Measuring and interpreting ammonia levels in cirrhosis

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Conflict of Interest:

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Dear Editor

We read with great interest the recent red section published by Deutsch-Link et al. in the *American Journal of Gastroenterology* (1). In their manuscript, the authors raised the "good", "bad" and "ugly" of ammonia testing in clinical practice. We would like to add that the pendulum has swung in the direction of the importance of hyperammonemia in the management of cirrhosis. Therefore, we would like to enhance the "good" and contend the "bad and ugly".

Enhancing the "good"
We and others have demonstrated that hyperammonaemia is an independent risk factor for hospitalization with not only HE but all liver-related complications as well as mortality in outpatients with cirrhosis (2-3). In addition, the prognostic value of ammonia was independent of established prognostic indicators including hepatic dysfunction, systemic inflammation and severity of portal hypertension, suggesting direct toxicity (4).

Contending the "bad and ugly"
1. Ammonia testing: Standard and disciplined operating procedure for ammonia testing involves collection of venous blood sample in cooled EDTA tubes, rapid transport to the laboratory on ice and standard laboratory assays.
2. Factors affecting ammonia levels: We agree that ammonia levels can be altered by gastrointestinal bleeding, renal failure, exercise, and diet. In the former two situations, the measured ammonia levels contribute to its pathological effect and therefore any elevations detected should be treated. For the latter two conditions, the measured ammonia levels can be transiently increased and therefore, it should not be measured for at least 2-hours after strenuous exercise and 4 hours of a meal.
3. Standardisation of ammonia levels: To account for different 'normal ranges' in ammonia levels in different laboratories, we suggest that the crude ammonia measurement is transformed into a calibrated ammonia level; creating the idea of ammonia-upper limit of normal (AMM-ULN), using the formula: *serum ammonia (μmol/L) / reference laboratory upper limit of normal (μmol/L)* (3). This approach has already been validated (4). We recommend this approach to ensure uniformity and generalisability across hospitals.
4. Relationship between ammonia levels and severity of HE: First, we do agree with the authors that there is no clear relationship between ammonia levels and severity of HE but high levels in different clinical situations are associated with risk of mortality. Second, elevated ammonia levels are required for the diagnosis of HE. Third, a change in ammonia levels defines outcomes of patients with HE. Fourth, it is important to understand that from the pathophysiological perspective, many factors such as age, underlying co-morbidities, severity of inflammation, electrolyte status and severity of liver disease dictates the sensitivity of the brain upon exposure to elevated ammonia levels (5).

In conclusion, although correct measurement of ammonia requires disciplined sample collection and rapid transport to the laboratory, the measurement is relatively straightforward and cheap. It provides extremely useful clinical guidance for the diagnosis of HE, it defines a therapeutic target and offers prognostic information.

References:

1. Deutsch-Link S, Moon AM. The Ongoing Debate of Serum Ammonia Levels in Cirrhosis: the Good, the Bad, and the Ugly. Am J Gastroenterol. 2023 Jan 1;118(1):10-13. doi: 10.14309/ajg.0000000000001966. Epub 2022 Aug 23. PMID: 36001400; PMCID: PMC9822843.
2. Tranah TH, Ballester MP, Carbonell-Asins JA, et al. Plasma ammonia levels predict hospitalisation with liver-related complications and mortality in clinically stable outpatients with cirrhosis. J Hepatol. 2022 Dec;77(6):1554-1563. doi: 10.1016/j.jhep.2022.07.014.
3. Patwardhan VR, Jiang ZG, Risech-Neiman Y, et al. Serum Ammonia is Associated With Transplant-free Survival in Hospitalized Patients With Acutely Decompensated Cirrhosis [corrected]. J Clin Gastroenterol. 2016 Apr;50(4):345-50. doi: 10.1097/MCG.0000000000000443. Erratum in: Clin Spine Surg. 2020 Jan;54(1):95.
4. Balcar L, Krawanja J, Scheiner B, et a. Impact of ammonia levels on outcome in clinically stable outpatients with advanced chronic liver disease. In press. DOI:https://doi.org/10.1016/j.jhepr.2023.100682
5. Jalan R, Rose CF. Heretical thoughts into hepatic encephalopathy. J Hepatol. 2022 Aug;77(2):539-548. doi: 10.1016/j.jhep.2022.03.014.