

Novel therapies in the management of acute episodes of hepatic encephalopathy

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Potential conflict of interest: Prof. Jalan has research collaborations with Ocera and Grifols, consults for Ocera (manufacturer of OCR-002, a drug invented at University College London [UCL] by Prof. Jalan and licensed to Ocera), and has received speaking fees from Norgine and Grifols. Prof. Jalan is the founder of a UCL spinout, Yaqrit Limited.

Patients presenting with an acute decompensation of cirrhosis and associated episode of hepatic encephalopathy (HE) represent a large heterogenous group, which until recently has been difficult to address because of the huge differences in short-term mortality varying from 2% to more than 90%. The recent studies defining acute-on-chronic liver failure (ACLF) help to identify a subgroup of patients with higher mortality rates, in whom the mechanisms of HE may differ.^{1, 2}

Pathophysiological Basis of Therapeutic Targets in Patients With Overt HE With and Without ACLF

Animal studies into mechanisms underlying the development of overt HE pointed to the importance of ammonia and neuroinflammation.³ Overt HE is not one condition, and the mortality of patients is related to its severity and whether it is associated with ACLF⁴ (Fig. 1). From the pathophysiological perspective, the severity of inflammation was the key difference between the groups. To clarify whether the differences were due to ACLF itself or whether superimposed HE was contributory, Sawhney et al.⁵ followed a group of patients with ACLF, with or without HE, and pointed to ammonia, inflammation, and cerebral oxygenation as potential therapeutic targets.

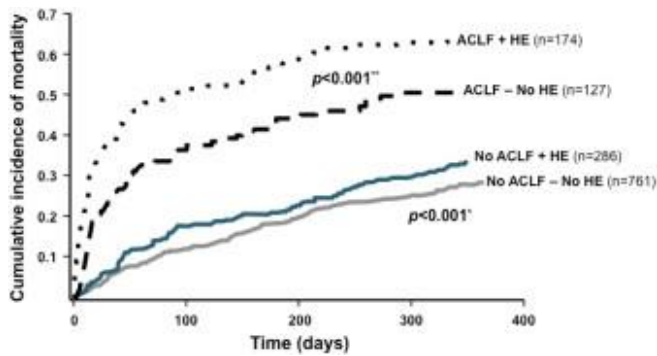


Figure 1

Mortality of patients with acute episode of HE with and without concurrent ACLF. Adapted from

Novel Therapeutic Approaches

Currently, the approach to patients with overt HE, with or without ACLF, is essentially similar with some differences, as pointed out in the following subsections.

Ammonia

To target ammonia, it is important to consider interorgan ammonia metabolism (Fig. 2). Metabolism of ammonia involves multiple organs, in which gut and kidneys are ammonia producers and the muscle and liver are ammonia removers, making these the ammonia-removing targets. Portosystemic shunts enhance the systemic exposure of gut-derived ammonia.

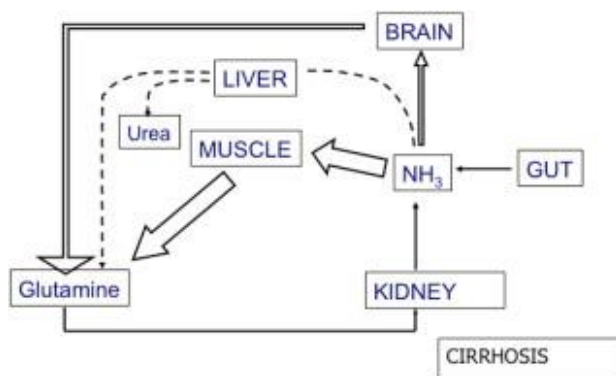


Figure 2

Interorgan ammonia metabolism. When the liver becomes cirrhotic, ammonia is metabolized into glutamine by the muscles, but this circulates back to the gut and the kidneys to regenerate

ammonia. Adapted with permission from *Liver International*.⁶ Copyright 2011, John Wiley & Sons
Cordoba et al. (4). A/S

Targeting the Gut

The main strategies to target the gut use lactulose that has been shown to be effective and remains the mainstay of therapy. Recently, lactulose was compared with polyethylene glycol (PEG), which is essentially used as a preparation for colonoscopy.⁷ The data clearly showed that the administration of PEG resulted in faster patient recovery from HE, but, paradoxically, this effect was independent of changes in ammonia levels. A larger, multicenter study is needed.

Targeting Portosystemic Shunts

Large, spontaneous portosystemic shunts are increasingly recognized as a cause of overt and recurrent HE. This diagnosis should be considered in all patients with HE because its closure using radiological techniques has been shown to be very successful. The benefit in patients with a Model for End-Stage Liver Disease score greater than 11 is limited and, conversely, may be detrimental.⁸

Targeting the Muscle

Traditionally, there was a suggestion that patients with HE should be treated with a low-protein diet. In a randomized controlled clinical trial, it was clearly demonstrated that there was no benefit of restricting protein in these patients. In addition, more evidence of protein breakdown was observed; therefore, protein restriction may be detrimental in patients with HE.⁹

Targeting Multiple Organs

The drug ornithine phenylacetate (OCR-002) was described to harness the multiorgan pathways involved in ammonia metabolism. Essentially, ornithine drives generation of glutamine in the muscle, thus capturing a molecule of ammonia in the process, which is then removed by phenylacetate as phenylacetylglutamine by the kidneys.^{10, 11} This has been tested in many animal models, and pilot studies have shown potential usefulness. A large, randomized study is under way.

Inflammation

Antibiotics are routinely administered to patients with overt HE, but they have never formally been put to clinical trials. Rifaximin, in addition to lactulose, has been shown to be beneficial at reducing the severity of HE and also improved survival in patients with overt HE. In-hospital mortality rate in the control group was nearly 60%, making these data difficult to interpret and generalize to patients with overt HE. More rigorous trial data are necessary before this can be adopted in clinical practice.¹²

Albumin, traditionally considered a volume expander, has been shown to have anti-inflammatory properties. Its administration to patients with HE did not result in improvement of HE, but it did improve the survival of patients.¹³ Using albumin in an extracorporeal circuit for dialysis of patients with severe HE who did not respond successfully to conventional therapy showed that the patients treated with albumin dialysis spent less time in coma, recovering significantly faster, but there was no improvement in survival.^{14, 15} Albumin dialysis treatment is recommended for ACLF patients with HE that is refractory to current therapy, but routine albumin infusion is not recommended.

Cerebral Perfusion

A careful attempt should be made to keep the patient well hydrated. No specific therapy is available, but jugulovenous oxygen saturation is a novel biomarker.⁵

Conclusions

The evidence-based strategies to treat overt HE are limited to lactulose, closure of portosystemic shunts, albumin dialysis for those with refractory HE, and meticulous treatment of precipitating events. Clinical trial results of the emerging strategies highlighted are awaited.

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