The American Journal of Medicine (2007) Vol 120 (11A), S1–S21

ELSEVIER

THE AMERICAN JOURNAL *of* MEDICINE®

Hyponatremia Treatment Guidelines 2007: Expert Panel Recommendations

Joseph G. Verbalis, MD,[a] Stephen R. Goldsmith, MD,[b] Arthur Greenberg, MD,[c] Robert W. Schrier, MD,[d] and Richard H. Sterns, MD[e]

[a]Division of Endocrinology and Metabolism, Department of Medicine, Georgetown University Medical Center, Washington, District of Columbia, USA; [b]Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA; [c]Division of Nephrology, Department of Medicine, Duke University, Durham, North Carolina, USA; [d]Department of Medicine, University of Colorado, Denver, Colorado, USA; [e]Department of Medicine, University of Rochester, Rochester, New York, USA

ABSTRACT

Although hyponatremia is a common, usually mild, and relatively asymptomatic disorder of electrolytes, acute severe hyponatremia can cause substantial morbidity and mortality, particularly in patients with concomitant disease. In addition, overly rapid correction of chronic hyponatremia can cause severe neurologic deficits and death, and optimal treatment strategies for such cases are not established. An expert panel assessed the potential contributions of aquaretic nonpeptide small-molecule arginine vasopressin receptor (AVPR) antagonists to hyponatremia therapies. This review presents their conclusions, including identification of appropriate treatment populations and possible future indications for aquaretic AVPR antagonists.

KEYWORDS: Antidiuretic hormone; Aquaretics; Hypo-osmolality; Natriuresis; Syndrome of inappropriate antidiuretic hormone secretion; Vasopressin

Hyponatremia is the most common disorder of electrolytes encountered in clinical practice, occurring in up to 15% to 30% of both acutely and chronically hospitalized patients.[1] Although most cases are mild and relatively asymptomatic, hyponatremia is important clinically because: (1) acute severe hyponatremia can cause substantial morbidity and mortality; (2) mortality is higher in patients with hyponatremia who have a wide range of underlying diseases; and (3) overly rapid correction of chronic hyponatremia can cause severe neurologic 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, and its multiple etiologies with differing pathophysiologic mechanisms.[2] Optimal treatment strategies have not been well defined, both for these reasons and because of marked differences in symptomatology and clinical outcomes based on the acuteness or chronicity of the hyponatremia.[3]

Vasopressin receptor antagonists have long been anticipated as a more effective method to treat hyponatremia by virtue of their unique aquaretic effect to selectively increase solute-free water excretion by the kidneys.[4] The recent approval of the first such agent, conivaptan, for clinical use by the US Food and Drug Administration (FDA) heralds the beginning of a new era in the management of hyponatremic disorders. However, effective therapy with these agents will require intelligent guidelines for their use. To this end, a panel of experts in hyponatremia convened to review current therapies for hyponatremia and to evaluate the situations in which aquaretic agents should be considered as alternatives or supplements to accepted current therapies. This review is a summary of the conclusions of this panel.

ROLE OF VASOPRESSIN IN HYPONATREMIA

Most hyponatremic states are characterized by inappropriately elevated plasma levels of arginine vasopressin

Statement of author disclosure: Please see the Author Disclosure section at the end of this article.

Requests for reprints should be addressed to Joseph G. Verbalis, MD, Department of Medicine, 5 PHC, Georgetown University Hospital, 3800 Reservoir Road NW, Washington, District of Columbia 20007.

E-mail address: verbalis@georgetown.edu.

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2007.09.001

(AVP).[5] 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 the syndrome of inappropriate antidiuretic hormone secretion (SIADH), despite hypo-osmolality AVP release is not fully suppressed owing to a variety of causes, including ectopic production of AVP by some tumors. The persistence of AVP release due to non-osmotic hemodynamic stimuli is also predominantly responsible for water retention and hyponatremia with hypovolemia, as well as in edema-forming disorders such as heart failure and cirrhosis.[6] Because of the critical role of AVP in abnormal water retention, all patients with hyponatremia and inappropriately elevated plasma AVP levels relative to osmolality are potential candidates for treatment with agents that block activation of AVP-mediated antidiuretic effects in the kidneys.

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 referred to as the tonicity of the plasma. 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, thereby effecting osmotic movement of water between the ICF and the ECF compartments. Consequently, 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 in which hyponatremia and hypo-osmolality are discordant.

Pseudohyponatremia. Marked elevations of either lipids or proteins in plasma can cause artifactual decreases in serum sodium 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.[7]

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, which in turn produces a dilutional decrease in the serum sodium. This situation most commonly is seen with hyperglycemia. Depending on the severity of hyperglycemia and the duration and magnitude of the accompanying glucose-induced osmotic diuresis, such patients actually may be hypertonic despite hyponatremia. In this setting, osmolality is best assessed by measuring plasma osmolality directly or by correcting the measured serum sodium for the glucose elevation.[8] When the plasma contains significant amounts of unmeasured solutes, such as mannitol or radiographic contrast agents, plasma osmolality cannot be calculated accurately and must be ascertained by direct measurement.

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 and the exchangeable K^+ (K^+_E) in the ICF along with their associated anions, total body osmolality will largely be a function of these parameters:

$$OSM_{ECF} = OSM_{ICF} = \frac{(\text{ECF solute} + \text{ICF solute})}{\text{body water}}$$

$$= \frac{(2 \times Na^+_E + 2 \times K^+_E + \text{nonelectrolyte solute})}{\text{body water}}$$

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, resulting in a dilution of 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 framework for appreciating appropriate therapies of hyponatremic disorders.

Table 1 Etiologies of depletional (hypovolemic) hyponatremia

Renal Loss of Sodium with Water Retention	Extrarenal Loss of Sodium With Water Retention
● Diuretic therapy	● Gastrointestinal losses
● Cerebral salt wasting	— Vomiting
● Mineralocorticoid deficiency	— Diarrhea
— Autoimmune	● Third space losses
○ Adrenal only	— Bowel obstruction
○ Polyglandular endocrinopathy	— Pancreatitis
— Adrenal hemorrhage	— Muscle trauma
○ Meningococcemia	— Burns
○ Idiopathic	● Sweat losses
— Infection	— Endurance exercise
○ Tuberculosis	
○ Fungus	
○ CMV	
— Adrenal enzyme deficiencies (congenital adrenal hyperplasia)	
● Salt-wasting nephropathy	
● Bicarbonaturia, glucosuria, ketonuria	

CMV = cytomegalovirus.

CLASSIFICATIONS AND DIAGNOSIS OF HYPOTONIC HYPONATREMIA

A definitive diagnosis of the underlying etiology of hyponatremia is not always possible at the time of initial presentation. Nonetheless, in most cases, a diagnostic approach based on clinical assessment of the patient's ECF volume status and urine sodium excretion permits a sufficient categorization of the underlying etiology to allow initiation of therapy and to plan further diagnostic evaluation. The sections below 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.

Hypovolemic hyponatremia. The presence of clinically detectable decreased ECF volume generally reflects hypovolemia from some degree of body solute depletion. Hyponatremia with volume depletion can arise in a variety of settings (**Table 1**). Because intravascular volume cannot be easily measured directly, volume depletion is generally diagnosed clinically from the history, physical examination, and laboratory results. Patients with clinical signs of volume depletion (eg, orthostatic decreases in blood pressure and increases in pulse rate, dry mucus membranes, decreased skin turgor) should be considered 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, 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 they can be affected by other factors (eg, dietary protein intake, use of glucocorticoids). The urine sodium excretion is usually more helpful. A spot urine $[Na^+]$ should be <30 mmol/L in patients with hypovolemic hyponatremia unless the kidney is the site of sodium loss.[9] 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 decrease as the administered water is retained and the sodium load excreted in a smaller volume of concentrated urine.

Euvolemic hyponatremia. Many different hypo-osmolar disorders can potentially present clinically with a normal ECF volume, or euvolemia, in part because it is difficult to detect modest changes in volume status using standard methods of clinical assessment. Most patients with hyponatremia have clinical euvolemia, in part because of the large number of diseases associated with SIADH (**Table 2**). Euvolemia is generally diagnosed clinically from the history, physical examination, and laboratory results. Patients without clinical signs of volume depletion (orthostatic decreases in blood pressure and increases in pulse rate, dry mucus membranes, decreased skin turgor) or volume expansion (subcutaneous edema, ascites) should be considered to have euvolemia unless there is alternative evidence suggesting an abnormal ECF volume status. Supportive laboratory results include a normal or low BUN, and a low serum uric acid level.[10] However, the urine $[Na^+]$ is most helpful in this regard. A spot urine $[Na^+]$ should be ≥ 30 mmol/L in most patients with euvolemic hyponatremia unless they have become secondarily sodium depleted.[9] When the clinical assessment of ECF volume is equivocal, or the urine $[Na^+]$ is <30 mmol/L, a trial of volume expansion with isotonic saline can be helpful to ascertain the correct diagnosis (see above under "Hypovolemic hyponatremia").

Hypervolemic hyponatremia. The presence of clinically detectable increased ECF volume generally reflects hypervolemia from some degree of body Na^+ excess. In these patients hypo-osmolality results from an even greater expansion of body water caused by a reduction in water excretion secondary to decreased effective arterial blood volume (EABV).[11] The latter increases the reabsorption of glomerular filtrate not only in the proximal nephron but also in the collecting tubules by stimulating AVP secretion. Hyponatremia with ECF volume excess can arise in a variety of diseases (Table 2). Because intravascular volume cannot be easily measured directly, vol-

Table 2 Etiologies of dilutional (euvolemic and hypervolemic) hyponatremia

- Impaired Renal Free Water Excretion
  - Euvolemic
    - SIADH
      - Tumors
        - Pulmonary/mediastinal (bronchogenic carcinoma, mesothelioma, thymoma)
        - Nonchest (duodenal carcinoma, pancreatic carcinoma, ureteral/prostate carcinoma, uterine carcinoma, nasopharyngeal carcinoma, leukemia)
      - CNS disorders
        - Mass lesions (tumors, brain abscesses, subdural hematoma)
        - Inflammatory diseases (encephalitis, meningitis, systemic lupus, acute intermittent porphyria, multiple sclerosis)
        - Degenerative/demyelinative diseases (Guillain-Barré syndrome; spinal cord lesions)
        - Miscellaneous (subarachnoid hemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk section, transphenoidal adenomectomy, hydrocephalus)
      - Drug induced
        - Stimulated AVP release (nicotine, phenothiazines, tricyclics)
        - Direct renal effects and/or potentiation of AVP antidiuretic effects (DDAVP, oxytocin, prostaglandin synthesis inhibitors)
        - Mixed or uncertain actions (ACE inhibitors, carbamazepine and oxcarbazepine, chlorpropamide, clofibrate; clozapine, cyclophosphamide, 3,4-methylenedioxymethamphetamine ["Ecstasy"], omeprazole; serotonin reuptake inhibitors, vincristine)
      - Pulmonary diseases
        - Infections (tuberculosis, acute bacterial and viral pneumonia, aspergillosis, empyema)
        - Mechanical/ventilatory (acute respiratory failure, COPD, positive pressure ventilation)
      - Other
        - AIDS and ARC
        - Prolonged strenuous exercise (marathon, triathalon, ultramarathon, hot-weather hiking)
        - Senile atrophy
        - Idiopathic
    - Glucocorticoid deficiency
    - Hypothyroidism
    - Decreased urinary solute excretion
      - Beer potomania
      - Very-low-protein diet
  - Hypervolemic
    - CHF
    - Cirrhosis
    - Nephrotic syndrome
    - Renal failure
      - Acute
      - Chronic
- Excessive Water Intake
  - Primary polydipsia
  - Dilute infant formula
  - Freshwater drowning

ACE = angiotensin-converting enzyme; AIDS = acquired immune deficiency syndrome; ARC = AIDS-related complex; AVP = arginine vasopressin; CHF = congestive heart failure; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; DDAVP = desmopressin acetate; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

ume excess is generally diagnosed clinically from the history, physical examination and laboratory results. Patients with clinical signs of volume overload (subcutaneous edema, ascites, pulmonary edema) should be considered to have hypervolemia unless there are alternative explanations for these findings. When available, hemodynamic measurements can provide corroboration of the clinical impression. Elevation of plasma levels of brain natriuretic peptide (BNP) provides useful laboratory support for the presence of volume overload. The urine sodium, or fractional sodium excretion, is usually low (spot urine $[Na^+] < 30$ mmol/L) in patients with hypervolemic hyponatremia due to activation of the renin-angiotensin-aldosterone system (RAAS) with secondary renal sodium conservation despite the whole-body volume overload.

