address the issue of whether mild or moderate hyponatremia causes symptoms or directly contributes to poor outcome in patients with HF, despite the tight association of even mild hyponatremia with poor outcomes. Substantial neurocognitive deficits have been reported with hyponatremia in other conditions; there is no reason to suspect they do not also occur in HF, but data are lacking. Loop diuretic therapy, as noted, is not necessarily effective in correcting hyponatremia, and commonly worsens the condition. When hyponatremia develops or worsens with loop diuretic therapy, a common response is to decrease or stop the use of these agents. However, this is undesirable because persistent clinical congestion is associated with poor outcomes in patients with HF.[206,207] Following this line of reasoning leads to the possibility that one of the reasons hyponatremia contributes to poor outcome in patients with HF is because it may lead clinicians to limit use of other needed therapies, such as loop diuretics. A different treatment strategy, such as the use of antagonists to the V2R, would theoretically be preferable because these agents can be used safely with furosemide. However, no outcomes-related studies, much less comparative effectiveness studies, have been conducted in patients with HF and hyponatremia. Such trials are clearly warranted, especially because post hoc analysis of hyponatremic patients in 2 HF studies in which tolvaptan was compared with placebo (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist [ACTIV][208] and EVEREST[40]) did show a significant association of improved serum [Na^+] and either mortality or a combined end point of cardiovascular morbidity and mortality.[208,209] In the absence of prospective trials data, no guidelines for treating hyponatremia in patients with HF have currently been developed or endorsed, leaving the choice of therapy for hyponatremia in HF a matter of individual clinical judgment.

Of the vaptans, tolvaptan has been the best studied among patients with HF.[210] Results from both the ACTIV and the EVEREST trials, which together studied nearly 4500 patients with acute HF regardless of serum [Na^+], indicated that hyponatremia can be corrected acutely and durably with this compound.[211] When compared with patients who received placebo, those treated with tolvaptan in the EVEREST trial lost slightly more weight during hospitalization; however, no effects on mortality or morbidity were seen with long-term follow-up. As previously alluded, a post hoc analysis of patients in the ACTIV trial linked an improvement in serum [Na^+] with an improvement in survival.[208] A similar analysis of EVEREST trial data showed that patients with serum [Na^+] $<$130 mmol/L had a significantly lower rate of the combined end point of cardiovascular morbidity and mortality when treated with tolvaptan.[162] Along with mechanistic considerations and the absence of other safe and effective pharmacological treatment for chronic hyponatremia in patients with HF, these observations connecting an improvement in hyponatremia with improved outcomes when V2R antagonism is used provide a strong rationale for the use of this agent when correction of serum [Na^+] is desired.

There may be other reasons to consider tolvaptan use in selected patients with HF and hyponatremia. These agents may have advantages over loop diuretics for volume control (even in the absence of hyponatremia), because they do not cause significant direct intravascular volume depletion. As a consequence, compared with loop diuretics, they do not cause neurohormonal activation or worsen renal function—sometimes important concerns with loop diuretics[212,213]—and they do not deplete electrolytes such as potassium and magnesium. Reducing the use of traditional loop diuretics, therefore, could represent a beneficial effect of V2R antagonists in selected hyponatremic patients with HF. Recent studies in normonatremic HF patients suggest that tolvaptan can be safely substituted for loop diuretics for up to a week and that the acute administration of conivaptan increases the natriuretic effect of furosemide.[214,215] Based on both the available data and on mechanistic considerations, the use of V2R or combined V1aR/V2R AVP receptor antagonists would seem to be the most useful and effective method of treating hyponatremia in patients with HF; to date, the use of these agents represents the only approach approved by the FDA as safe and effective in this patient population.

