

They point out 2 recent studies casting doubt on the long-held concept that rapidly correcting hyponatremia may contribute to the development of osmotic demyelination syndrome (ODS).^{2,3} These papers also suggested that a conservative rate of correction increases intensive care unit length of stay and may even increase mortality. As such, Drs. Katyal and Joshi pose an excellent question of whether the goals of hyponatremia correction should be liberalized in the first 24 hours. We sincerely appreciate their comments and discuss below why such a generalized conclusion should not be inferred based on these studies.

MacMillan et al² conducted a multicenter retrospective study in Toronto examining the association of hyponatremia with ODS. While the inclusion of 22,858 admissions with 17,254 unique patients is certainly laudable, about 87% of the cohort had a plasma sodium level of 120 mmol/L or greater and therefore had a negligible risk of ODS.⁴ In fact, only 265 patients had a plasma sodium below 110 mmol/L, which would confer a real risk of ODS. The authors reported a 0.05% total incidence of ODS, a reflection of the overall low risk of the entire cohort. However, of the patients with a plasma sodium below 110 mmol/L, 2.6% of them developed ODS,² an incidence 52-fold higher than the entire cohort's and more in line with other studies.

Patients with blood glucose levels up to 450 mg/dL were included.² When examining translocational hyponatremia (hyperglycemia-mediated hyponatremia), a correction factor of 1.6 is commonly employed. However, a sodium decrease of 2.4 mmol/L for every 100 mg/dL increase in glucose concentration is more accurate, especially at higher glucose concentrations.^{5,6} For example, a patient with a measured plasma sodium level of 109 mmol/L and a blood glucose level of 300 mg/dL corrects to a plasma sodium of about 114 mmol/L. MacMillan et al² did not account for this, which likely inflated the cohort of patients with a true plasma sodium of less than 110 mmol/L, further decreasing the number of patients truly at risk for ODS. In addition, hyperglycemia treatment would increase the sodium levels independently, thus potentially inflating the reported "overcorrection" rates.

The adjudication of ODS in the MacMillan study² also has been called into question. The diagnosis was solely based on neuroimaging, but only 64% of patients underwent imaging. Symptoms of ODS vary, and milder manifestations may not have warranted neuroimaging; as such, these milder cases may be missed. Furthermore, when examining overcorrection (defined by the authors as an increase in sodium

In Reply: We appreciate the letter from Drs. Katyal and Joshi regarding our Symptoms to Diagnosis article.¹

levels > 8 mmol/L in a 24-hour period), the authors fail to mention whether they adjudicated for sodium relowering. Sodium relowering after an overcorrection has been shown to reverse ODS in animal models,⁷ and, more importantly, MacMillan et al^{8,9} did not find harm or adverse events associated with addressing sodium overcorrection by relowering. Of note, patients with an identified overcorrection appropriately underwent more corrective rescue strategies (desmopressin and free water utilization) to relower sodium levels, further mitigating their ODS risk.

Katyal and Joshi note that 7 out of 12 patients with identified ODS did not undergo rapid sodium correction. However, most of these patients overcorrected all the way to hypernatremia within 2 to 11 days after admission. The reported serum sodium level in this patient subset ranged from 153 to 164 mmol/L over 7 to 11 days. This is highly unusual but highlights the role of changes in sodium levels in ODS pathophysiology.

Given the above limitations, the applicability of these results to the population of interest (patients at legitimate risk of ODS) is severely limited. To illustrate this, we note a nationwide study from Sweden examining the incidence of ODS in which 75% of identified ODS cases had a serum sodium of 110 mmol/L or less, with a median sodium of 104 mmol/L.¹⁰ About 90% of patients with identified ODS had a sodium correction exceeding 8 mmol/L in 24 hours.¹⁰

The second cited paper, Seethapathy et al,³ suggests that a slow correction of hyponatremia leads to increased mortality. The authors indeed found improved outcomes when sodium correction rates exceeded 10 mmol/L daily compared with rates less than 6 mmol/L daily. However, the population's baseline characteristics (Table 1 of Seethapathy et al³) reveal an interesting pattern. The cohort with sodium correction rates less than 6 mmol/L per 24 hours had a significantly higher prevalence of cirrhosis, congestive heart failure, malignancy, and metastatic cancer. It is well known that hyponatremia is an indicator of disease severity predicting adverse outcomes in cirrhosis,¹¹ heart failure,¹² and malignancy.¹³ Therefore, it is highly plausible that the higher mortality observed corresponds to the underlying disease process, as opposed to the rate of correction.

The rarity of ODS is repeatedly cited as a reason to forego conservative correction goals. While ODS

is rare overall, it can be catastrophic. ODS manifestations can be as severe as locked-in syndrome, with prolonged symptoms lasting a year before independence in activities of daily living is regained.¹⁴ In this context, we pose the question: Does rarity negate significance? In the words of Dr. Richard Sterns, "We do not treat acutely hyponatremic patients aggressively because they WILL die of cerebral edema but because they CAN die from it. We should apply the same standard to our efforts to avoid osmotic demyelination in patients with chronic hyponatremia," specifically in those at highest risk.¹⁵ Conservative correction rates will inherently require more time, which may include longer intensive care unit lengths of stay. However, until this approach is conclusively identified as a driver of mortality and morbidity, it should remain the standard of care for patients at high risk of ODS.

We realize that ODS in the setting of hyponatremia remains poorly understood and is likely a multifactorial phenomenon encompassing more than just nadir sodium levels or correction rates. We and other authors cite many of these contributing risk factors, reinforced by the findings of both cited cohorts. Conceivably, not every hyponatremic patient requires strict correction goals, but the 2 cited studies do not warrant abandoning our long-held strategy for patients considered at high risk for ODS.

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