ETIOLOGIES AND PATHOPHYSIOLOGIES OF HYPOTONIC HYPONATREMIAS

Hypovolemic Hyponatremia

Hypovolemic hyponatremia is generally caused by loss of body sodium or potassium with secondary water retention. The solute losses are generally classified as of renal or extrarenal origin (Table 1). The pathophysiologies underly-

ing 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 (e.g., "tea and toast") in conjunction with a baroreceptor-mediated stimulus to AVP secretion, hyponatremia will result instead. The diagnosis can usually be made readily 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 case the urine [Cl^-], which is a more reliable indicator of volume depletion with vomiting, should be low.

Excessive sweating. Hyponatremia after vigorous endurance exercise such as marathons, ultramarathons, and triathlons is well described.[12] Exercise-associated hyponatremia (EAH) had previously been considered a form of volume depletion–related hyponatremia occurring as a result of loss of sodium and chloride in sweat during exercise. However, more recent evidence indicates that excessive water retention is principally responsible for EAH; thus, this disorder is covered in the section entitled "Euvolemic Hyponatremia."

Diuretic therapy. Hyponatremia is a well-documented complication of diuretic use, and the diagnosis is generally evident from the clinical setting. Because the sodium loss is renal, a high urine [Na^+] level is expected if diuretic use is ongoing. Presumably because they impair distal tubule–diluting capacity without affecting urinary concentration, thiazide drugs are the predominant cause of diuretic-induced hyponatremia. In a literature review, 73% of cases of hyponatremia were caused by use of thiazides alone, 20% were caused by use of thiazides in combination with antikaliuretic agents, and 8% were caused by use of furosemide.[13] Furosemide-related hyponatremia tends to occur after many months of therapy, often when an intercurrent illness develops, whereas thiazide-related hyponatremia frequently occurs within a few days or weeks after initiation of therapy.[13,14] Patients with thiazide-induced hyponatremia typically are elderly women. In 1 study, the mean age was 76.4 ± 9.6 years, 90% of those affected were aged ≥65 years, and 70% were women.[14] Although most patients with diuretic-induced hyponatremia are women, whether female sex or lower body weight confers increased risk is uncertain.[15]

Patients with a prior 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 decrease 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.[16] Serum uric acid levels, which typically rise with volume depletion, were lower in patients with thiazide-induced hyponatremia as compared with normonatremic patients taking thiazides.[15] Taken together, these data suggest a role for abnormal thirst and water intake in individuals who develop thiazide-induced hyponatremia.

Cerebral salt wasting. Cerebral salt wasting (CSW) is a syndrome that occurs after head injury or neurosurgical procedures. 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. Superficially, CSW resembles SIADH: both are hyponatremic disorders seen after head injury with relatively high urine sodium excretion rates and urine osmolality, along with plasma AVP levels that are inappropriately high in relation to serum osmolality. However, in patients with CSW the increase in AVP is secondary to volume depletion, whereas a high AVP level is the primary etiologic event in patients with SIADH, who are euvolemic or have a modest increase in plasma volume from water retention. The typically high urine [Na^+] is not the cause of the hyponatremia in SIADH; rather, it is an expected response given the modest volume expansion and the need to maintain sodium balance in the face of continuing sodium intake.

The relative distribution of CSW and SIADH among neurosurgery patients with hyponatremia is unknown, and the etiology of CSW has not been definitively established. Abnormal sympathetic outflow to the kidney with a pressure natriuresis as well as abnormal secretion of atrial natriuretic peptide (ANP) or BNP have been proposed as potential causes.[17,18] Differentiation of CSW from SIADH hinges on establishing that a period of urinary sodium loss and volume depletion preceded development of hyponatremia. Because infusion of isotonic saline into a patient with euvolemia and SIADH results in a rapid excretion of the salt 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, 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. The BUN may be high with volume depletion, but the BUN can also be influenced by protein intake and use of corticosteroids. Uric acid tends to be low in both disorders.[19]

Mineralocorticoid deficiency. Patients with isolated glucocorticoid deficiency from adrenocorticotropic hormone (ACTH) deficiency do not have mineralocorticoid defi-

ciency, 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. In contrast, in patients with mineralocorticoid deficiency from primary adrenal insufficiency caused by adrenal destruction or hereditary enzyme deficiencies (Table 1), renal sodium wasting leads to hypovolemia and a secondary volume stimulus to AVP release. Ingestion of water or administration of hypotonic fluids in such patients may lead to water retention and hyponatremia, just as with diuretic therapy. Volume depletion with high urine [Na^+] and accompanying hyperkalemia should raise suspicion of mineralocorticoid deficiency. A low urine [K^+] or transtubular potassium gradient can provide additional confirmation. Once suspected, corticosteroids should be administered promptly even as diagnostic confirmation by measurement of cortisol response to cosyntropin stimulation, aldosterone, and ACTH levels is undertaken.

Euvolemic Hyponatremia

Because the presence of dilutional hyponatremia always implies an excess of body water either absolutely or relatively, it is generally the result of fluid intake in excess of the kidney's ability to excrete water. Although this rarely can be caused by excessive drinking alone, most cases involve impairments of renal ability to excrete water maximally, either owing to AVP effects at the vasopressin V_2 receptor (V_2R) or to non–AVP-mediated mechanisms (Table 2). The pathophysiologies underlying the major disorders associated with euvolemic hyponatremia are described below.

SIADH. SIADH is the most common cause of euvolemic hyponatremia in clinical medicine. The criteria necessary for a diagnosis of SIADH remain essentially as originally defined by Bartter and Schwartz in 1967.[20] First, true ECF hypo-osmolality must be present and hyponatremia secondary to pseudohyponatremia or hyperglycemia must be excluded. Second, urinary osmolality must be inappropriate for plasma hypo-osmolality. This does not require a urinary osmolality that is greater than plasma osmolality, but simply that the urine osmolality is greater than maximally dilute (ie, urinary osmolality $>$100 mOsm/kg H_2O in adults). Furthermore, urine osmolality need not be inappropriately elevated at all levels of plasma osmolality but simply at some level $<$275 mOsm/kg H_2O, because in patients with a reset osmostat AVP secretion can be suppressed at some level of osmolality, resulting in maximal urinary dilution and solute-free water excretion at plasma osmolalities below this level.[21] Third, clinical euvolemia must be present to diagnose SIADH, and this diagnosis cannot be made in a patient with hypovolemia or edema. This does not mean that patients with SIADH cannot become hypovolemic for other reasons, but in such cases it is impossible to diagnose the underlying SIADH until the patient is rendered euvolemic. The fourth criterion, urine sodium excretion, has probably caused the most confusion regarding SIADH. The importance of this criterion lies in its usefulness in differentiating hypo-osmolality caused by a decreased EABV (in which case renal Na^+ conservation occurs) from dilutional disorders in which renal Na^+ excretion is normal or increased owing to ECF volume expansion. However, urine [Na^+] can also be high in renal causes of solute depletion such as diuretic use or Addison's disease, and conversely patients with SIADH can have low urine [Na^+] levels if they subsequently develop hypovolemia or solute depletion, conditions sometimes produced by imposed sodium and water restriction. Consequently, although high urine [Na^+] excretion generally occurs in patients with SIADH, its presence does not confirm this diagnosis, nor does its absence rule out the diagnosis. 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. Many different disorders are associated with SIADH, which can be divided into several major etiologic groups (Table 2).

Nephrogenic syndrome of inappropriate antidiuresis. Recent studies of children with hyponatremia have discovered 2 genetic mutations of the V_2R that were responsible for constitutive activation of antidiuresis in the absence of AVP–V_2R ligand binding.[22] 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.[23] The true incidence of these and similar V_2R 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,[24] remains to be determined.

Glucocorticoid deficiency. Isolated glucocorticoid deficiency occurs with secondary adrenal insufficiency, generally caused by pituitary disorders that impair normal ACTH secretion but leave other stimuli to aldosterone secretion intact. That glucocorticoid deficiency alone also impairs water excretion was recognized based on longstanding clinical observations that anterior pituitary insufficiency ameliorates, and sometimes even completely masks, the polyuria of patients with coexistent central diabetes insipidus.[25] Consequently, it is not surprising that hyponatremia occurs relatively frequently in patients with pituitary insufficiency who do not have diabetes insipidus.[26] However, patients with hypopituitarism generally do not develop ECF volume contraction, because they maintain adequate aldosterone secretion to prevent renal sodium wasting. Consequently, volume replacement with isotonic NaCl does not reverse the impaired water excretion of patients with secondary adrenal insufficiency as it does in primary adrenal insufficiency.

Despite the lack of an apparent hypovolemia-mediated stimulus to AVP secretion, nonosmotic AVP secretion has

been strongly implicated in the impaired water excretion of glucocorticoid insufficiency. Elevated plasma AVP levels have been documented clearly in animals and patients[27] with hypopituitarism. That these elevated AVP levels were causally related to the impaired water excretion was again proved by studies using an AVP V_2R receptor antagonist, which demonstrated near normalization of urinary dilution in adrenalectomized mineralocorticoid-replaced rats.[28]

Hypothyroidism. Although hypothyroidism is more common than adrenal insufficiency, hyponatremia secondary to hypothyroidism occurs much less frequently than hyponatremia from adrenal insufficiency. The infrequent occurrence of hyponatremia with hypothyroidism has led some investigators to question whether hypothyroidism is in fact causally related to hyponatremia,[29] but this is likely a manifestation of the fact that impaired water excretion is only seen in patients with more severe hypothyroidism. Typically such patients are elderly and meet criteria for myxedema coma as a result of their altered mental status.[30]

Similar to adrenal insufficiency, hypothyroidism can result from either dysfunction or damage to the thyroid gland itself (primary hypothyroidism) or from inadequate thyrotropin-stimulating hormone (TSH) stimulation from the pituitary (secondary hypothyroidism). Also like adrenal insufficiency, there can be significant differences in the presentation of these 2 disorders. However, because the only biologically active products of the thyroid gland are the hormones thyroxine (T_4) and triiodothyronine (T_3), in this case the clinical variations are due mainly to quantitative differences in the severity of the thyroid hormone deficiency rather than to qualitative differences in the nature of the hormone deficits. Because hyponatremia is only seen in patients with hypothyroidism who have progressed to severe degrees of myxedema, this manifestation generally occurs in patients with primary hypothyroidism. When hyponatremia accompanies hypopituitarism it is usually a manifestation of secondary adrenal insufficiency from glucocorticoid deficiency rather than coexisting hypothyroidism.