A reasonable overall approach to treating hyponatremia in patients with HF, therefore, might be to start with a combination of fluid restriction and furosemide while background therapy with neurohormonal antagonism is optimized. This assumes that hyponatremia is mild and minimally symptomatic and not in need of urgent treatment. For severely symptomatic patients with very low or rapidly

falling serum [Na^+], the treatment would be hypertonic saline combined with loop diuretics. In the patient who is not severely symptomatic—but who either has milder symptoms thought to be due to hyponatremia or in whom the level of hyponatremia is compromising the use of needed diuretic therapy—vaptans should then be employed. Conivaptan would be a possible choice if the patient cannot take medicine by mouth. If the patient can, tolvaptan is reasonable, especially because it is an oral agent that may be continued in the outpatient setting. Many patients will not need chronic therapy because hyponatremia may resolve as AVP levels fall in response to overall treatment for HF, particularly when HF improvement occurs rapidly. Consequently, the duration of treatment should be individualized. All patients treated with vaptans should be given a trial off vaptan therapy at some point. The FDA has recently recommended that therapy with tolvaptan not be given for more than 30 days, due to the small excess of liver function abnormalities seen with chronic therapy in patients with ADPKD (see previous section: *Vasopressin Receptor Antagonists*). However, the dose of tolvaptan in those patients was 3- to 4-fold higher than that used for hyponatremia, and cases of clinically significant liver function abnormalities were not reported during long-term treatment with this drug in the EVEREST trial. Therefore, the necessity for long-term vaptan therapy should be determined for each patient. If a patient becomes clearly symptomatic due to a decrease in serum [Na^+] $\geq$30 days after the drug is stopped, or if hyponatremia again limits the use of adequate decongestive therapy, it may be reasonable to re-start the drug if simpler measures fail to improve the serum [Na^+]. It is necessary to monitor the patient carefully for any signs of new liver dysfunction if chronic therapy continues beyond 30 days (see previous section: *Vasopressin Receptor Antagonists*).

Expert Panel Recommendations: Hyponatremia with Heart Failure

- For severely symptomatic patients with very low or rapidly falling serum [Na^+], treatment should consist of hypertonic (3%) NaCl combined with loop diuretics to prevent fluid overload; for patients with mild to moderate symptoms, begin with fluid restriction (1 L/d total) and, if signs of volume overload are present, administer loop diuretics.
- If the serum [Na^+] does not correct to the desired level, lift the fluid restriction and start either conivaptan (if intravenous route is preferred or required) or tolvaptan (if oral therapy is preferred) (see *Vasopressin Receptor Antagonists*).
- Hyponatremia in HF is almost always chronic, so current limits for rate of correction of chronic hyponatremias should be observed (see *Current Recommendations for Rate of Correction of Hyponatremia*).
- If tolvaptan is used, it may be up-titrated from 15 to 30 to 60 mg/d as necessary to achieve the desired level of correction of serum [Na^+].
- Continue treatment until the serum [Na^+] has either normalized, symptoms have improved, or the level of serum [Na^+] is no longer compromising administration of needed diuretic therapy.
- The stimuli for AVP secretion may be more dynamic than in other disease states; if prescribed after discharge, assessing the need for chronic therapy of hyponatremia by providing a window of observation off therapy 2-4 weeks after treatment initiation is a reasonable approach.

Cirrhosis. Conventional therapies used to treat ascites include sodium restriction, diuretic therapy, and large-volume paracentesis.[19] The most effective diuretic combination consists of spironolactone along with a loop diuretic. The development of either diuretic-resistant or diuretic-intractable ascites occurs in approximately 5%-10% of cases of ascites and is a poor prognostic sign. Currently, there are no guidelines that specifically address treatment of hyponatremia in patients with cirrhosis. Demeclocycline is contraindicated because of a high incidence of nephrotoxicity in cirrhotic patients.[183] Fluid restriction necessitates a decrease in intake below urine output plus insensible losses (**Table 5**). In cirrhotic patients, this generally means a daily fluid intake <750 mL. The ability to increase serum [Na^+] with fluid restriction is limited, because this severe degree of daily fluid restriction is very poorly tolerated. The availability of vaptans now has provided another therapeutic approach to treat hyponatremia associated with cirrhosis.[4] In the SALT study, a subanalysis of the patients with a diagnosis of cirrhosis demonstrated an improvement in scores on the self-reported SF-12 Mental Component Summary Scale following correction of the hyponatremia using tolvaptan.[4] In the cirrhotic patient with ascites, hepatic encephalopathy might be precipitated or worsened by hyponatremia.[18,216] The symptoms of hepatic encephalopathy and hyponatremic encephalopathy overlap;[217] in many cases, the only way symptoms can be evaluated is by raising the serum [Na^+] to $\geq$130 mmol/L while assessing improvements in neurological status.

