Review

Overview on Current Management of Hepatic Encephalopathy

Zhixian Guo, MD;[1] Zujiang Yu, MD;[1]* Ke-Qin Hu, MD[2]*

[1]*Department of Infectious Diseases, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China*
[2]*Division of Gastroenterology and Hepatology Univ. of California, Irvine Medical Center, CA*

Hepatic encephalopathy (HE) is one of the most serious complications of chronic or fulminant liver failure. It's main clinical manifestations involving disturbance of consciousness, behavioral disorders and coma. According to the degree of impaired consciousness, neurological signs and EEG changes, the clinical course of HE may be divided into four phases, ranging from cognitive alteration to coma and even death, staging contribute to early diagnosis, prognosis and therapeutic evaluation. Management of HE primarily involves avoidance of precipitating factors, protect live function from further damage, treatment of ammonia poisoning and regulation of neurotransmitter. This review mainly discusses the current available options for therapy in Hepatic encephalopathy and some new studied agents.
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INTRODUCTION

Hepatic encephalopathy (HE) is a reversible and devastating complication of advanced liver disease, occurs in approximately 30-45% of patients with cirrhosis.[1-3] Compared with cirrhotic patients who have not had HE, the patients who had HE accounts for frequent hospitalization, decrease in the quality of life, and poorer outcomes. The high morbidity and mortality combined with the costs underline the importance of effective treatment and prevention of HE.

The clinical manifestations of HE range from altered mental status to deep coma and even death,[4] the West Haven scale are most often used to grade HE, the scale ranges from trivial lack of awareness, alteration in sleep-wake cycle to coma.[5] Current treatment strategies are aimed at reducing the serum level of ammonia. This is done by introducing agents that reduce or inhibit production of intestinal ammonia or minimize its absorption from the gastrointestinal tract and correcting precipitating factors such as gastrointestinal hemorrhage, electrolyte imbalances and constipation.

CLASSIFICATION OF HE

According to the Working Party at the 11th World Congress of Gastroenterology, HE is classified into three different types.[4] Type A describes HE associated with acute liver failure. Type B describes HE associated with portal-systemic shunting without associated intrinsic liver disease. Type C describes HE associated with underlying cirrhosis and portal hypertension or portal-systemic shunts. Type C is further subcategorized as covert HE (minimal HE and West-Haven grade I HE) and overt HE (West-Haven grades II-IV HE).

CHE can affect up to 80% of cirrhotic patients. Because of lack of clinical symptoms, it is difficult to diagnosis. It can only be diagnosed through specialized neurophysiologic and psychometric tests.[6] Patients with CHE have defects in attention, vigilance and orientation. It is very dangerous for them to drive.[7] It negatively affects the patients' quality of life and their families. CHE is associated with mortality and increased risk of hospitalization and OHE development.[8,9] We will discuss CHE later. Here, we mainly discuss OHE.

PATHOGENESIS OF HE

The pathogenesis of HE is multifactorial, and is not completely understood, but the elevated blood ammonia levels are a key factor in the process of the disease.[10] Ammonia is mainly generated in the intestine as a result of bacterial breakdown of dietary protein metabolism of glutamine.[11] The absorption of ammonia occurs in the colon via nonionic diffusion and is transported through the portal vein to the liver.[12] Hyperammonemia induces encephalopathy by promoting cerebral edema, modulating the blood-brain barrier, decreasing blood flow, or modulating neuroinhibition. Recently, more and more people demonstrated that inflammation,[13,14] including systemic inflammation, neuroinflammation, oxidative stress,[15] and neurosteroids,[16] acts in concert with ammonia in the pathogenesis of HE. But they are not well understood by now. Therefore, a number of treatments aim at lowering the level of blood ammonia.[17]

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***Corresponding Author:** Division of Gastroenterology and Hepatology Univ. of California, Irvine Medical Center, CA
(Email: kqhu@uci.edu, johnyuem@zzu.edu.cn)

MANAGEMENT OF HE

The management of HE is mainly supportive care, primarily involves identification and treatment of underlying etiologies and precipitating factors, and administration of various ammonia-lowering therapies.

Effectively Treaing Underlying Etiologies for Hepatic Decompensation or Liver Failure

Although most unserlying eitologies are difficult to manage, especially in the acute care setting, some of these etiologies could be treated simultaneously. For instance, HBV and HCV cirrhosis is no reversiable; acetaminophen overdose should be treated immediately on admission. Alcohol liver disease could be another sample that can be treated. Final para of this session: for those liver injury is chronic and cirrhosis is advanced, especially those with high MELD score, liver Tx evaluation and listing should also be considered.

Early Identification and Prompt Treatment of Precipitating Factors

The main step in treatment of HE is identifying and treating precipitating factors.[18] Commonly precipitating factors are listed in **table 1**. It is estimated that over 80% of HE patients are caused by reversible factors.[19] In clinical, Infection is very common in HE patients, all patients with ascites should have a diagnostic paracentesis, if infection is found, it should be treated with appropriate antibiotics. Constipation is also very easy to be found, it is important to assess recent bowel habit, it is appropriate to produce two to three soft bowel movements per day. Blood biochemical test results can indicate electrolyte abnormality. Addressing these factors in time have been proved to be crucial in effectively treating most patients with HE.[20]

Table 1. Precipitating factors for hepatic encephalopathy

Drugs benzodiazepines narcotics alcohol	**Hypovolemia** diureses, diarrhea vomit, bleeding large volume paracentesis
Increase the production and absorption of ammonia excessive dietary protein gastrointestinal bleeding infections constipation hypokalemia	**Portosystemic shunting** surgery or natural diversion
	Angiemphraxis portal thrombosis hepatic vein thrombosis
	Hepatocellular carcinoma