The major cause of impaired water excretion in hypothyroidism appears to be an alteration in renal perfusion and glomerular filtration rate (GFR) secondary to systemic effects of thyroid hormone deficiency on cardiac output and peripheral vascular resistance.[31] In uncomplicated hypothyroidism there appears to be little elevation of plasma AVP levels. However, as the hypothyroidism becomes more severe, the EABV can decrease sufficiently to stimulate AVP secretion secondarily via baroreceptor mechanisms. Additionally, the impaired cardiac function that often occurs with advanced myxedema can lead to an elevation in plasma AVP levels, and in experimental hypothyroidism, the impaired response to an acute water load was reversed by a V_2R antagonist.[32] Whether hyponatremia develops at any stage of disease progression depends on the relative balance between water intake and excretory capacity; since 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 finishers with normonatremia who excreted a small volume of highly concentrated urine; both groups had equivalent sodium losses as reflected by positive sodium balances during recovery.[33] The change in serum sodium concentration after endurance exercise is inversely proportional to the change in body weight, and the athletes with EAH tended to gain weight during the exercise.[34] 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 but not all studies, female sex and the use of nonsteroidal anti-inflammatory drugs also were risk factors.[12] Thus, while athletes with both normonatremia and hypernatremia often are 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 osmotically stimulated AVP secretion.[35,36]

Low solute intake. Some cases of euvolemic hyponatremia do not fit particularly well into either a dilutional or depletional 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, because $\geq$50 mOsmol of urinary solute excretion are required to excrete each liter of maximally dilute urine. Consequently, water retention with hyponatremia will result when fluid intake exceeds the maximum volume of urine that can be excreted based on the available solute.[37] Similar cases have been reported in patients on very-low-protein diets.[38] 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 only 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 solute-free water excretion. The most dramatic cases of primary polydipsia are seen in psychiatric patients, particularly those with acute psychosis secondary to schizophrenia.[39] The prevalence of this disorder based on hospital admissions for acute symptomatic hyponatremia may have been underestimated, because studies of psychiatric patients

with polydipsia have shown a marked diurnal variation in serum [Na^+] (eg, from 141 mmol/L at 7 AM to 130 mmol/L at 4 PM), suggesting that many such patients drink excessively during the daytime but then correct themselves via a water diuresis at night.[40] 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% to 10%.[41] Despite the frequent occurrence of polydipsia in psychiatric patients, it is important to recognize that not all polydipsia is caused by psychiatric disease; infiltrative diseases such as central nervous system (CNS) sarcoidosis[42] or critically located brain tumors can also be associated with increased thirst and fluid ingestion. Consequently, patients with polydipsia should be evaluated with a computed tomography or magnetic resonance imaging (MRI) scan of the brain before concluding that excessive water intake is due to a psychiatric 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 adult kidneys can exceed 20 L/day, maximum hourly rates rarely exceed 800 to 1,000 mL/hr. Recent studies of water loading in nonexercising athletes have indicated a similar peak urine excretion rate of 778 ± 39 mL/hr.[43] 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.[44] However, other cases have been found to meet the criteria for SIADH, suggesting nonosmotically stimulated AVP secretion. As might be expected, in the face of much higher than normal water intake, virtually any impairment of urinary dilution and water excretion can exacerbate the development of a positive water balance and thereby produce hypo-osmolality. Thus, hyponatremia has been reported in patients with polydipsia 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.[45] Although no single mechanism can completely explain the occurrence of hyponatremia in psychiatric patients with polydipsia, the combination of higher than normal water intake plus even modest elevations of plasma AVP levels from a variety of potential sources appears to account for a significant 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, mostly due to AVP effects at V_2R or to non–AVP-mediated mechanisms (Table 2). The pathophysiologies underlying the major disorders associated with hypervolemic hyponatremia are described below.

Heart failure. Hyponatremia is a relatively common electrolyte disorder in both acute and chronic heart failure (CHF), occurring in ≥20% of patients, particularly those with advanced disease.[1] In both inpatient and outpatient populations, hyponatremia is a strong predictor of poor outcome, including hospitalization and death.[46] The power of hyponatremia to predict adverse outcome has been established for many years and persists despite modern treatment with neurohormonally-based therapies.[47]

The renal regulation of sodium and water excretion in HF involves multiple factors. Under normal circumstances there are several atrial-renal reflexes that modulate renal sodium and water excretion. An increase in left atrial pressure suppresses the release of AVP and causes a water diuresis, the Henry-Gauer reflex. An increase in transmural atrial pressure is also known to increase atrial natriuretic peptide (ANP) secretion, with a resultant 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 CHF, atrial pressure is increased but these reflexes are blunted.[48,49] There is, however, an increase in the ventricular synthesis and release of BNP, which attenuates the sodium and water retention associated with CHF.[50]

There are high-pressure baroreceptors in the left ventricle, carotid body, aortic arch, and juxtaglomerular apparatus. Normally, tonic inhibition of central AVP release and adrenergic stimulation is present via the vagus and glossopharyngeal nerves from the arterial baroreceptors in the carotid and aortic arch bodies. With a decrease in stretch on these receptors, however, the central inhibition is removed so that there is an increase in AVP release and enhanced adrenergic stimulation. This increased AVP release occurs even in the presence of hypo-osmolality, which normally suppresses AVP release. This baroreceptor-mediated, nonosmotic release of AVP is characteristic of CHF, and is accompanied by an increase in circulatory norepinephrine and sympathetic tone.[51] The increase in β-adrenergic stimulation also increases renal renin synthesis and release with resultant activation of the RAAS.[52]

Studies in humans and nonhuman primates have suggested that short of overt hypotension, both the high- and low-pressure baroreceptors are less active in controlling AVP secretion in humans than has been found in prior studies using dogs and rats. The quantitative contribution of abnormalities in baroreflex function to enhanced AVP secretion in CHF therefore is not clear, although it almost certainly does contribute to increased sympathetic tone. The increase in β-adrenergic stimulation also increases renal-renin synthesis, with resultant activation of the RAAS. Nonetheless, some form of nonosmotic stimulation of AVP clearly occurs in CHF, because plasma AVP levels are increased despite normal or low serum osmolalities. Other

possible stimuli include increased adrenergic effects in the CNS and/or the presence of increased angiotensin II activation of CNS sites known to be involved in regulation of AVP secretion.

Whereas the nonosmotic release of AVP is the dominant factor for the occurrence of water retention and hyponatremia in CHF, there are intrarenal events that also attenuate maximal solute-free water reabsorption in patients with CHF. With severe renal vasoconstriction in CHF a decrease in GFR occurs, and peritubular Starling forces are also altered in a direction to enhance tubular sodium and water reabsorption.[53,54] In addition to the effect of adrenergic stimulation and angiotensin II on renal vascular tone, both pathways activate receptors on the proximal tubular epithelium and increase sodium and water reabsorption by the kidneys.[55]

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, theoretically a GFR of 100 mL/min leads to a daily filtrate of 144 L with 20% (i.e., 28 L) reaching the distal diluting segment.[6] With normal renal function and maximal AVP suppression, the renal capacity to excrete solute-free water is therefore enormous. This aspect of normal renal physiology explains why psychogenic or compulsive water drinkers usually do not develop hyponatremia unless another factor (eg, AVP release, diuretic administration) intervenes. Because most patients with CHF develop hyponatremia with only 2 to 3 L/day of fluid intake, the nonosmotic release of AVP, rather than intrarenal hemodynamic abnormalities, is the dominant factor in the pathogenesis of hyponatremia in CHF.

Cirrhosis. Hyponatremia occurs even more commonly in cirrhosis, in upwards of 30% to 35% of patients, particularly those with advanced chronic disease.[1] Just as for CHF, hyponatremia is a strong predictor of poor outcome, including hospitalization and death.[56] Multiple studies found hyponatremia to be associated with poor prognosis, although multivariate analyses have not uniformly demonstrated its independent association with adverse clinical outcomes.[57]

In cirrhosis there is also clear evidence of nonosmotic release of AVP, but as with CHF, the precise contributions of baroreceptor-mediated and other neurohormonal factors have not been clearly established. The portal hypertension associated with cirrhosis provides the stimulus for the splanchnic vasodilatation.[58] Several humoral mediators for this splanchnic vasodilatation have been suggested, but to date the role of increased nitric oxide secondary to endothelial nitric oxide synthase (eNOS) and/or inducible nitric oxide synthase (iNOS) appears to be most convincing.[59] As with cardiac failure, the increased RAAS and sympathetic stimulation in cirrhosis enhance tubular sodium and water reabsorption and limit fluid delivery to the distal diluting segment of the nephron. These intrarenal events can occur before a fall in GFR in patients with cirrhosis, but in advanced stages the decline in GFR inhibits maximal solute-free water excretion. However, as in cardiac failure, nonosmotic release of AVP appears to be the most important factor in causing hyponatremia in patients with cirrhosis. This conclusion is derived from studies in cirrhotic patients receiving an AVP V_2R antagonist that demonstrate urinary dilution and increased serum $[Na^+]$.[60]

Nephrotic syndrome, acute and chronic renal failure. Hyponatremia occurs commonly in both acute and chronic renal failure, because the kidneys cannot maximally excrete excess ingested or infused water. In contrast, hyponatremia is not very common in the nephrotic syndrome unless associated with a substantial decrease in GFR. However, with severe hypoalbuminemia of <2 g/dL, intravascular hypovolemia may occur and lead to the nonosmotic release of AVP[53,54] with subsequent retention of ingested or infused hypotonic fluids.

RATE OF CORRECTION OF HYPONATREMIA

There are no data to suggest that the etiology of the hyponatremia, nor the methodology used to correct hyponatremia, alters the susceptibility for producing osmotic demyelination with overly rapid correction. Consequently, the rate of correction of hyponatremia must be taken into account before deciding on the most appropriate therapy for any patient with hyponatremia.

Brain Adaptation to Hyponatremia

In order to understand the scientific rationale supporting guidelines for correcting hyponatremia, and how this differs in cases of acute versus chronic hyponatremia, it is essential to appreciate how the brain adapts to hyponatremia and the time course over which this process occurs.

Outcomes in 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 sodium concentration is low.[61,62] Given the confines of the skull, cell swelling is most important in the brain. When hyponatremia develops over a few hours, outpacing the brain's ability to adapt, cerebral edema results. Thus, patients with acute ($<$48 hours) hyponatremia may present with alarming neurologic findings, and they sometimes die of brain herniation.[63] Given time, brain cells extrude organic solutes from their cytoplasm, allowing intracellular osmolality to equal plasma osmolality without a large increase in cell water. Therefore, when hyponatremia develops over several days, brain swelling is minimized so that patients with chronic ($\geq$48 hours) hyponatremia have more modest symptoms and almost never die of brain herniation.[64]

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, enough to increase the serum sodium concentration by about 4 mmol/L.[65] Over the years there have been few refinements to this approach. To avoid confusion with 5% dextrose in water, 5% saline has been largely replaced with 3% saline. In 2005, a consensus conference, convened to develop treatment guidelines for acute water intoxication in competitive runners from EAH, advocated treatment with a 100-mL bolus of 3% saline, enough to increase the serum sodium concentration by about 2 mmol/L.[35] A small, quick increase in the serum sodium concentration (2 to 4 mmol/L) is effective in acute hyponatremia because reducing brain swelling even slightly results in a substantial decrease in intracerebral pressure.[66]

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, outpacing the brain's ability to recapture lost organic osmolytes, osmotic demyelination can result.[67,68] 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 disease could be reproduced in chronically hyponatremic dogs, rabbits, and rats. Animals with severe uncorrected chronic hyponatremia do not develop brain lesions, confirming that myelinolysis is a complication of the rapid correction of hyponatremia and not the electrolyte disturbance itself. The neurologic complications of chronic hyponatremia present in a stereotypical biphasic pattern that has been called the osmotic demyelination syndrome.[67] Patients initially improve neurologically with correction of hyponatremia, but then, 1 to several days later, new, progressive, and sometimes permanent neurologic deficits emerge. Most patients with the osmotic demyelination syndrome survive, and those with persistent deficits can be diagnosed with magnetic resonance imaging.[69]

Several lines of evidence have linked the pathogenesis of myelinolysis to the slow reuptake of organic osmolytes by the brain. In experimental models, brain regions that are slowest to recover osmolytes are the most severely affected by myelinolysis.[70] Uremia protects against myelinolysis and brain osmolytes are recovered more rapidly during correction of hyponatremia in animals that are uremic than in nonuremic animals.[71] Finally, infusion of myoinositol (a major osmolyte lost in the adaptation to hyponatremia) protects against mortality and myelinolysis from rapid correction of hyponatremia.[3]

Current Recommendations for Rate of Correction of Hyponatremia

Five cohort studies[64,68,69,72,73] and 3 reviews of the literature by 3 different authors[13,67,74] have concluded that in patients with chronic hyponatremia, neurologic sequelae are associated with more rapid rates of correction. The osmotic demyelination syndrome can usually be avoided by limiting correction of chronic hyponatremia to $<$10 to 12 mmol/L in 24 hours and to $<$18 mmol/L in 48 hours.[68] These estimates should be regarded as approximate limits and not goals of therapy. Patients with severe malnutrition, alcoholism, or advanced liver disease may be especially susceptible to the osmotic demyelination syndrome.[75] In high-risk patients, therapy should be tailored to stay well below limits that have been established in patients without these risk factors.

