Severe Acute Hepatic Encephalopathy in Cirrhotic patients: The gut remains an important target of therapy

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Hepatic encephalopathy (HE) is a common complication of cirrhosis manifested by a range of neuro-psychiatric abnormalities and associated with significantly increased mortality, particularly in patients requiring acute hospitalization.[1] Prognosis of acutely decompensated cirrhosis is dependent on the number and type of associated organ failures.[2] Indeed, in cirrhotic patients with HE, not only is the occurrence of other organ failures associated with higher mortality rates, but the presence of HE in patients with multiorgan dysfunction adds to the risk of death suggesting that HE is prognostically important in this cohort of patients.[1] However, patients with severe HE are difficult to study and consequently clinical trials in this patient population are rare. Therefore, we welcome this recent randomized clinical trial published in JAMA from Rahimi et al. who suggest that polyethylene glycol (PEG) may be more effective in cirrhotic patients with acute HE compared with the current gold-standard, lactulose.[3]

Lactulose is widely available, inexpensive and is the standard of care for patients with HE despite a lack of high-quality robust placebo-controlled randomized controlled clinical trial data.[4] More recently, the use of the non-absorbable antibiotic Rifaximin has shown promise, initially approved for secondary prophylaxis and also demonstrating benefit in the treatment of overt HE but is less cost-effective as initial therapy.[5-7] Rahimi et al. compared the administration of 4L of PEG, a commonly used purgative for bowel preparation for colonoscopy, against lactulose for the treatment of patients with cirrhosis admitted to hospital with an acute episode of HE. The study was based on the hypothesis that a rapid catharsis of the gut using PEG may be more effective than lactulose at clearing the bowel of toxins such as ammonia. The most outstanding findings were greater improvement in HE at 24 hours (based on objective scoring) and more rapid resolution of HE in patients receiving PEG therapy compared with lactulose. The study also reported a potential reduction in the hospital length of stay, which did not reach statistical significance. HE is not a homogenous condition, often with non-specific neurological symptoms and concomitant disorders, which makes these studies more difficult. One of the innovative solutions to study the mental state was their use of the HESA scoring system, which serves to objectify assessments and avoid bias.[8]

The pathophysiology of HE is complex and incompletely understood. Multiple factors have been implicated including systemic inflammation, oxidative stress, genetic factors and altered gut microbiome.[9] However, hyperammonaemia remains central to pathogenesis, although evidence directly correlating ammonia levels with severity of HE is limited.[9] The data from Rahimi et al. are the first to show that ammonia levels in these acute HE cirrhotic patients is massively increased (mean 159 (+/- 70) µmol/L). Although the variability is high, these levels are seen in patients with severe acute liver failure at risk of brain herniation.[10] Lactulose resulted in greater reductions but the changes in ammonia in the two groups are difficult to interpret as only a single measurement was made following initiation of therapy. Furthermore, ammonia was measured only in a small proportion of patients and the variation was massive, limiting attribution of cause effect relationship.

Nevertheless, rapid ‘gut cleansing’ improved HE faster indicating the importance of the gut/liver/brain axis in the pathogenesis of HE.

They correctly identify some weaknesses, most notably that it involves a relatively small cohort of patients (25 in each arm) from a single center, which makes the data prone to possible statistical errors. It was interesting to note that PEG treatment was safe and well tolerated with no deterioration of fluid or electrolyte status. Although the patients reportedly favored PEG therapy, any practical issues of managing this acute treatment on the hospital ward when significant gut catharsis is achieved in patients with altered conscious state are not described. PEG patients, not surprisingly, experienced more diarrhoea but the number of bowel actions achieved to assess adequate response to lactulose is not reported. Furthermore, patients treated with Rifaximin were excluded from this study. This may have helped to preserve the integrity of the treatment arms in a study of this small size and avoid confounding variables but also suggest that patients with more severe background HE may be missing from the study population. Rifaximin may be more expensive but is well tolerated. Given its reported efficacy for treatment and prophylaxis of HE in addition to lactulose, it would be interesting to explore in future studies the comparative benefit of PEG or Rifaximin as well as the role of combination therapies in treating acute HE. It is also worth noting that although patients in each treatment group were generally quite similar, there were a greater proportion of patients in the PEG arm whose HE was precipitated by non-adherence with previous lactulose therapy. The significance of this is uncertain and would require a larger patient population to elucidate further, but raises the possibility that the lactulose group were a more refractory phenotype in terms of response to therapy.

The importance of the study by Rahimi et al. goes beyond the clinical findings. It highlights the scarcity of rigorous clinical trial data, particularly for acute treatment of episodic HE. There is an unmet need for new effective therapies for this group of patients. Several other agents have attracted interest with some promising results although data remain limited and preliminary. These include various therapeutic strategies, such as ammonia reduction using ornithine phenylacetate or glycerol phenylbutyrate; probiotics and non-absorbable antibiotics to manipulate the gut microbiome; as well as novel approaches such as albumin infusions and albumin dialysis.[4, 9] The study by Rahimi et al. will no doubt allow these other interventions to be tested in these acute situations by providing insight into the clinical and pathophysiological issues.

Emerging clinical trial data have started to provide important new insights into the spectrum of the clinical problem with distinct phenotypes seen in patients with different types of HE.[1] The approach used to treat minimal HE will be different to approaches to primary and secondary prophylaxis, which will be different, as shown by Rahimi et al. to cirrhotic patients with acute HE. In this era of personalized medicine, it may be that treatment should entail different targets or combinations depending on the patient’s clinical presentation and pathophysiology. Ultimately, studies such as this provide hope for the

emergence of more treatment options for this challenging and significant clinical problem, for which PEG may be a useful part of our armamentarium.

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