# RAPID REVIEW

## Dispelling the Myths in the treatment of Hepatic Encephalopathy

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**Abbreviations:**

ALF: acute liver failure

HE: hepatic encephalopathy

MARS: Molecular Adsorbent Recirculating System

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**SUMMARY**

**Context.**

Current guidelines for the treatment of Hepatic Encephalopathy (HE) suggest that ammonia reduction is the main focus of therapy. The conceptual framework for ammonia lowering is based upon strategies to reduce its generation and absorption in the colon through the use of lactulose and reduced protein diet.

**Starting point.**

Two recently published studies provide compelling and provocative data that questions the relevance of these interventions. The first is a systematic review of randomised trials of non-absorbable disaccharides in the treatment of HE by Als-Nielsen et al. which concluded that there is 'insufficient evidence' to determine whether non-absorbable disaccharides are of benefit to patients with HE. The second is a small randomised study by Cordoba et al. which showed that diets with normal protein content can be administered safely to cirrhotics with episodic HE and that protein restriction does not have any beneficial effect for cirrhotic patients during an episode of HE.

**Where next?**

Two simultaneous approaches to developing new therapies for HE are needed. Firstly, it is important to focus upon the interorgan metabolism of ammonia. Indeed, data from recent studies suggest that the small intestine and kidneys are important ammonia producers and the muscle is an important organ that can remove ammonia. Novel therapeutic approaches targeting these organs reduce ammonia. Secondly, new research is urgently needed to explore factors other than ammonia that may be important in the pathogenesis of HE and recent studies point to the important synergistic role of inflammation.

**Conclusion.**

The lack of conclusive data about the therapeutic efficacy of any treatment regime supports the view that placebo-controlled trials of newer agents are both urgently needed and ethical. Currently, the emphasis of treatment of HE should shift from existing therapies to aggressive management of the precipitating event.

Hepatic encephalopathy (HE) remains a major clinical problem in patients with cirrhosis and is the feature that defines the prognosis of patients with acute liver injury. In acute liver failure (ALF) rapid deterioration in consciousness level and increased intracranial pressure may result in brain herniation and death. The manifestations of HE in cirrhosis seriously affect the quality of life of patients and impair daily functioning in both the physical and psychological domains. When HE is severe in cirrhosis, patients may develop varying degrees of confusion and coma. (1)

Since the initial description of ammonia in the pathogenesis of HE over 100 years ago, more than 1200 papers have explored it's role and confirmed that ammonia is central in the pathogenesis of HE. In patients with severe liver dysfunction and therefore impaired urea synthesis, glutamine is synthesised from ammonia and glutamate and, acts as a major alternative ammonia detoxification pathway. Glutamine synthesis occurs within astrocytes and causes brain swelling. The degree of brain swelling was shown to correlate with neuropsychological function and normalised after liver transplantation. (2) More recently, direct evidence for the ammonia-glutamine-brain swelling hypothesis of HE has been provided in patients with cirrhosis. (3)

Current therapies for HE are based upon ammonia lowering strategies. Up until now this has been based on the hypothesis that the colon is the primary organ responsible for the generation of ammonia. Therefore the mainstay of current therapy of HE are non-absorbable antibiotics, lactulose and protein restricted diets. However, the results of two recently published studies (4;5) suggest that the colon may not be the only focus for ammonia reduction indicating that the role of other organs in ammonia metabolism needs to be explored.

**LACTULOSE IN HE:**

Traditionally, the colon has been thought of as the major site of ammonia production and lactulose/lactitol has been considered the standard of care to which all other newer therapies have had to be compared to. Its use was prompted by studies suggesting that the colonic bacterial flora is the main source of ammonia production in the body. (6) Colonic bacteria are thought to produce ammonia by splitting urea and possibly amino acids. (7) With this in mind, poorly absorbed antibiotics such as neomycin were introduced and lactulose was introduced as a safer alternative. (8) On the basis of 2 small trials, lactulose was considered as effective as neomycin. (9;10) Hence for over 25 years, non-absorbable disaccharides have been considered as the first line pharmacological treatment for HE.

In the recently published systematic review of 22 randomised trials using non-absorbable disaccharides (lactulose/lactitol) for HE, Als-Nielsen et al. conclude that there is 'insufficient' evidence at present to recommend or refute the use of them in HE. (4) Compared with placebo or no intervention, lactulose/lactitol had no significant effect on mortality. Only 4 placebo-controlled trials were considered of high enough quality and in these trials a total of 57 patients were included (Table 1). Only low quality trials in patients with minimal HE found that lactulose had a beneficial effect as assessed by various non-validated psychometric tests. Furthermore, although it was shown that lactulose/lactitol was inferior to antibiotics such as neomycin and rifamixin, in reducing the risk of no improvement and of lowering blood ammonia concentration, there was no significant difference in mortality.

This review has important implications and qualifies that non-absorbable disaccharides have been introduced into clinical practice without the appropriate

evidence base. Moreover, most randomised trials of new treatments for HE use lactulose as a comparator and performing large placebo-controlled trials has so far been viewed as unethical.

**PROTEIN RESTRICTION IN HE:**

Historically, protein restriction for the treatment of HE has been advocated based on anecdotal observations. (11) This is in direct opposition to the fact that in cirrhosis, higher protein intakes are required to maintain a positive nitrogen balance. Cordoba et al. showed in a small randomised study in 20 cirrhotic patients with HE that diets with a normal protein content can be administered safely. (5) Ten patients underwent protein restriction followed by progressive increments, whilst 10 followed a normal protein diet (1.2g/kg/day). Enteric nutrition was delivered by a nasogastric tube for 2 weeks. The low protein group received no protein for the first 3 days, increasing every 3 days until 1.2 g/kg/day for the last 2 days. Both groups received the same amount of calories. Protein metabolism was studied on days 2 and 14 with the glycine-$N^{15}$ infusion method and showed that protein synthesis was similar in the low and normal protein groups but protein breakdown was higher in the low-protein group. The lack of any significant differences between the two groups in the course of HE and the reduced protein breakdown in the normal protein group argues against the restriction of protein in patients with HE. However, the results of this study should be confirmed in a larger trial as it was not adequately powered.

