Hyponatremia, the most common electrolyte disorder encountered, is associated with increased morbidity and mortality even in its milder forms. Despite novel pathophysiologic insights, diagnostic approaches, and management options, hyponatremia remains a challenge for clinicians. In a recent article copublished in the *European Journal of Endocrinology*, *Intensive Care Medicine*, and *Nephrology Dialysis and Transplantation*, Spasovski et al reported a clinical practice guideline on the diagnosis and treatment of hyponatremia that aims to assist clinicians in everyday practice. Revisiting hyponatremia was considered necessary to incorporate evidence-based approaches to patient care and provide reliable evaluation of key clinical decisions. The guideline was developed jointly by the European Society of Intensive Care Medicine, the European Society of Endocrinology, and the European Renal Association–European Dialysis and Transplant Association, represented by the European Renal Best Practice. Established databases were searched for evidence and searches were updated on December 10, 2012.

**WHAT DOES THIS IMPORTANT GUIDELINE RECOMMEND?**

The guideline covers hypotonic hyponatremia in adults. A threshold of 48 hours is used to distinguish acute from chronic hyponatremia. The initial diagnostic step is establishing that the hyponatremia is hypotonic and whether acute or severe symptoms are present; in that case, the clinician should consider immediate treatment with hypertonic saline solution. In the absence of such symptoms, the algorithm advises measuring urine osmolality but rejects clinical assessment of extracellular fluid volume at this early step, fearing misclassification of hyponatremia. Urine osmolality ≤ 100 mOsm/kg indicates excessive water intake. Urine osmolality > 100 mOsm/kg triggers measurement of urine sodium. Urine sodium concentration ≤ 30 versus >30 mEq/L in conjunction with the now allowed clinical assessment of extracellular fluid volume is used to define diagnostic categories and underlying causes.

Management of hyponatremia starts by establishing whether severe symptoms are present. Regardless of pathogenesis or duration, first-hour management of severely symptomatic hyponatremia includes a rapid intravenous infusion of 150 mL of 3% sodium chloride solution that can be repeated twice if symptoms do not improve. Additional hypertonic saline solution is administered, aiming at increasing serum sodium concentration by 1 mEq/L per hour using the Adrogue–Madias formula if symptoms fail to improve after correcting serum sodium concentration by 5 mEq/L in the first hour. Patients with moderately severe symptoms are treated with a single rapid infusion of 150 mL of 3% sodium chloride solution followed by cause-specific treatment. In hyponatremia with severe or moderately severe symptoms, correction of serum sodium concentration should be limited to 10 mEq/L in the first 24 hours and 8 mEq/L per subsequent day.

For patients with chronic hyponatremia without severe or moderately severe symptoms, moderate hyponatremia is treated with vaptans or demeclocycline. First-line treatment of the syndrome of inappropriate antidiuresis (SIAD [the preferred current term instead of the previous term, syndrome of inappropriate secretion of antidiuretic hormone, SIADH]) is fluid restriction followed by increasing solute intake (urea or sodium chloride and low-dose loop diuretics). Vaptans are not recommended in SIAD with moderate hyponatremia, and the recommendation is against their use in profound hyponatremia.

Strengths of the report include the multidisciplinary expertise of the development group, an elaborate
process for rating the quality of the evidence and formulating and grading recommendations, submission to internal and external review, and posing questions for future research. The report also has several limitations. As the authors acknowledge, there is a scarcity of rigorous studies on various aspects of hyponatremia. Therefore, the report constitutes expert recommendations rather than a guideline. The presentation of some concepts is confusing. For example, causes of nonhypotonic hyponatremia should not include hyponatremia in the presence of “ineffective” osmole (eg, increased urea), a true hypotonic hyponatremia. The formulas for calculating effective osmolality should not include serum potassium concentration because doubling the serum sodium concentration overestimates the osmotic force created by sodium salts, thus compensating for the osmotic contribution of other serum electrolytes. Measuring the serum concentration of additional osmole should not include lactate, an anion for which osmotic contribution is accounted for by doubling the serum sodium concentration.

**HOW DOES THIS GUIDELINE COMPARE WITH PRIOR GUIDELINES?**

Owing to the paucity of hard evidence, expert recommendations on hyponatremia largely reflect synthesis of physiologic and pathophysiologic principles, results of animal studies, and clinical experience. Therefore, it is not surprising that recommendations differ among experts.

Measuring urine osmolality as the first diagnostic step of hyponatremia is not a recommendation shared by other experts. Although urine osmolality is a useful ancillary test, it is not essential for the initial diagnostic evaluation; it is unavailable in many health centers.

Most experts initiate the evaluation of hyponatremia with a careful history and physical examination, assessment of extracellular fluid volume, and measurement of urine electrolytes. We very much doubt that this approach leads to misclassification of hyponatremia. In some ambiguous cases, a limited infusion of isotonic saline solution can differentiate between mild hypovolemia and euvoledemia. We consider it unreasonable to recommend deferring evaluation of the extracellular fluid volume until urine osmolality and urine sodium concentration are first assessed.