Only tolvaptan can be used orally on an outpatient basis. However, because of possible hepatic injury in patients treated with higher doses of tolvaptan, the FDA has recommended that tolvaptan therapy should be avoided in patients with underlying liver disease, including cirrhosis. Consequently, with rare exception, tolvaptan should not be used in patients with underlying liver disease given the difficulty of attributing causation to any observed deterioration of hepatic function[170] (see previous section: *Vasopressin Receptor Antagonists*). In addition, because conivaptan is a combined V1aR/V2R antagonist, it is not recommended in patients with cirrhosis and portal hypertension because blocking the V1aR in the splanchnic circulation may increase portal blood flow and precipitate variceal bleeding.

Nephrotic Syndrome: Acute and Chronic Impairment of Renal Function. In patients with hyponatremia with acute or chronically reduced kidney function and GFR <20 mL/min, fluid restriction to amounts less than insensible losses plus urine output is necessary to effect a negative solute-free water balance and correct hyponatremia. Vaptans would not be expected to cause a water diuresis with markedly impaired kidney function; however, with less severe dysfunction and an estimated GFR >50 mL/min, an aquaresis should occur. Hyponatremia in patients with nephrotic syndrome and a normal GFR should respond to fluid restriction. If this approach is not well tolerated, then a trial of a vaptan is a reasonable alternative.

SUMMARY OF CURRENT TREATMENT RECOMMENDATIONS

The updated recommendations of the Expert Panel for treatment of hyponatremia based on the underlying etiology, the serum [Na^+], and the severity of symptoms have been presented for the major etiologies of hyponatremia seen commonly in clinical practice. While these recommendations are intended to be generalizable, therapy of hyponatremia must always be tailored to the specific patient at hand. Most of the recommendations lack the rigor of evidence-based data from double-blinded placebo-controlled studies; nonetheless, they represent the consensus opinion of the Expert Panel on the current best practices in this field based on the accumulated clinical and research experience to date. Undoubtedly, these recommendations will change as further understanding of the effectiveness and safety of the various treatment modalities for this disorder accumulates.

Expert Panel Recommendations: Hyponatremia with Cirrhosis

- Hyponatremia is an independent risk factor for decreased quality of life, hepatic encephalopathy, hepatorenal syndrome, and survival in cirrhotic patients.
- Severe daily fluid restriction—less than daily urine output plus insensible losses (**Table 5**)—is necessary to increase the serum [Na^+] in patients with cirrhosis, but often cannot be maintained because of poor compliance with this therapy.
- Vaptans have been an alternative choice for treating cirrhotic patients with hyponatremia in whom fluid restriction has failed to maintain a serum [Na^+] ≥130 mmol/L; however, because of recent FDA recommendations that tolvaptan not be used in patients with underlying liver disease, its use in cirrhotic patients should be restricted to cases where the potential clinical benefit outweighs the risk of worsened liver function, such as in patients with end-stage liver disease and severe hyponatremia who are awaiting imminent liver transplantation (see *Vasopressin Receptor Antagonists*).