One group has suggested that severe demyelinating brain lesions rarely complicate therapy unless the rate of correction is $>$25 mmol/L in 48 hours (an estimate based on patients with severe autopsy-proven myelinolysis).[76] Although many patients tolerate increases in serum [Na^+] of this magnitude, such therapy cannot be justified unless there is proof that it is beneficial. There is some evidence that correction by $<$3 to 4 mmol/L in 24 hours may be associated with excess mortality in patients with acute[77] or postoperative hyponatremia.[78] There is no evidence that correction of serum [Na^+] by $>$10 mmol/L in 24 hours or 18 mmol/L in 48 hours improves outcomes in patients with acute or chronic hyponatremia.

Complications of therapy often occur in patients whose hyponatremia "autocorrects" unexpectedly during the course of treatment.[79,80] Patients with hyponatremia caused by volume depletion, cortisol deficiency, desmopressin acetate (DDAVP), or thiazides are particularly vulnerable. In these disorders, once the cause of hyponatremia is eliminated by volume repletion, cortisol replacement, or discontinuation of DDAVP or thiazides, a water diuresis emerges. Without a nonosmotic stimulus for AVP secretion, patients who have hyponatremia excrete maximally dilute urine, which can increase the serum [Na^+] by $>$2 mmol/L/hr, and potentially life-threatening overcorrection may result in only 12 hours. Given the risk of overshooting maximal recommended increases, it is best to aim for correction by approximately 8 mmol/L per day and to monitor the serum [Na^+] and the urine output frequently.

To be meaningful, rates of correction of hyponatremia should be expressed as an increment (in mmol/L) over a specified time period (eg, 12 hours, 24 hours, or 48 hours). Rates expressed in millimoles per liter per hour 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 serum [Na^+] from its initial value to a final value. This methodology (which is in essence an averaged rate) can lead to misleading conclusions, particularly in patients with very low serum [Na^+]. If an end point of 130 mmol/L is used to compute the rate (as it was for a frequently cited series[81]), one might conclude erroneously that patients with neurologic sequelae had not been corrected

rapidly despite treatment with hypertonic saline and correction by >25 mmol/L in 48 hours.[82]

Patients with severe symptoms from chronic hyponatremia, particularly those with seizures, may benefit from a brief infusion of hypertonic saline, increasing the serum [Na^+] by 2 to 4 mmol/L within 2 to 4 hours (an increase that could be expressed as 1 to 2 mmol/L per hr). There is no evidence that a quick but limited increase in the serum [Na^+] is harmful; such therapy should not be considered "rapid" if the total increase in serum [Na^+] over 24 hours is maintained at <10 mmol/L in 24 hours or <18 mmol/L in 48 hours.

CONVENTIONAL THERAPY OF HYPONATREMIAS

Hypovolemic Hyponatremia

The key step in the successful treatment of hypovolemic hyponatremia is to first establish that volume depletion is indeed present. Once this is done, treatment is straightforward: with correction of the volume deficit, the relative water excess will correct itself. When ECF volume depletion is obvious and potentially life-threatening, resuscitation with isotonic fluid will likely have been initiated empirically even before results of routine laboratory testing have returned. Volume expansion should be continued until blood pressure is restored and the patient has clinical euvolemia. When the initial volume estimate is equivocal, a fluid challenge with 0.5 to 1 L of isotonic (0.9%) saline can be both diagnostic and therapeutic. With the exception of CSW, and cases occurring soon after thiazides are started, hypovolemic hyponatremia is usually chronic rather than acute. Consequently, hypertonic (3%) saline is seldom indicated in such cases. If hypertonic saline is used, a diuretic should not be added until the volume deficit is fully corrected. Current conventional recommendations for treatment of hyponatremia in specific disorders associated with hypovolemia are given below. (For information on how these recommendations may change with increasing experience using these new agents, see below under "Vasopressin Receptor Antagonists.")

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 sodium chloride and sodium bicarbonate can be used when metabolic acidosis is because of diarrhea. Specific therapy for the underlying disorder should be initiated, and antiemetics and antidiarrheal agents can be used as appropriate.

Excess sweating. Individuals subjected to prolonged increased sweat losses should be evaluated with both a physical examination and a serum [Na^+]. Obvious signs of dehydration and volume depletion (particularly hypotension and tachycardia while supine) should be treated promptly with rehydration using isotonic (0.9%) NaCl. However, in the absence of obvious dehydration, therapy should be guided by the serum [Na^+]. Individuals with hyponatremia should not receive isotonic saline (if already started, it should be discontinued unless the patient is hemodynamically unstable) and treatment guidelines for EAH should be followed, as discussed later.

Diuretic therapy. Treatment consists of withholding all diuretics and repleting the patient with isotonic fluid if CNS abnormalities are mild. Hypertonic saline can be used to raise the serum sodium level 4 to 5 mmol/L when seizures or a significantly altered level of consciousness are present, but furosemide should not be used with the hypertonic saline. Rapid correction of diuretic-induced hyponatremia is associated with an increased death rate, so precautions regarding the maximal magnitude of daily correction should be followed.[13] Patients with thiazide-induced hyponatremia are at high risk for a recurrence and should not be rechallenged with a thiazide. 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.

CSW. Because hypovolemia may exacerbate CNS injury, patients with volume depletion from CSW should be resuscitated by administration of isotonic saline until they are euvolemic and then maintained in neutral fluid 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 in other hyponatremic states. One frequently cited paper suggests combined use of isotonic saline and NaCl tablets, but this is not substantially different than using hypertonic saline.[17]

Mineralocorticoid deficiency. Volume repletion with isotonic saline will be required initially in patients with primary adrenal insufficiency. Hydrocortisone and fludrocortisone replacement therapy are used chronically. In sick patients, glucocorticoid administration at stress doses (eg, hydrocortisone 100 mg parenterally every 8 hours) is essential while the adequacy of the cortisol reserve is being assessed.

Euvolemic Hyponatremia

Treatment of patients with euvolemic hyponatremia will vary greatly depending on their presentation. The single most important factor guiding initial therapy is the presence of neurologic symptoms. Cases of acute hyponatremia (arbitrarily defined as <48 hours' duration) are usually symptomatic if the hyponatremia is severe (≤120 mmol/L).

These patients are at greatest risk from neurologic 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 neurologic symptomatology are at little risk from complications of hyponatremia itself, but can develop osmotic demyelination following rapid correction. There is no indication to correct these patients rapidly, and they should be treated using slower-acting therapies. Although the above extremes have clear treatment indications, most patients with hyponatremia present with hyponatremia of indeterminate duration and with varying degrees of milder neurologic symptomatology. This group presents the most challenging treatment decision, because the hyponatremia will have been present sufficiently long to allow some degree of brain volume regulation, but not long enough to prevent some brain edema and neurologic symptomatology.[2] Prompt treatment of such patients is generally recommended because of their symptoms, but using methods that allow a controlled and limited correction of their hyponatremia based on parameters discussed later. In any patient with hyponatremia, one must address the question of how quickly the plasma osmolality should be corrected (see the Rate of Correction of Hyponatremia section on page S9). Current conventional recommendations for treatment of hyponatremia in specific disorders associated with euvolemia are given below (but also see Vasopressin Receptor Antagonists on page S15 for how these recommendations may change with increasing experience using these new agents).

SIADH. Correction of acute symptomatic hyponatremia is best accomplished with hypertonic (3%) saline given via continuous infusion, because patients with euvolemic hypo-osmolality such as SIADH will not respond to isotonic saline. An initial infusion rate can be estimated by multiplying the patient's body weight in kilograms by the desired rate of increase in serum [Na^+] in millimoles per liter per hour (eg, in a 70-kg patient an infusion of 3% NaCl at 70 mL/hour will increase serum [Na^+] by approximately 1 mmol/L per hr, while infusing 35 mL/hr will increase serum [Na^+] by approximately 0.5 mmol/L per hr). Intravenous furosemide 20 to 40 mg should be used to treat volume overload, in some cases anticipatorily in patients with known cardiovascular disease. Regardless of the initial rate of correction chosen, acute treatment should be interrupted once any of 3 end points is reached: (1) the patient's symptoms are abolished; (2) a safe serum [Na^+] level (generally ≥120 mmol/L) is achieved; or (3) a total magnitude of correction of 18 mmol/L is achieved. It follows from these recommendations that serum [Na^+] levels must be carefully monitored at frequent intervals (preferably every 2 hours, but at least every 4 hours) during the active phases of treatment in order to adjust therapy so that the correction stays within these 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 a water diuresis. If the hyponatremia is acute (eg, psychogenic polydipsia with water intoxication) such patients do not appear to be at risk for subsequent demyelination[44]; however, in cases where the serum [Na^+] rises quickly with the correction of chronic hyponatremia (e.g., cessation of desmopressin therapy, repletion of cortisol deficiency, or withdrawal of diuretic therapy), intervention should be considered to limit the rate and magnitude of correction of serum [Na^+] (eg, administration of desmopressin 1 to 2 μg intravenously or infusion of hypotonic fluids to match urine output) using the same end points as for active corrections.[2,79]

Treatment of chronic hyponatremia entails choosing among several suboptimal therapies. One important exception is in those patients with the reset osmostat syndrome; because the hyponatremia of such patients is not progressive but, rather, fluctuates around their reset level of serum [Na^+], no therapy is generally required. For most other cases of mild-to-moderate SIADH, fluid restriction represents the least toxic therapy, and has generally been the treatment of choice. Several points should be remembered when using this approach: (1) all fluids, not only water, must be included in the restriction; (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/day below the average daily urine volume[83]); (3) several days of restriction are usually necessary before a significant increase in plasma osmolality occurs; and (4) only fluid, not sodium, 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 relatively high NaCI intake unless otherwise contraindicated. However, just as failure to correct a presumed depletion-induced hyponatremia with isotonic saline should lead one to consider the possibility of a dilution-induced hypo-osmolality, 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 (eg, newer-generation oral hypoglycemic agents, which in general have not been associated with hyponatremia, should be substituted for chlorpropamide).

Fluid restriction should generally be tried as the initial therapy, with pharmacologic intervention 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 maintain it. In general, the higher the urine osmolality, indicating higher plasma AVP levels, the less likely that fluid restriction will be successful. In such cases reasonable efforts should be made to ameliorate

thirst, such as substituting hard candy or ice chips for drinking fluids. Pharmacologic intervention should also be avoided initially in patients with SIADH that is secondary to tumors, because successful treatment of the underlying malignant lesion often eliminates or reduces the inappropriate AVP secretion.[84] However, alternative pharmacologic management is often necessary. In such cases the preferred drug is the tetracycline derivative demeclocycline.[85] This agent causes a nephrogenic form of diabetes insipidus,[86] thereby decreasing urine concentration even in the presence of high plasma AVP levels. Appropriate doses of demeclocycline range from 600 to 1,200 mg/day administered in divided doses. Treatment must be continued for several days to achieve maximal diuretic effects; consequently, one should wait 3 to 4 days before deciding to increase the dose. Demeclocycline can cause reversible azotemia and sometimes nephrotoxicity, especially in patients with cirrhosis.[87] Renal function should therefore be monitored in patients treated with demeclocycline on a regular basis, and the medication should be discontinued if increasing azotemia is noted.

