Reviewer's report

**Title:** A capillary blood ammonia bedside test following glutamine load to improve the diagnosis of hepatic encephalopathy in cirrhosis

**Version:** 1  **Date:** 12 August 2011

**Reviewer:** Debbie Shawcross

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This study describes an exploration of the role of capillary blood ammonia estimation in conjunction with a 20 gram oral glutamine challenge (OGC) in 57 patients with advanced cirrhosis with and without a prior history of overt hepatic encephalopathy (HE). The authors conclude that by itself, capillary blood ammonia is not a good biomarker of minimal HE and does not reliably predict future episodes of HE. However, use of the OGC with capillary blood ammonia estimation improves the diagnostic yield of minimal HE from 44% to 67%.

The notion that isolated blood ammonia level (whether venous or arterial) are poor predictors of minimal or overt HE has been well established in the literature by several groups and baseline systemic inflammation has been shown to have some influence on the cerebral effects of ammonia, in minimal HE using an amino acid challenge [Shawcross DL, Wright G, Olde Damink SWM and Jalan R. Role of Ammonia and Inflammation in Minimal Hepatic Encephalopathy. Metabolic Brain Disease 2007; 22(1):125-38].

The novelty of this study therefore lays in the proposition that OGC and capillary blood ammonia estimation may be utilised as a point of care diagnostic test for minimal HE (AUROC 0.727) in patients with cirrhosis. Nevertheless, the time taken to perform the OGC and 2 sets of neuropsychometry must still have taken a minimum of 2 hours which may not be feasible to do in all patients presenting with moderate or advanced cirrhosis.

- **Major Compulsory Revisions**

1. The authors state that healthy controls were enrolled (Figure 2) and a subset of patients who had ammonia levels determined simultaneously in 2 vascular beds (Figure 3). How many controls were used and did they also have neuropsychometry performed as well as capillary ammonia? These data need to be added to the manuscript, table 2 and figure 2. How many patients had 2 vascular beds examined and were they part of the n=57 patients with cirrhosis? These data need to be added to Figure 3 and discussed in a little more detail in the manuscript body.

2. The numbers of patients stated to have minimal HE at baseline varies from 45% in the abstract, to 48% in the results and discussion. I calculate 25/57 with baseline HE to be 44%. Please amend throughout manuscript.

3. The same applies to patients diagnosed with HE post OGC. The abstract says
69% and the results say 67%. I make 38/57 to be 67%. Please amend.

4. This therefore makes me wary that there are other mathematical errors in the numbers and statistics throughout the manuscript. Please re-check thoroughly.

5. It is contentious to give an amino acid challenge to a patient with TIPSS who is at high risk of developing overt HE as the glutamine will largely bypass the liver. Previous studies using amino acid challenge and OGC have largely excluded TIPSS patients. Furthermore, many patients with TIPSS have evidence of minimal HE at baseline. Please explain the reasoning behind their inclusion and detail the presence or absence of minimal HE in these 4 who will behave slightly differently from the remaining 53/57 of the cohort.

6. The authors state that blood sodium levels are important in dictating the presence or absence of minimal or overt HE in the discussion (ref 34). I’d like to see some more patient details including whether baseline blood sodium had any bearing on the presence of minimal HE at baseline or on the response to the OGC. Likewise what was the serum creatinine (ammonia is also excreted renally), white cell count and C reactive protein.

- Discretionary Revisions

1. I would change the word ‘attribution’ to ‘distribution’ in the last line of paragraph 1 of the introduction.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

'I declare that I have no competing interests'