Erroneous ammonia measurement is not synonymous with a lack of efficacy of ammonia-lowering therapies in hepatic encephalopathy

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Title: Erroneous ammonia measurement is not synonymous with a lack of efficacy of ammonia-lowering therapies in hepatic encephalopathy

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Conflict of interests:
Christopher Rose has research collaborations with Mallinckrodt Pharma and is an advisor for Axcella, Morphocell Technologies, Sana Biotechnologies, Horizon Therapeutics and Lupin Pharma.
Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Discovery, a spin out company from University College London, Hepyx Limited and Cyberliver. He has research collaborations with Takeda and Yaqrit Discovery. Debbie Shawcross is an advisor for Norgine, Kaleido Biosciences, Alfa Sigma, Mallinckrodt Pharma and Falk Pharma.

We write to express some significant concerns regarding the editorial accompanying the STOP-HE trial1, published in the November 2020 Clinical Gastroenterology and Hepatology issue2. Whilst it can be argued ammonia estimation may have no role in the routine management of overt hepatic encephalopathy (HE), we dispute that ‘the arc of ammonia’s history has bent to irrelevance’. The significant body of evidence spanning 130 years demonstrating that hyperammonemia is required for
HE to develop is incontrovertible and even in the presence of inflammation/infection, ammonia must be present in order for HE to develop\textsuperscript{3}.

The design of the STOP-HE trial was finally going to provide the hepatology community quality data on the role of ammonia in overt HE. Patients with hyperammonemia (\textgreater ULN, measured at onsite laboratory) were included and randomized to Ornithine-Phenylacetate (OP) or placebo. The primary endpoint was time to improvement in HE. With 231 patients included in the study, the trial did not meet its primary endpoint. However, when the admission ammonia levels were re-measured at a centrally located laboratory it revealed that 30 patients were erroneously diagnosed as being hyperammonemic. When excluded from the analysis, the median time to clinical improvement was significantly shorter in the patients treated with OP vs placebo (p<0.034). This secondary analysis concludes that OP may have efficacy in the treatment of overt HE. Nevertheless, this important trial raises two important questions:

1. What were the reasons for the discrepancy in the ammonia levels in these 30 patients? The important implication of the trial is that the diagnosis of HE should be ruled out if ammonia levels are normal. Therefore the 30 patients with normal ammonia and brain dysfunction did not have HE but rather something else.

2. What were the changes in ammonia levels after administration of the drug or placebo in the different dose ranges? It is inexplicable that ammonia levels were not reported especially since post-treatment ammonia values were previously presented at the American Association for the Study of Liver Disease conference\textsuperscript{4}. This study, for the first time, would confirm a clear cause-effect relationship between ammonia and HE.

The 4 reasons provided in the accompanying editorial as rationale for not measuring ammonia levels are inaccurate and warrant to be challenged;

1. Although the ammonia levels may be labile, a ‘correctly-measured’ normal ammonia level is incompatible with the diagnosis of HE\textsuperscript{3}. Ammonia measurements, therefore require to be performed carefully using clear, validated, standard operating procedures. This issue of erroneous ammonia measurement impacting on outcome of drug therapy is well-illustrated in the STOP-HE study.

2. The argument presented about variability in normal levels and wide ranges in the trials further supports the idea that ammonia measurements must be standardized rather than ‘not-measured’ as is suggested.
3. We agree that unlike in acute liver failure, ammonia levels do not correlate directly with severity of HE in cirrhosis. However, higher levels of ammonia are seen in patients with more severe HE grades and are associated with risk of death in cirrhosis\(^5\) with a reduction in ammonia level being associated with resolution of HE. The retrospective study by Haj et al.\(^6\) which measured ammonia levels in a non-standardized fashion in just 46% of the cohort and that the dose of lactulose was administered independent of blood ammonia levels, is not a robust rationale for disregarding the role of ammonia.\(^7\)

4. We agree that infection and inflammation are important precipitants of HE but the editorial fails to mention that inflammation induces HE in ‘synergy’ with hyperammonemia as illustrated by Shawcross et al., in both animals and humans (reviewed in Rose et al.,)\(^3\). Infection-induced or septic encephalopathy without hyperammonemia is pathophysiologically distinct from HE.

Taken together, we believe that absence of a robust system for the measurement of ammonia is not synonymous with a lack of efficacy of ammonia-lowering therapies in HE nor negates ammonia as being acknowledged as being central to its pathogenesis.

The value of any biomarker is only evident if it is measured properly. The best example in the hepatology community is the measurement of hepatic venous pressure gradient, which also proved to be useless if not evaluated properly\(^8\). *Every line is the perfect length if you don't measure it* (by Martin Rubin). If ammonia is correctly and rigorously measured in a standardised fashion, it may still have a role in the therapy of HE. It would be dangerous to discard it.

References:

7. Rose CF and Jalan R, Canadian Liver Journal, *in press*