Other agents, such as lithium, have similar renal effects but are less desirable because of inconsistent results and significant side effects and toxicities.[88] Urea has also been described as an alternative mode of treatment for SIADH as well as for other hyponatremic disorders.[89] Although it has long been recognized that any osmotic diuretic can be used to treat hypo-osmolality by virtue of increasing solute-free water excretion, such therapeutic modalities have generally proved impractical for chronic ambulatory use. Urea is an exception because it can be administered orally; furthermore, it corrects hypo-osmolality not only by increasing solute-free water excretion but also by decreasing urinary sodium excretion. Dosages of 30 g/day are generally effective; 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, the development of azotemia at higher doses, and the unavailability of a convenient form of the agent. Several other drugs that have been described appear to decrease AVP hypersecretion in some cases (eg, diphenylhydantoin, opiates, ethanol), but responses are erratic and unpredictable.[90] One potential exception is the recent development of agonists selective for κ-opioid receptors, which appear to be more specific for inhibition of AVP hypersecretion in animal studies[91] and in clinical trials have successfully produced aquaresis in patients with cirrhosis.[92]

Nephrogenic syndrome of inappropriate antidiuresis (NSIAD). Because patients with activating mutations of the V_2R present clinically with the characteristics of patients with SIADH, they should be treated as described in the previous section. Urea therapy has been found to be particularly effective in young children with this disorder.[93]

Glucocorticoid deficiency. If there is any suspicion of either primary or secondary adrenal insufficiency, glucocorticoid replacement should be started immediately after completion of a rapid ACTH stimulation test. Prompt water diuresis after initiation of glucocorticoid treatment strongly supports glucocorticoid deficiency, but the absence of a quick response does not negate this diagnosis because several days of glucocorticoids are sometimes required for normalization of the plasma osmolality. In such cases, primary treatment of hyponatremia may be indicated if significant neurologic symptoms are present. However, serum $[Na^+]$ must be followed carefully, because subsequent development of a water diuresis may result in a more rapid correction than predicted from the rate of saline 3% infusion, and intervention should be considered to limit the rate and magnitude of correction of serum $[Na^+]$, as discussed in the section on SIADH.

Hypothyroidism. The primary therapy of hypothyroidism is thyroid hormone replacement. Because hyponatremia with hypothyroidism is infrequent and generally of mild severity, modest fluid restriction is generally the only treatment necessary. However, because symptomatic hyponatremia is seen primarily in patients with 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 neurologic symptoms.

EAH. EAH can be severe and life threatening as a result of cerebral edema and noncardiogenic pulmonary edema.[33,94] Prevention is paramount. Guidelines for appropriate fluid ingestion during marathons are available.[35] In general, runners should drink primarily when thirsty with an input no greater than 400 to 800 mL/hr; the greater amount is for heavier, faster runners during high-temperature conditions and the lesser amount for lighter, slower runners during lower-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, but seizures, profoundly altered level of consciousness, ataxia, or focal neurologic deficits should raise suspicion of severe hyponatremia and require emergent treatment. A treatment algorithm has been proposed, although it has not been validated in a large series. With significant CNS impairment, hypertonic saline should begin at once while the serum $[Na^+]$ result is awaited. The infusion is continued 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 125 mmol/L or below, but is probably not needed if the serum $[Na^+]$ is above 130 mmol/L.[95]

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 intakes into normal ranges. Unfortunately, this can prove difficult to accomplish. Patients with a reset thirst threshold will be resistant to fluid restriction because of the resulting thirst from stimulation of brain thirst centers at higher plasma osmolalities.[96] 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 behavior modification and pharmacologic therapy. Several 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[97]; this appears to be a specific property of this agent because similar results have not been observed with other antipsychotic drugs.[98]

Hypervolemic Hyponatremia

For all diseases associated with edema formation, dietary sodium restriction and diuretic therapy are the mainstays of therapy. When hyponatremia occurs, 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. It is not known whether hyponatremia is just a marker for disease severity in CHF and cirrhosis or an actual contributor to poor outcome. However, because hyponatremia may cause cognitive deficits,[99] 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 CHF and cirrhosis.[100] A recent clinical study reinforced this idea by demonstrating that correction of serum [Na^+] using hypertonic saline infusions was associated with improved outcomes in a group of patients with advanced CHF.[101] Current conventional recommendations for treatment of hyponatremia in specific disorders associated with hypervolemia are given below (also see "Vasopressin Receptor Antagonists" for details on how these recommendations may change with increasing experience using these new agents).

CHF. Conventional therapies used for the treatment of CHF include sodium restriction, diuretic therapy, and neurohormonal blockade. The most effective agents consist of a combination of loop diuretics, angiotensin-converting enzyme inhibitors, and β-adrenergic antagonists. Currently, there are no guidelines specifically regarding treatment of hyponatremia in CHF. Severely symptomatic hyponatremia is uncommon in CHF, but in theory it can be treated with hypertonic saline provided adequate diuresis is established. However, the volume expansion associated with the use of hypertonic saline makes this an unattractive option for all but emergent situations.

No data specifically address the issue of whether mild or moderate hyponatremia causes symptoms or should be treated in CHF, despite the association of even mild hyponatremia with poor outcomes. Substantial neurocognitive deficits have been reported with hyponatremia in other conditions and there is no reason to suspect they might not occur in CHF as well, but data are lacking. Likewise, the presence of hyponatremia may limit the use of loop diuretics and thereby permit continuing congestion, but no studies have addressed this issue specifically. There are also no guidelines or published regimens addressing the best method of treating mild or moderate hyponatremia in the event treatment is desired. Accordingly, treatment of hyponatremia in CHF at this time is largely empiric. Options include demeclocycline, urea, and fluid restriction. Difficulty in use coupled with toxicity make the first 2 options unattractive, leaving fluid restriction as the usual approach. In view of the renal dynamics governing water excretion in CHF as discussed above, fluid restriction is not particularly effective unless quite drastic ($\leq$1 L/day), in which case it generally is not well tolerated. There are no procedural or outcomes studies available to guide even this approach in acute or chronic CHF.

Cirrhosis. The development of ascites indicates progression of underlying cirrhosis and is associated with a 50% 2-year survival rate. Conventional therapies used for the treatment of ascites include sodium restriction, diuretic therapy, and large-volume paracentesis. The most effective diuretic combination consists of a potassium-sparing, distal-acting diuretic such as spironolactone along with a loop diuretic. The development of either diuretic-resistant or diuretic-intractable ascites occurs in approximately 5% to 10% of cases of ascites and is a poor prognostic sign.[102] As for CHF, currently there are no guidelines specifically regarding treatment of hyponatremia in cirrhosis. Demeclocycline is relatively contraindicated because of a high incidence of nephrotoxicity, and urea has not been used very often; again, this leaves fluid restriction as the usual approach, but without outcome studies to assess its effectiveness. The only definitive therapy for refractory ascites with cirrhosis is orthotopic liver transplantation.

Nephrotic syndrome, acute and chronic renal failure. In patients with hyponatremia with advanced acute and chronic renal failure and GFR $<$20 mL/min, fluid restriction to amounts less than insensible losses plus urine output is generally necessary to cause a negative solute-free water balance and correction of hyponatremia.

VASOPRESSIN RECEPTOR ANTAGONISTS

Vasopressin receptor antagonists 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.[4] The recent approval of the first such agent, conivaptan, for clinical use by the FDA and the active phase 2/3 clinical programs of other drugs in this class, known as the "vaptans" (for vasopressin antagonists), heralds 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 multiple clinical trials.

Vasopressin receptors. AVP receptors (AVPR) are G-protein–coupled receptors. The 3 known subtypes differ in localization and signal transduction mechanisms.[103] The AVP V_{1a} ($V_{1a}R$) and V_{1b} ($V_{1b}R$) receptors are Gq-coupled receptors that activate phospholipase C and increase cytosolic free calcium; the physiologic effects caused by activation depend primarily on the localization of the receptors and include vasoconstriction ($V_{1a}R$), platelet aggregation ($V_{1a}R$), ionotropic stimulation and myocardial protein synthesis ($V_{1a}R$), and pituitary ACTH secretion ($V_{1b}R$). AVP V_2 receptors (V_2R) are found on the principal cells of the renal collecting tubules and vascular endothelium, where they mediate the antidiuretic effects of AVP and stimulate release of von Willebrand factor and factor 8, respectively. V_2R-mediated vasodilatation has also been described at high concentrations of AVP. Binding of AVP to its V_2R activates the G_s-coupled adenylyl cyclase system, increasing intracellular levels of cyclic adenosine monophosphate. In the kidney, this activates protein kinase A, which then phosphorylates preformed aquaporin-2 (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.[104] 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.

Development of vasopressin receptor antagonists. Initial development of AVP receptor antagonists during the 1970s focused on peptide analogues of AVP. In the late 1980s, it seemed likely that such agents would be successfully developed for use in humans. However, further development was halted because some of these agents manifested weak V_2R agonist properties in humans.[105] Several nonpeptide small-molecule AVP receptor antagonists were subsequently identified via functional screening strategies. The first successful use of a nonpeptide V_2R antagonist to produce aquaresis in humans was reported in 1993.[106]

Mechanism of action. Molecular modeling of binding sites indicates that the nonpeptide antagonists penetrate deeper into the transmembrane region of the V_2R than does native AVP, thereby preventing binding of native hormone without themselves interacting with the H1 helix site that is critical for V_2R-mediated G-protein activation.[107] Consequently, binding of the antagonists to V_2R blocks activation of the receptor by endogenous AVP. The increased urine output produced by the V_2R antagonists is quantitatively equivalent to diuretics such as furosemide, but qualitatively it is different in that only water excretion is produced without significant increases in urine solute excretion, including sodium and potassium.[106] Thus, AVP V_2R antagonists produce solute-sparing water excretion in contrast to classic diuretic agents that cause both water and electrolyte excretion by virtue of their effects to block distal tubular sodium transporters. For this reason, the renal effects produced by AVP V_2R antagonists have been termed aquaretic to distinguish them from the renal effects produced by diuretic agents, which include not only increased water excretion but also natriuresis and kaliuresis. 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.

Vasopressin antagonists in clinical development. Currently, there are 4 nonpeptide agents in various stages of clinical trials (**Table 3**).[108] Conivaptan is a combined $V_{1a}R$ and V_2R antagonist, whereas the others are selective V_2R antagonists. In December 2005, conivaptan was approved by the FDA for the treatment of euvolemic hyponatremia, and in February 2007 this indication was extended by the FDA to include hypervolemic hyponatremia. All agents of this class are inhibitors of the cytochrome P450 3A4 (CYP3A4) system, but conivaptan appears to be the most potent in this regard. Although the drug is orally active,[109] to minimize the possibility of drug interactions, the FDA has restricted its distribution to a parenteral form for short-term (4-day) in-hospital use only. The remaining V_2R antagonists appear to have more limited CYP3A4 interactions and are currently being developed for long-term oral use.[110]

Use of Vasopressin Receptor Antagonists in Hypovolemic Hyponatremia

To date, the use of AVPR antagonists in clinical trials has been limited to patients with euvolemic and hypervolemic hyponatremia, because induced aquaresis would aggravate the underlying volume depletion in hypovolemic hyponatremia. As greater clinical experience with these agents in acute hyponatremia is gained, selective V_2R antagonists may prove of limited use in thiazide-induced hyponatremia or EAH, as excess water ingestion may drive these disorders more than true sodium depletion. The available data do not permit any firm recommendations as yet, except that combined $V_{1a}R/V_2R$ receptor antagonists are contraindicated in severe hypovolemic hyponatremia, because blocking $V_{1a}R$

Table 3 Arginine vasopressin receptor antagonists currently in clinical development

	Conivaptan	Lixivaptan	Satavaptan	Tolvaptan
Compound	YM-087	VPA-985	SR-121463	OPC-41061
Receptor	V_{1a}/V_2	V_2	V_2	V_2
Route of administration	IV	Oral	Oral	Oral
Urine volume	↑	↑	↑	↑
Urine osmolality	↓	↓	↓	↓
Na^+ excretion/24 hr	↔	↔ At low dose ↑ At high dose	↔	↔
Company developing agent	Astellas Pharma US, Inc.	CardioKine	sanofi-aventis	Otsuka America Pharmaceutical, Inc.

