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Panel Recommendations on Hyponatremia

To the Editor:

The American Journal of Medicine Supplement on hyponatremia[1] raises several issues:

- More than 90% of hyponatremia is between 128 and 134 mmol/L. The article does not state clearly when, why, and how such hyponatremia should be treated—or why not;
- In "Clinical Significance of Hyponatremia," the article quotes the association of hyponatremia with increased mortality. The meaning of this association is not commented on sufficiently and fully on page S7. Non-specialists in hyponatremia may be misled by the article into assuming that the association represented a proven cause-and-effect relationship;
- In "Economic Burden of Hyponatremia," the article quotes a reduced length of stay in the hospital in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST). However, the latter was a study of cardiac failure using tolvaptan. It did not have hyponatremia as an inclusion criterion nor as an end point; only a small minority of the study patients did have hyponatremia. Hence, any changes in length of stay in the EVEREST trial are most likely related to aspects other than correction of hyponatremia;
- In "Role of vasopressin …" the article states: "… persistent [arginine vasopressin] (AVP) release … is predominantly responsible for … hyponatremia …" This is a 50% incomplete explanation. The persistence of thirst and drinking fluid (or of having fluid input occur) is equally predominant. If hyponatremic patients discontinued drinking fluid, hyponatremia would disappear fully — no matter what the AVP release would be;
- In "Classification … of … hyponatremia," the 3 categories are mostly treated as if hyponatremia almost always occurred as pure textbook cases falling into a single category. However, clinical experience shows many or most hyponatremias are mixed. For example, the hyponatremic patient with syndrome of inappropriate antidiuretic hormone secretion (SIADH) from small-cell lung cancer may have had episodes of vomiting, resulting in an element of hypovolemia. How is the clinician to decide which category is the leading one? How does one go about treating such mixed hyponatremia?
- On page S29, the article fails to mention that currently available tablets of tolvaptan (15, 30 mg) provide too large a dose for initial treatment of SIADH in many or most cases. This has been mentioned in the literature. All colleagues I know of work with a reduced dose in the initial treatment of SIADH. There has been a warning letter by the manufacturer in cooperation with the European Medicines Agency basically addressing this. The manufacturer is in the process of developing a smaller tablet.
- On page 6 the article states, "… the … rationale for … (these) recommendations is the need for understanding the consequences of not … treating hyponatremia …" This should be clarified. It is not plausible that "recommendations" could replace placebo-controlled prospective studies.

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Reference

1. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med*. 2013;126(10 Suppl 1):S1-S42.