Expert Panel Recommendations: Hyponatremia with Nephrotic Syndrome and Impaired Kidney Function

- Restricting fluid intake to amounts less than insensible losses plus urine output is the mainstay of therapy (**Table 5**).
- Aquaretics (vaptans) can be employed in selected cases where fluid restriction is not successful or not well tolerated (see *Vasopressin Receptor Antagonists*).
- Vaptans should not be expected to cause a clinically significant aquaresis with severe renal impairment (ie, serum creatinine >3 mg/dL).

POTENTIAL FUTURE INDICATIONS FOR TREATMENT OF HYPONATREMIA

The Expert Panel considers the following areas to be of highest priority for clinical research studies to better ascertain which hyponatremic patients should be candidates for therapy in the future.

Short-term Treatment of Inpatient Hyponatremia

Because of the high prevalence of hyponatremia in hospitalized patients and the strong independent association of hyponatremia with a variety of adverse clinical outcomes, the following studies of the impact of more effective treatment of hyponatremia in hospitalized inpatients are considered to be a high priority.

Improvement of Symptomatic Hyponatremia. Although it is clear that correction of hyponatremia can improve many of the neurological symptoms associated with hyponatremia and is life-saving in cases with severe neurological symptomatology, assessment of symptomatic improvement of the more subtle neurocognitive symptoms associated with milder degrees of hyponatremia is challenging. This is further complicated by the fact that these symptoms often occur in older patients with varying degrees of baseline dementia and in patients with other comorbidities such as HF, cirrhosis, pulmonary disease, cancer, and psychiatric disease that can also cause neurocognitive impairments.

Reduction of Hospital Resource Utilization. Given the substantial economic burden associated with hyponatremia, whether more effective treatment of hyponatremia can reduce the increased costs that have been found to be associated with hyponatremia is a crucial question. This is particularly important for assessing the cost−benefit ratio of new therapies for hyponatremia, such as the vaptans, in view of their high costs.

Improvement of Clinical Outcomes. The strong independent association of hyponatremia with a variety of adverse

clinical outcomes makes randomized controlled trials of the impact of more effective treatment of hyponatremia in hospitalized patients a high priority for the many diseases in which hyponatremia is known to be associated with adverse outcomes.

Long-term Treatment of Outpatient Hyponatremia

Most studies in hyponatremic patients to date have been of relatively short duration. Thus, the following factors are unknown at present and will require additional studies of long-term therapies of hyponatremia: 1) the most appropriate way to use more effective therapies for chronic treatment of hyponatremia, 2) the long-term response rates associated with hyponatremic therapies, 3) whether the role of water restriction will remain important during chronic use, and 4) whether correction of chronic hyponatremia will result in improved cognitive function, quality of life, or functional status as suggested by 30-day studies of tolvaptan.[112] Future studies to assess the impact of more effective chronic treatment of hyponatremia in outpatients are considered to be a high priority.

Improvement in Neurocognitive Function. While most of the symptoms of hyponatremia are neurological, once the brain has volume regulated in response to decreased osmolality, the neurological manifestations are markedly reduced as a result of decreased cerebral edema. Nonetheless, residual neurocognitive deficits remain in many chronically hyponatremic patients. Assessment of these deficits and improvements with correction of chronic hyponatremia is essential if we are to develop scientifically valid guidelines to identify which patients will benefit from active chronic treatment.

Prevention of Falls, Osteoporosis, and Fractures. The strong association of hyponatremia with increased fracture rates as independently documented in diverse geographic areas has established hyponatremia as a previously unrecognized risk factor for fractures. Although this association is clear and the mechanisms whereby hyponatremia could increase risk of falls and fractures is becoming known, whether treatment of chronic hyponatremia with more effective therapies can improve bone health and reduce falls and fracture rates, particularly in elderly patients, remains to be studied.

Improvement of Clinical Outcomes in Chronic Diseases. Hyponatremia has a strong and independent association with a variety of serious adverse clinical outcomes such as hospitalization rate and mortality. This makes randomized controlled trials of the impact of more effective treatment of chronic hyponatremia a high priority for the many diseases in which chronic hyponatremia is strongly associated with adverse outcomes.

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