**FUTURE DIRECTIONS:**

**(a) Other Organs:**

Given that the metabolic capacity of the liver to remove ammonia is severely curtailed in liver disease, a reduction in ammonia concentration will require one to focus upon the different organs involved in its metabolism. (Figure 1)

**(i) Gut:** It has become clear that the small intestine is an important source of ammonia generation through the uptake of glutamine. (12) The observation of hyperammonemia and HE in germ-free dogs with a portacaval shunt suggests that colonic bacteria play a limited role in producing ammonia. (13) The enterocytes have a high glutaminase activity making them a major ammonia producing site during breakdown of glutamine. Indeed, in patients with cirrhosis, glutamine uptake and ammonia production has been demonstrated, and increased glutaminase activity was shown to correlate with the severity of minimal HE. (14) Therefore, the small intestine may be a new target for therapy.

**(ii) Kidneys:** The kidneys possess the ability to both produce ammonia and also to excrete it. (15) During hyperammonemia the kidneys switch from net ammonia production to net ammonia excretion. (16) Recently, studies in patients with cirrhosis have shown that the kidneys are an important target. Volume expansion in cirrhotics produces significant increases in renal ammonia excretion resulting in a reduction in plasma ammonia concentration. This was shown to improve mental state supporting the notion that the kidneys can be manipulated favorably. (17)

**(iii) Muscle:** During the hyperammonemic state, muscle detoxifies ammonia through conversion to glutamine. (12;16) L-ornithine L-aspartate (LOLA), which is a mixture of 2 amino acids, provides intermediates that increase glutamate availability for synthesis of glutamine and illustrates the concept that muscle can detoxify ammonia. Administration into animals with ALF resulted in reduced

brain water (18) and into patients with HE resulted in an improvement in HE compared with placebo-treated controls. (19) However the jury with respect to the efficacy of LOLA in HE is still out, as only 3 of the 11 trials using LOLA have been fully published. (20)

**(b) Other Factors:**

Although we know that ammonia is critical in the pathogenesis of HE, clinical observations do not always show a consistent correlation between the concentration of ammonia in the blood and the manifest symptoms of HE. (21) Therefore, it is probable that other factors in addition to hyperammonemia are important in modulating the effects of hyperammonemia.

**(i) Inflammation:** Recently the role of inflammation on the development of HE has been highlighted. Sepsis is a frequent precipitant of HE and studies have suggested rapid progression in the severity of HE in those patients with ALF that have more marked inflammation. These observations have been confirmed in cirrhotic patients. (22) Nitric oxide, proinflammatory cytokines and free radicals are all therefore possible targets. Measurement of circulating inflammatory mediators may prove useful in evaluating the systemic inflammatory response and assist in tailoring the administration of anti-inflammatory agents. Altering the gut flora and modulation of the gut permeability may justify the use of probiotic therapy. (23)

The use of a 'detoxification device' in liver failure might lead to a temporary improvement in the patient's condition, allowing the liver to recover spontaneously. Liver support systems, such as The Molecular Adsorbents Recirculating System (MARS) may have a role. MARS has been found to be of benefit in improving HE grade in patients with decompensated

cirrhosis independently of changes in ammonia and cytokines. (24) Therefore other toxins such as nitric oxide, oxygen-based free radicals and endocannibinoids may be important.

**(ii) Cerebral Blood Flow:** Cerebral hyperemia is critical in the development of intracranial hypertension in ALF. (25) Moderate hypothermia has been shown to be useful in the treatment of an uncontrolled increase in intracranial pressure in patients with ALF by reducing cerebral blood flow. (26) In cirrhosis, changes in regional cerebral blood flow may account for the attention deficit that is a characteristic feature of minimal HE. (27) Recent evidence suggests that an acute increase in ammonia alters regional cerebral blood flow and this is associated with memory deficits. (28)

## CONCLUSIONS:

We have entered an exciting phase in HE research with novel therapies evolving from the discovery of new targets. Current evidence supports the view that lactulose and low protein diets should no longer be part of standard care in patients with HE but this does not necessarily mean that these therapies do not work in selected patients. Further trials of lactulose, protein restriction and newer agents should be placebo-controlled. Given that the variability in the improvement of HE with placebo is between 20-40%, power calculations will be difficult and a multicentre approach will be necessary to enroll adequate numbers of patients. Current guidelines will need to be revised with strict attention being paid to treating the precipitating factors, with correction of dehydration, electrolyte and acid-base imbalance, constipation and infection.

## FIGURE LEGEND

**Figure 1**

A diagrammatic representation to show the inter-organ trafficking of ammonia in health, and in cirrhosis. In healthy individuals the liver removes ammonia by detoxification into urea. In patients with cirrhosis, the metabolic capacity of the liver is reduced resulting in hyperammonemia. In this situation the muscle becomes an important organ of ammonia detoxification into glutamine. This glutamine acts as a temporary buffer which has the potential to both regenerate ammonia (enterocytes) and also to excrete ammonia (kidneys). This highlights the importance of organs such as the gut, kidney and muscle in the homeostasis of ammonia levels in patients with liver disease.

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