↑ = increase; ↓ = decrease; ↔ = no change.
Adapted from *Am Heart J.*[108]

sites on vascular smooth muscle cells may cause or worsen the hypotension often associated with volume depletion.

Use of Vasopressin Receptor Antagonists in Euvolemic Hyponatremia

Based on the results of multiple clinical trials with 4 different AVPR antagonists, it is likely they will become a mainstay of treatment for euvolemic hyponatremia. One exception will likely be patients with euvolemic hyponatremia with NSIAD who have activating mutations of V_2R.[22] A recently described kindred bearing this mutation was identified as a result of failure to respond to V_2R antagonists with the expected aquaresis.[23] As detailed in several recent reviews,[110,111] these agents predictably cause an aquaresis leading to increased serum [Na^+] in the majority of patients with hyponatremia due to SIADH, CHF, and cirrhosis.

The optimum use of AVPR antagonists in any setting has not yet been determined, but some predictions can be made with reasonable certainty. For hyponatremia in hospitalized patients who are unable to take medication orally or for those in whom a more rapid correction of hyponatremia is desired, conivaptan will likely be the preferred agent. Phase 3 studies show that it reliably raises serum [Na^+] over the short term beginning as early as 1 to 2 hours after administration, and permits normalization of serum [Na^+] in most patients with hyponatremia over a 4-day course of treatment. Selective V_2R antagonists, such as lixivaptan, satavaptan, or tolvaptan, will likely prove useful in patients for whom oral therapy is suitable and for more chronic forms of hyponatremia.[112]

Despite the attractiveness of using a pure aquaretic agent to correct life-threatening hyponatremia, insufficient data are available from clinical trials to know if sufficiently rapid correction can be achieved without the use of hypertonic saline in patients with acute severe hyponatremia. Theoretically, both saline and an aquaretic agent could be used initially; the hypertonic saline could then be stopped after the serum [Na^+] increases by a few millimoles per liter, with the remainder of the first day's correction accomplished by the AVPR antagonist-induced aquaresis. The 2 agents may be complementary in that the hypertonic saline infusion would cause sufficient expansion to mitigate any volume depletion resulting from the aquaresis.

Most placebo-controlled studies using AVPR antagonists to treat hyponatremia have been of limited duration, generally ranging from 1 to 7 days. However, recent data from 30-day placebo-controlled clinical trials[112] as well as from longer-term open-label studies have indicated that these agents retain efficacy over prolonged periods of time and therefore will likely prove to be highly useful in patients with chronic hyponatremia due to SIADH, cirrhosis, and CHF. Although the effect of AVPR antagonists on plasma AVP levels is variable, it bears emphasis that they often increase thirst even in patients with hyponatremia and, unless restricted, water intake generally increases as well. As an example of this, in some clinical trials the serum [Na^+] increased only during the first day despite a persistently dilute urine.[113] Thus, use of AVPR antagonists will mitigate,[112] but in many cases not altogether eliminate, the need for fluid restriction.

Safety issues must also be considered carefully with any new class of drugs. The possibility of overcorrection has been of significant concern in all of the AVPR antagonist clinical trials, but to date osmotic demyelination has not been reported with any agent. Nonetheless, it is anticipated that the agents will need to be used judiciously if correction of the serum [Na^+] at a rate faster than 8 to 12 mmol/L per 24 hours is to be avoided,[114] as discussed below under "Rate of Correction Using Vasopressin Receptor Antagonists." Because of their <12-hour half-life, all of the agents will require daily or continuous dosing to maintain activity, so it will be possible to limit the increase in serum [Na^+] by stopping the drug or reducing the dosage. If necessary, hypotonic fluid can be infused to abrogate the increase in serum [Na^+] until the aquaresis abates. These safeguards should be sufficient to protect against overly rapid correction if serum [Na^+] levels are monitored frequently during the course of active treatment. A second major concern is the use of AVPR antagonists in cases of hypovolemic hyponatremia, where an aquaresis would aggravate underlying volume contraction and potentially cause hypotension. This can be avoided by careful attention to appropriate differen-

tial diagnosis among the different subtypes of hyponatremia. The potential for serious drug interactions via interference with CYP3A4-mediated metabolism of other drugs must also be recognized. This will likely not be of concern with short-term use of AVPR antagonists such as conivaptan, but may cause problems during long-term therapy, making appropriate monitoring necessary. Finally, whether there will be any adverse effect of V_2R inhibition in vascular endothelium is unknown. Bleeding complications have not been reported to date, but surveillance will be needed now that a combined $V_{1a}R/V_2R$ antagonist is in general use.

Use of Vasopressin Receptor Antagonists in Hypervolemic Hyponatremia

Although several factors may contribute to the development of hyponatremia in edematous states, excess secretion of AVP is by far the most important. A very small excess of AVP can lead to substantial water retention, limiting the excretion of maximally dilute urine and leading to a dilutional decrease in serum [Na^+] as a result of renal water retention. The most physiologic approach to hyponatremia in a volume-expanded setting therefore is to diminish AVP secretion or interfere with the effects of AVP at the renal V_2R. The only known direct suppressant of AVP secretion is ethanol, but its effects are transient. For obvious reasons, continuous or intermittent use of ethanol would also not represent a practical approach to chronic hyponatremia.

Antagonism of the V_2R therefore represents the best approach to treating hyponatremia in most edema-forming states, because excess AVP is the most important pathophysiologic factor involved.[115] Phase 2 and 3 studies are underway with several different compounds in acute and chronic CHF (ie, tolvaptan, lixivaptan, and conivaptan). Results to date suggest that all 3 compounds are highly effective in producing an acute solute-free water diuresis and raising the serum sodium concentration. Only tolvaptan has thus far been studied extensively in the setting of chronic CHF. Results from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial indicate that hyponatremia can be corrected chronically with this compound, and that this effect can be maintained for up to 60 days.[116]

More recently, the EVEREST trial reported long-term results of morbidity and mortality outcomes in patients treated with tolvaptan versus placebo. No effects on long-term mortality or CHF-related morbidity were observed in 4,133 patients randomized to tolvaptan or placebo, including a subgroup analysis of the patients with hyponatremia.[117] Consequently, based on this study, the long-standing association between adverse outcomes and hyponatremia in patients with CHF[46,47] does not appear to be due to adverse effects of the hyponatremia itself.

Although there appears to be no overall mortality benefit from the use of a vaptan in chronic CHF, nonetheless there may be other potential advantages that should be considered. Foremost among these is the possibility that these agents may have advantages over loop diuretics for ECF volume control even in the absence of hyponatremia, because they do not deplete electrolytes, stimulate neurohormonal secretion from activation of the RAAS, or contribute to renal toxicity, which represent significant limitations of chronic therapy with loop diuretics.[100,118] Reducing the use of traditional loop diuretics therefore could represent a beneficial effect of vaptans in chronic CHF. Based on the acute and chronic data with these compounds, the use of V_2R or combined $V_{1a}R/V_2R$ antagonists is likely to emerge as the preferred method of treating hyponatremia in CHF, assuming no issues with toxicity emerge with longer exposure in larger numbers of patients.[100]

Lastly, it should be noted that combined $V_{1a}R/V_2R$ antagonism does offer a theoretical additional benefit in CHF.[119] Whereas only limited information is currently available regarding the effect of $V_{1a}R$ antagonism in clinical HF, a considerable body of data suggests the effectiveness of this approach in experimental models. If systemic hemodynamic improvement occurs with $V_{1a}R$ antagonism, it is conceivable that renal hemodynamics could be improved as well, leading to greater clinical benefit and potentially a more robust effect on the establishment and maintenance of sodium and water homeostasis. Only comparative study of selective and nonselective agents would provide information on this issue, but because such agents are now available, it is possible to answer this question with appropriately designed clinical trials.

Many of the same general arguments apply to the potential use of AVP antagonists in cirrhosis, and several clinical trials have demonstrated efficacy of the oral V_2R-selective antagonists to improve serum [Na^+] in these patients.[110,111] However, whether this will result in benefit regarding clinically significant outcomes is not yet known. In contrast to CHF, where there is a theoretical advantage to using a combined $V_{1a}R/V_2R$ antagonist, this is not the case in cirrhosis, where such an agent might increase portal hypertension and its associated complications by blocking the vasoconstrictive effects of AVP in the splanchnic circulation.

At the low GFRs generally associated with acute and chronic renal failure, a significant effect of aquaretic agents would not be expected. Although V_2R antagonists would be expected to increase solute-free water excretion in patients with nephrosis and hyponatremia, there are no reported results using aquaretic agents in patients with nephrosis.

Rate of Correction Using Vasopressin Receptor Antagonists

There are no data to suggest that the methodology used to correct hyponatremia alters the susceptibility for producing osmotic demyelination with overly rapid correction. Consequently, patients with hyponatremia treated with AVPR antagonists will likely be at the same risk for this complication as those treated with hypertonic saline. To date,

neurologic adverse events consistent with demyelinative complications have not been reported in any of the V_2R or combined $V_{1a}R/V_2R$ clinical trials.[110] This is likely due to a combination of factors, including the following: (1) the induced increases in serum [Na^+] rarely exceeded accepted clinical guidelines for rapidity of correction of hyponatremia; (2) few patients with severe hyponatremia (serum [Na^+] <115 mmol/L) were enrolled in the clinical trials; and (3) the clinical trial protocols generally required stopping and/or decreasing dosing if the maximum allowed correction parameters were exceeded. Nonetheless, appropriate care in dosing and monitoring should allow successful adherence to the same guidelines for limited controlled correction that apply to other correction methods.

SUMMARY

Currently Approved Indications for Vasopressin Receptor Antagonists

Conivaptan is FDA-approved for use in patients with euvolemic and hypervolemic hyponatremia. Current dosing recommendations are for a 20-mg loading dose to be infused over 30 minutes, followed by a 20-mg/day continuous infusion for up to 4 days. If adequate correction of the serum [Na^+] is achieved in shorter periods of time, the infusion can be stopped at the physician's discretion; however, continued infusion may be necessary to continue aquaresis with lesser chance of recurrence of hyponatremia due to continued fluid ingestion or administration. If inadequate correction of the serum [Na^+] is achieved in the first 24 hours, conivaptan infusion can be increased to 40 mg/day. Conversely, if too rapid correction of the serum [Na^+] is produced (ie, >12 mmol/L in the first 24 hours or >18 mmol/L in the first 48 hours), the infusion should be stopped until the serum [Na^+] returns to desired levels and consideration should be given to administration of hypotonic fluids orally or intravenously as 5% dextrose in water (D_5W) to return the serum [Na^+] to desired levels, after which a lower infusion rate can be restarted if necessary to achieve the desired goal. Although it is recommended that other drugs metabolized by the CYP3A4 system be withheld during conivaptan administration, it is unlikely that clinically significant drug interactions could occur with any of these agents within a 4-day treatment period. There are no current guidelines regarding retreatment with conivaptan if hyponatremia recurs. In many inhospital cases this will not be necessary, as the hyponatremia will be transient (eg, postoperative, following pneumonia, or drug related). However, if necessary to retreat, it would be prudent to allow sufficient time for drug levels from the previous infusion to clear (ie, 4 to 5 days, given a drug half-life of 5 to 9 hours in humans) before restarting the infusion. Caution should be used in children, in whom effective and safe doses have not yet been established, and in those with serum creatinine levels >2.5 mg/dL.