The guideline recommends identical management of patients with impaired aquareis and those with excessive water intake. Even profound hyponatremia secondary to polydipsia usually lends itself to rapid autocorrection without requiring infusion of hypertonic saline solution.

Contrary to other guidance, the report prescribes hypertonic saline solution to patients with less than severe symptoms. Furthermore, the recommended amount of hypertonic saline solution in severely symptomatic hyponatremia (up to 450 mL in the first hour) is much larger than what other experts advise and can cause overcorrection of hyponatremia in small individuals, especially if aquareis is ongoing. It is puzzling that fixed amounts of 3% sodium chloride solution are administered initially, but additional quantities are prescribed using the Adrogue-Madias formula.

The guideline misrepresents the predictive utility of the Adrogue-Madias formula by judging its performance in a cohort that included many patients undergoing aquareis. The infusate formula was not designed to anticipate the impact of ongoing fluid losses on serum sodium concentration; its predictive accuracy has been validated in patients free of aquareis. The recommendation of limiting correction of serum sodium concentration to 10 mEq/L during the first 24 hours in hyponatremia with severe or moderately severe symptoms and particularly in chronic hyponatremia without severe or moderately severe sympotms is much larger than that recommended by other experts and risks the development of osmotic demyelination. This risk is magnified because correction of hyponatremia frequently overshoots the intended mark. Additionally, the report does not recommend a smaller daily correction for patients with predisposing factors for osmotic demyelination, as other guidance does.

The guideline ignores the utility of computing the urine to serum electrolyte ratio (ie, the sum of urine sodium concentration and urine potassium concentration divided by serum sodium concentration) in diagnosing and treating hyponatremia. Determining this ratio at baseline and in the course of treatment can provide important information to clinicians about the impact of the urine output on the level of serum sodium.

The effect of potassium replacement on the correction of hyponatremia is largely ignored. Considering that 1 mEq of retained potassium increases serum sodium concentration by as much as 1 mEq of retained sodium, even partial correction of potassium depletion can cause an excessive increase in serum sodium concentration without sodium administration.

The guideline recommends against the use of vaptans in patients with expanded extracellular fluid volume and does not recommend their use in patients with SIAD. Other experts recommend vaptans for managing oligosymptomatic/moderately symptomatic hyponatremia associated with SIAD or heart failure. These agents decrease the stringency of fluid restriction, can shorten hospital stay, and enable other therapeutic interventions (eg, initiation of chemotherapy, parenteral nutrition, and administration of drugs associated with SIAD). Because the
aqueletic response to these drugs is variable, close attention to the trend of serum sodium concentration is required. Vaptans should not be used in patients with hyponatremic emergencies, volume depletion, or underlying liver disease.

**WHAT SHOULD CLINICIANS AND RESEARCHERS DO?**

Meeting the challenge of hyponatremia requires a simple but reliable diagnostic approach coupled with effective and safe therapy. Figure 1 summarizes such an approach that in our view satisfies clinicians’ needs. Determining the pathogenesis of hyponatremia is critical because rapid autocorrection is expected if excessive water intake is involved. Assessing the state of the body stores of sodium, potassium, and water—the determinants of serum sodium concentration—is essential to sound diagnosis. Urgent management aimed at increasing serum sodium concentration by 4-6 mEq/L within a few hours is necessary for hyponatremic encephalopathy and hyponatremia associated with neurologic or neurosurgical disease. Selection of specific therapies for nonurgent management depends on underlying cause(s), clinical presentation, and the state of the determinants of serum sodium concentration. Correction of serum sodium concentration should not exceed 6-8 mEq/L in any 24-hour period regardless of duration of hyponatremia, clinical presentation, and method of treatment. Although the likelihood of demyelination caused by overcorrection of acute hyponatremia is low, no clinical advantage is derived from exceeding this cutoff. Moreover, an acute decrease in serum sodium concentration often is superimposed on chronic hyponatremia. The specific prescription must be based on a quantitative approach to management, thus preventing overcorrection of hyponatremia and the development of osmotic demyelination.

The report by Spasovski et al4-6 points to a number of interesting research questions. Exploring whether correction of hyponatremia favorably affects the morbidity and mortality associated with the disorder (other than its neurologic complications) is a most important topic. The availability of vaptans enables investigation of this and many other research questions.

**Figure 1.** Diagnostic and therapeutic approach to hyponatremia. Abbreviations: H2O, water; K+, potassium; Na+, sodium; SIAD, syndrome of inappropriate antidiuresis.
ACKNOWLEDGEMENTS

Support: None.

Financial Disclosure: Dr Adrogué has served on an advisory board for Astellas Pharma and Otsuka America Pharmaceutical. Dr Madias has served as a consultant to Astellas Pharma and Otsuka America Pharmaceutical.

REFERENCES