Potential Future Indications for Vasopressin Receptor Antagonists

Symptomatic hyponatremia. Insufficient data are available from clinical trials to know whether sufficiently rapid correction can be achieved without the use of hypertonic saline in patients with acute severe hyponatremia, in large part because it would be unethical to include such patients in a placebo-controlled trial. Theoretically, both AVPR antagonists and hypertonic saline could be used initially and the hypertonic saline stopped after the serum [Na^+] increases sufficiently to improve clinical symptomatology, with the remainder of the correction accomplished via a water diuresis. However, formal recommendations for this indication must await the results of further clinical trials.

Long-term treatment of hyponatremia. Most studies to date in patients with hyponatremia have only been of relatively short duration. Thus, the most appropriate way to use these agents, their long-term response rates, how important the role of water restriction will remain during chronic use, and whether correction of chronic hyponatremia will result in improved cognitive function as suggested by 30-day studies of tolvaptan,[112] and quality of life, or functional status, as suggested by initial studies of gait stability and falls,[120] are unknown at the present time and will require additional study.

Need for Additional Studies

Many further studies will be needed to assess the appropriate use of AVPR antagonists in many different contexts, such as for correction of symptomatic hyponatremia either alone or in conjunction with hypertonic saline infusions; to assess the benefits of correction of hyponatremia in hospitalized patients in terms of disease outcomes and decreased lengths of intensive care unit and hospital stay; and for long-term treatment of minimally symptomatic hyponatremia in order to decrease the risks of neurocognitive dysfunction and gait instability. These as well as presently unrecognized uses must await the results from both large-scale outcome trials and focused small-scale studies with these agents.

Despite many yet unanswered questions about their optimal use, the new class of aquaretic AVPR antagonists will undoubtedly prove to be highly useful and promise to usher in a new era in the treatment of hyponatremia. The challenge for clinicians and physician scientists is to use these new agents intelligently and study them further in a manner that will eventually define their true place and value in the treatment of patients with hyponatremia.

AUTHOR DISCLOSURES

The authors who contributed to this article have disclosed the following industry relationships.

Joseph G. Verbalis, MD, has served as a consultant and member of advisory boards and Speakers' Bureau for As-

tellas Pharma US, Inc.; as a consultant and member of advisory boards for sanofi-aventis, and as a consultant to Otsuka.

Stephen R. Goldsmith, MD, has served as a consultant and member of advisory boards for Astellas Pharma US, Inc.

Arthur Greenberg, MD, has served as a member of advisory boards and Speakers' Bureau for Astellas Pharma US, Inc., and as a consultant to sanofi-aventis.

Robert W. Schrier, MD, has served as a consultant to Otsuka.

Richard H. Sterns, MD, has served as a member of advisory boards and Speakers' Bureau for Astellas Pharma US, Inc.

References

1. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med.* 2006;119(suppl 1):S30–S35.
2. Verbalis JG. The syndrome of inappropriate antidiuretic hormone secretion and other hypoosmolar disorders. In: Schrier RW, ed. *Diseases of the Kidney and Urinary Tract.* Philadelphia, Pa: Lippincott Williams & Wilkins; 2007:2214–2248.
3. Sterns RH, Silver SM. Brain volume regulation in response to hypoosmolality and its correction. *Am J Med.* 2006;119(suppl 1):S12–S16.
4. Schrier RW. Treatment of hyponatremia [review]. *N Engl J Med.* 1985;312:1121–1123.
5. Robertson GL. Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. *Am J Med.* 2006;119(suppl 1):S36–S42.
6. Schrier RW. Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. *Am J Med.* 2006;119(suppl 1):S47–S53.
7. Weisberg LS. Pseudohyponatremia: a reappraisal [review]. *Am J Med.* 1989;86:315–318.
8. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. *Am J Med.* 1999;106:399–403.
9. Schrier RW. Body water homeostasis: clinical disorders of urinary dilution and concentration. *J Am Soc Nephrol.* 2006;17:1820–1832.
10. Beck LH. Hypouricemia in the syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med.* 1979;301:528–530.
11. Schrier RW. Body fluid volume regulation in health and disease: a unifying hypothesis. *Ann Intern Med.* 1990;113:155–159.
12. Almond CS, Shin AY, Fortescue EB, et al. Hyponatremia among runners in the Boston Marathon. *N Engl J Med.* 2005;352:1550–1556.
13. Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients [review]. *Chest.* 1993;103:601–606.
14. Sharabi Y, Illan R, Kamari Y, et al. Diuretic induced hyponatraemia in elderly hypertensive women. *J Hum Hypertens.* 2002;16:631–635.
15. Chow KM, Szeto CC, Wong TY, Leung CB, Li PK. Risk factors for thiazide-induced hyponatraemia. *QJM.* 2003;96:911–917.
16. Friedman E, Shadel M, Halkin H, Farfel Z. Thiazide-induced hyponatremia. Reproducibility by single dose rechallenge and an analysis of pathogenesis. *Ann Intern Med.* 1989;110:24–30.
17. Damaraju SC, Rajshekhar V, Chandy MJ. Validation study of a central venous pressure-based protocol for the management of neurosurgical patients with hyponatremia and natriuresis. *Neurosurgery.* 1997;40:312–316; discussion: 316–317.
18. Palmer BF. Hyponatraemia in a neurosurgical patient: syndrome of inappropriate antidiuretic hormone secretion versus cerebral salt wasting. *Nephrol Dial Transplant.* 2000;15:262–268.
19. Maesaka JK, Gupta S, Fishbane S. Cerebral salt-wasting syndrome: does it exist? *Nephron.* 1999;82:100–109.
20. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med.* 1967;42:790–806.
21. Michelis MF, Fusco RD, Bragdon RW, Davis BB. Reset of osmoreceptors in association with normovolemic hyponatremia. *Am J Med Sci.* 1974;267:267–273.
22. Feldman BJ, Rosenthal SM, Vargas GA, et al. Nephrogenic syndrome of inappropriate antidiuresis. *N Engl J Med.* 2005;352:1884–1890.
23. Decaux G, Vandergheynst F, Bouko Y, Parma J, Vassart G, Vilain C. Nephrogenic syndrome of inappropriate antidiuresis in adults: high phenotypic variability in men and women from a large pedigree. *J Am Soc Nephrol.* 2007;18:606–612.
24. Zerbe R, Stropes L, Robertson G. Vasopressin function in the syndrome of inappropriate antidiuresis. *Annu Rev Med.* 1980;31:315–327.
25. Ikkos D, Luft R, Olivecrona H. Hypophysectomy in man: effect on water excretion during the first two postoperative months. *J Clin Endocrinol Metab.* 1955;15:553–567.
26. Diederich S, Franzen NF, Bahr V, Oelkers W. Severe hyponatremia due to hypopituitarism with adrenal insufficiency: report on 28 cases. *Eur J Endocrinol.* 2003;148:609–617.
27. Oelkers W. Hyponatremia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. *N Engl J Med.* 1989;321:492–496.
28. Ishikawa S, Schrier RW. Effect of arginine vasopressin antagonist on renal water excretion in glucocorticoid and mineralocorticoid deficient rats. *Kidney Int.* 1982;22:587–593.
29. Hanna FW, Scanlon MF. Hyponatraemia, hypothyroidism, and role of arginine-vasopressin. *Lancet.* 1997;350:755–756.
30. Chinitz A, Turner FL. The association of primary hypothyroidism and inappropriate secretion of the antidiuretic hormone. *Arch Intern Med.* 1965;116:871–874.
31. Derubertis FR Jr, Michelis MF, Bloom ME, Mintz DH, Field JB, Davis BB. Impaired water excretion in myxedema. *Am J Med.* 1971;51:41–53.
32. Chen Y-C, Cadnapaphornchai MA, Yang J, et al. Nonosmotic release of vasopressin and renal aquaporins in impaired urinary dilution in hypothyroidism. *Am J Physiol Renal Physiol.* 2005;289:F672–F678.
33. Irving RA, Noakes TD, Buck R, et al. Evaluation of renal function and fluid homeostasis during recovery from exercise-induced hyponatremia. *J Appl Physiol.* 1991;70:342–348.
34. Speedy DB, Noakes TD, Rogers IR, et al. Hyponatremia in ultradistance triathletes. *Med Sci Sports Exerc.* 1999;31:809–815.
35. Noakes T. Fluid replacement during marathon running. *Clin J Sport Med.* 2003;13:309–318.
36. Hew-Butler T, Almond C, Ayus JC, et al. Consensus statement of the 1st International Exercise-Associated Hyponatremia Consensus Development Conference, Cape Town, South Africa 2005. *Clin J Sport Med.* 2005;15:208–213.
37. Demanet JC, Bonnyns M, Bleiberg H, Stevens-Rocmans C. Coma due to water intoxication in beer drinkers. *Lancet.* 1971;2:1115–1117.
38. Thaler SM, Teitelbaum I, Berl T. "Beer potomania" in non-beer drinkers: effect of low dietary solute intake. *Am J Kidney Dis.* 1998;31:1028–1031.
39. Barlow ED, DeWardener HE. Compulsive water drinking. *Q J Med.* 1959;28:235–258.
40. Vieweg WV, Robertson GL, Godleski LS, Yank GR. Diurnal variation in water homeostasis among schizophrenic patients subject to water intoxication. *Schizophr Res.* 1988;1:351–357.
41. de Leon J, Verghese C, Tracy JI, Josiassen RC, Simpson GM. Polydipsia and water intoxication in psychiatric patients: a review of the epidemiological literature. *Biol Psychiatry.* 1994;35:408–419.
42. Stuart CA, Neelon FA, Lebovitz HE. Disordered control of thirst in hypothalamic-pituitary sarcoidosis. *N Eng J Med.* 1980;303:1078–1082.
43. Noakes TD, Wilson G, Gray DA, Lambert MI, Dennis SL. Peak rates of diuresis in healthy humans during oral fluid overload. *S Afr Med J.* 2001;91:852–857.

44. Cheng JC, Zikos D, Skopicki HA, Peterson DR, Fisher KA. Long-term neurologic outcome in psychogenic water drinkers with severe symptomatic hyponatremia: the effect of rapid correction. *Am J Med.* 1990;88:561–566.
45. Goldman MB, Luchins DJ, Robertson GL. Mechanisms of altered water metabolism in psychotic patients with polydipsia and hyponatremia. *N Engl J Med.* 1988;318:397–403.
46. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. *Circulation.* 1986;73:257–267.
47. Lee DS, Austin PC, Rouleau JL, Liu PP, Haimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA.* 2003;290:2581–2587.
48. Zucker IH, Share L, Gilmore JP. Renal effects of left atrial distension in dogs with chronic congestive heart failure. *Am J Physiol.* 1979; 236:H554–H560.
49. Zucker IH, Gorman AJ, Cornish KG, Lang M. Impaired atrial receptor modulation or renal nerve activity in dogs with chronic volume overload. *Cardiovasc Res.* 1985;19:411–418.
50. Abraham WT, Lowes BD, Ferguson DA, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. *J Card Fail.* 1998;4:37–44.
51. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med.* 1999;341:577–585.
52. Berl T, Henrich WL, Erickson AL, Schrier RW. Prostaglandins in the beta-adrenergic and baroreceptor-mediated secretion of renin. *Am J Physiol.* 1979;236:F472–F477.
53. Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (1) [review]. *N Engl J Med.* 1988;319:1065–1072 [published correction appears in *N Engl J Med.* 1989;320:676].
54. Schrier RW. Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy (2) [review]. *N Engl J Med.* 1988;319:1127–1134 [published correction appears in *N Engl J Med.* 1989;320:676].
55. Myers BD, Deen WM, Brenner BM. Effects of norepinephrine and angiotensin II on the determinants of glomerular ultrafiltration and proximal tubule fluid reabsorption in the rat. *Circ Res.* 1975;37:101–110.
56. Ruf AE, Kremers WK, Chavez LL, Descalzi VI, Podesta LG, Villamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. *Liver Transpl.* 2005; 11:336–343.
57. Porcel A, Diaz F, Rendon P, Macías M, Martín-Herrara L, Girón-González JA. Dilutional hyponatremia in patients with cirrhosis and ascites. *Arch Intern Med.* 2002;162:323–328.
58. Schrier RW, Niederberger M, Weigert A, Gines P. Peripheral arterial vasodilatation: determinant of functional spectrum of cirrhosis [review]. *Semin Liver Dis.* 1994;14:14–22.
59. Martin PY, Gines P, Schrier RW. Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. *N Engl J Med.* 1998;339:533–541.
60. Gerbes AL, Gulberg V, Gines P, et al. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist. A randomized double-blind multicenter trial. *Gastroenterology.* 2003;124:933–939.
61. McManus ML, Churchwell KB, Strange K. Regulation of cell volume in health and disease. *N Engl J Med.* 1995;333:1260–1266.
62. Pasantes-Morales H, Lezama RA, Ramos-Mandujano G, Tuz KL. Mechanisms of cell volume regulation in hypo-osmolality. *Am J Med.* 2006;119(suppl 1):S4–S11.
63. Sjoblom E, Hojer J, Ludwigs U, Pirskanen R. Fatal hyponatraemic brain oedema due to common gastroenteritis with accidental water intoxication. *Intensive Care Med.* 1997;23:348–350.
64. Sterns RH. Severe symptomatic hyponatremia: treatment and outcome. A study of 64 cases. *Ann Intern Med.* 1987;107:656–664.
65. Helwig FC, Schutz CB, Kuhn HP. Water intoxication: moribund patient cured by administration of hypertonic salt solution. *JAMA.* 1938;110:644–645.
66. Battison C, Andrews PJ, Graham C, Petty T. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. *Crit Care Med.* 2005;33:196–202.
67. Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. *N Eng J Med.* 1986; 314:1535–1542.
68. Sterns RH, Cappuccio JD, Silver SM, Cohen EP. Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. *J Am Soc Nephrol.* 1994;4:1522–1530.
69. Brunner JE, Redmond JM, Haggar AM, Elias SB. Central pontine myelinolysis and pontine lesions after rapid correction of hyponatremia: a prospective magnetic resonance imaging study. *Ann Neurol.* 1990;27:61–66.
70. Lien YH. Role of organic osmolytes in myelinolysis: a topographic study in rats after rapid correction of hyponatremia. *J Clin Invest.* 1995;95:1579–1586.
71. Soupart A, Silver S, Schrooeder B, Sterns R, DeCaux G. Rapid (24-hour) reaccumulation of brain organic osmolytes (particularly myo-inositol) in azotemic rats after correction of chronic hyponatremia. *J Am Soc Nephrol.* 2002;13:1433–1441.
72. Ellis SJ. Severe hyponatraemia: complications and treatment. *QJM.* 1995;88:905–909.
73. Tanneau RS, Henry A, Rouhart F, et al. High incidence of neurologic complications following rapid correction of severe hyponatremia in polydipsic patients. *J Clin Psychiatry.* 1994;55:349–354.
74. Cluitmans FH, Meinders AE. Management of severe hyponatremia: rapid or slow correction [review]? [See comments.] *Am J Med.* 1990;88:161–166.
75. Karp BI, Laureno R. Pontine and extrapontine myelinolysis: a neurologic disorder following rapid correction of hyponatremia. *Medicine.* 1993;72:359–373.
76. Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage: a prospective study. *N Engl J Med.* 1987;317:1190–1195.
77. Nzerue CM, Baffoe-Bonnie H, You W, Falana B, Dai S. Predictors of outcome in hospitalized patients with severe hyponatremia. *J Natl Med Assoc.* 2003;95:335–343.
78. Ayus JC, Arieff AI. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. [See comments.] *JAMA.* 1999;281:2299–2304.
79. Verbalis JG. Hyponatremia: endocrinologic causes and consequences of therapy. *Trends Endocrinol Metab.* 1992;3:1–7.
80. Lin SH, Chau T, Wu CC, Yang SS. Osmotic demyelination syndrome after correction of chronic hyponatremia with normal saline. *Am J Med Sci.* 2002;323:259–262.
81. Ashraf N, Locksley R, Arieff AI. Thiazide-induced hyponatremia associated with death or neurologic damage in outpatients. *Am J Med.* 1981;70:1163–1168.
82. Ayus JC, Krothapalli RK, Arieff AI. Changing concepts in treatment of severe symptomatic hyponatremia: rapid correction and possible relation to central pontine myelinolysis. *Am J Med.* 1985;78:897–902.
83. Robertson GL. Posterior pituitary. In: Felig P, Baxter J, Broadus A, Frohman L, eds. *Endocrinology and Metabolism*. New York, NY: McGraw-Hill; 1986:338–385.
84. List AF, Hainsworth JD, Davis BW, Hande KR, Greco FA, Johnson DH. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in small-cell lung cancer. *J Clin Oncol.* 1986;4:1191–1198.
85. Cherrill DA, Stote RM, Birge JR, Singer I. Demeclocycline treatment in the syndrome of inappropriate antidiuretic hormone secretion. *Ann Intern Med.* 1975;83:654–656.
86. Dousa TP, Wilson DM. Effect of demethylchlorotetracycline on cellular action of antidiuretic hormone in vitro. *Kidney Int.* 1974;5: 279–284.

87. Miller PD, Linas SL, Schrier RW. Plasma demeclocycline levels and nephrotoxicity: correlation in hyponatremic cirrhotic patients. *JAMA.* 1980;243:2513–2515.
88. Forrest JN Jr, Cox M, Hong C, Morrison G, Bia M, Singer I. Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med.* 1978;298:173–177.
89. Decaux G, Mols P, Cauchi P, Delwiche F. Use of urea for treatment of water retention in hyponatraemic cirrhosis with ascites resistant to diuretics. *BMJ.* 1985;290:1782–1783.
90. Robertson GL, Aycinena P, Zerbe RL. Neurogenic disorders of osmoregulation. *Am J Med.* 1982;72:339–353.
91. Bosch-Marce M, Poo JL, Jimenez W, et al. Comparison of two aquaretic drugs (niravoline and OPC-31260) in cirrhotic rats with ascites and water retention. *J Pharmacol Exp Ther.* 1999;289:194–201.
92. Gadano A, Moreau R, Pessione F, et al. Aquaretic effects of niravoline, a kappa-opioid agonist, in patients with cirrhosis. *J Hepatol.* 2000;32:38–42.
93. Huang EA, Feldman BJ, Schwartz ID, Geller DH, Rosenthal SM, Gitelman SE. Oral urea for the treatment of chronic syndrome of inappropriate antidiuresis in children. *J Pediatr.* 2006;148:128–131.
94. Ayus JC, Varon J, Arieff AI. Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. *Ann Intern Med.* 2000;132:711–714.
95. Davis TM, Singh B, Sheridan G. Parasitic procrastination: late-presenting ovale malaria and schistosomiasis. *Med J Aust.* 2001;175: 146–148.
96. Robertson GL. Abnormalities of thirst regulation. *Kidney Int.* 1984; 25:460–469.
97. Canuso CM, Goldman MB. Clozapine restores water balance in schizophrenic patients with polydipsia-hyponatremia syndrome. *J Neuropsychiatry Clin Neurosci.* 1999;11:86–90.
98. Kawai N, Baba A, Suzuki T. Risperidone failed to improve polydipsia-hyponatremia of the schizophrenic patients. *Psychiatry Clin Neurosci.* 2002;56:107–110.
99. Decaux G. Is asymptomatic hyponatremia really asymptomatic? *Am J Med.* 2006;119(suppl 1):S79–S82.
100. Goldsmith SR, Gheorghiade M. Vasopressin antagonism in heart failure. *J Am Coll Cardiol.* 2005;46:1785–1791.
101. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J.* 2003;145: 459–466.
102. Choudhury J, Sanyal AJ. Treatment of ascites. *Curr Treat Options Gastroenterol.* 2003;6:481–491.
103. Thibonnier M, Conarty DM, Preston JA, Wilkins PL, Berti-Mattera LN, Mattera R. Molecular pharmacology of human vasopressin receptors. *Adv Exp Med Biol.* 1998;449:251–276.
104. Knepper MA. Molecular physiology of urinary concentrating mechanism: regulation of aquaporin water channels by vasopressin. *Am J Physiol.* 1997;272(pt 2):F3–F12.
105. Kinter LB, Ileson BE, Caltabinol S, et al. Antidiuretic hormone antagonism in humans: are there predictors? In: Jard S, Jamison R, eds. *Vasopressin.* Paris: John Libbey Eurotext; 1991:321–329.
106. Ohnishi A, Orita Y, Okahara R, et al. Potent aquaretic agent: a novel nonpeptide selective vasopressin 2 antagonist (OPC-31260) in men. *J Clin Invest.* 1993;92:2653–2659.
107. Macion-Dazard R, Callahan N, Xu Z, Wu N, Thibonnier M, Shoham M. Mapping the binding site of six nonpeptide antagonists to the human V_2-renal vasopressin receptor. *J Pharmacol Exp Ther.* 2006; 316:564–571.
108. Lee CR, Watkins ML, Patterson JH, et al. Vasopressin: a new target for the treatment of heart failure. *Am Heart J.* 2003;146:9–18.
109. Ghali JK, Koren MJ, Taylor JR, et al. Efficacy and safety of oral conivaptan: a V_{1A}/V_2 vasopressin receptor antagonist, assessed in a randomized, placebo-controlled trial in patients with euvolemic or hypervolemic hyponatremia. *J Clin Endocrinol Metab.* 2006;91:2145–2152.
110. Greenberg A, Verbalis JG. Vasopressin receptor antagonists. *Kidney Int.* 2006;69:2124–2130.
111. Palm C, Pistrosch F, Herbrig K, Gross P. Vasopressin antagonists as aquaretic agents for the treatment of hyponatremia. *Am J Med.* 2006; 119(suppl 1):S87–S92.
112. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V_2-receptor antagonist, for hyponatremia. *N Engl J Med.* 2006;355:2099–2112.
113. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V_2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation.* 2003;107:2690–2696.
114. Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med.* 2000;342: 1581–1589.
115. Goldsmith SR. Vasopressin receptor antagonists: mechanisms of action and potential effects in heart failure. *Cleve Clin J Med.* 2006; 73(suppl 2):S20–S23.
116. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA.* 2004; 291:1963–1971.
117. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA.* 2007;297:1319–1331.
118. Singh A, Blackwell J, Neher J. Clinical inquiries: does furosemide decrease morbidity or mortality for patients with diastolic or systolic dysfunction? *J Fam Pract.* 2005;54:370–372.
119. Goldsmith SR. Is there a cardiovascular rationale for the use of combined vasopressin V_{1a}/V_2 receptor antagonists? *Am J Med.* 2006; 119(suppl 1):S93–S96.
120. Renneboog B, Musch W, Vandemergel X, Manto MU, DeCaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med.* 2006;119:71.e1–e8.