Reduce the Generation and Absorption of Nitrogen in the Intestine

Diet Management. Diet management is very important in the management of HE.[21] Usually, protein-restricted diets are prescribed for cirrhotic patients with hepatic encephalopathy.[22] However, protein restriction may worsen the patient's nutritional status.[23] A randomized study has proved that the outcome of hepatic encephalopathy was not significantly different between low-protein diet group and normal-protein diet group, they also proved that protein synthesis was similar for low and normal protein diet, but those of the low-protein diet group showed higher protein breakdown.[24] Clinical guidelines recommend protein intake begins at a dose of 0.5g/kg/day, with progressive increase to 1-1.5g/kg/day.[25] Vegetable protein may be better than animal protein.[26] In addition, high fiber diet may be helpful in decreasing the colonic transit time and absorption of ammonia. Small meals evenly distributed throughout the day and a late-night snack of complex carbohydrates will help minimize protein utilization.[27]

Nonabsorbable Disaccharides. Nonabsorbable disaccharides are the most accepted and widely used treatments for HE.[28,29] Nonabsorbable disaccharides, such as lactulose and lactitol, are synthetic disaccharides, they cannot be broken down in the small intestine after oral administration, after reaching the colon, they can be decomposed into lactic acid and acetic acid to reduce the pH value of the intestinal tract.[30] Acidified colon encourage the conversion of ammonia to ammonium, which is more membrane impermeable, as a result, less ammonia is absorbed by the colon.[31] Moreover, the acidification of gut lumen makes the enteric environment less suitable for ammoniagenic coliform bacteria and leads to increased levels of non-ammoniagenic lactobacilli.[19]

The side effect of lactulose therapy include flatulence, stomachache, nausea, emesis and so on.[32] Besides, its taste sweet and greasy, makes it can't be accepted by every patient. The optimal dose of lactulose is that the patient has two or three soft stools each day.[33] It can also be used to retention enema. The curative effect of lactitol is similar with lactulose, but its low sweetness, good taste and less adverse reaction, makes it more acceptable than lactulose.[34]

The curative effect of nonabsorbable disaccharides is exactly, they can be used for the treatment of every stage of hepatic encephalopathy and minimal hepatic encephalopathy.[35] A 2004 meta-analysis reported that nonabsorbable disaccharides were superior to placebo but did not improve survival. However, not all patients respond to lactulose, Praveen Sharma and his workmates analysed 231 cirrhosis patients with HE, they all treated with lactulose and

correction of any associated precipitating factors, they concluded that high baseline MELD, high total leukocyte count, low serum sodium, low MAP, and presence of hepatocellular carcinoma were predictors of nonresponse to lactulose.[36] Besides Nielsen et al found that non-absorbable disaccharides were inferior to antibiotics in reducing the risk of no improvement and lowering blood ammonia concentration, they concluded that there was insufficient evidence to support or refute the use of non-absorbable disaccharides for hepatic encephalopathy.[37] Lactulose or lactitol is recommended by clinical guidelines as the first line therapy, anyway.[28]

Antibiotics. The antibiotic therapies can reduce the enteric bacterial flora that may play a vital role in the production of neurotoxins leading to encephalopathy.[38,39] Commonly used antibiotics are neomycin, metronidazole, rifaximin and so on. Even though neomycin and metronidazole have been shown to be as effective as lactulose,[40] their side effect profile, such as ototoxicity and nephrotoxicity (neomycin) and neurotoxicity (metronidazole), limits their use, particularly in the long term.[41] Rifaximin is a synthetic antimicrobial, it is poorly absorbed in gastrointestinal tract, it has a broad spectrum of antibacterial action covering Gram-positive and Gram-negative organisms, both aerobes and anaerobes.[42] It binds to the b-subunit of the bacterial DNA dependent RNA polymerase and disrupts RNA synthesis. The therapeutic effect of rifaximin is similar with neomycin.[43,44] But the side effect of rifaximin is minimal, for example, headache, flatulence, abdominal pain, constipation, nausea, and vomiting, and no reported drug interactions make it relatively safe.[45,46]

Over recent years, rifaximin has become the most widely used antibiotic in the empiric and prophylactic treatment of HE due to its limited side effect profile. And many studies have demonstrated the efficacy of rifaximin in the management of hepatic encephalopathy (**Table 2**).

Table 2. The data.

Trial	Study design	Assessment	Cases	Duration of treatment	Conclusions
Loguercio et al 2003[48]	Prospective, randomized	Cancellation test, Reitan test, EEG, and PSE severity	40	3 months	Rifaximin > lactulose
Paik et al 2005[87]	Prospective, randomized	Gradation of blood ammonia, flapping tremor, mental status, number connection test	54	7 days	Rifaximin = lactulose
Jiang et al 2008[88]	Retrospective, randomized, comparative	-	264	-	Rifaximin = nonabsorbable disaccharides
Bass et al 2010[89]	Prospective, randomized	Conn score and asterixis grade	299	6 months	Rifaximin > placebo
Sanyal et al 2011[90]	Prospective, randomized	Conn score and asterixis grade	219	6 months	Rifaximin > placebo
Eltawil et al 2012[91]	Retrospective, randomized, comparative	Serum ammonia levels, mental status, asterixis	565	-	Rifaximin = disaccharides
Mullen et al 2014[92]	Prospective, randomized	Adverse events, clinical laboratory parameters	392	6 months	Rifaximin > placebo
Bajaj et al 2015[93]	Prospective, randomized	Rates of HE events, rates of HE-related hospitalisation	82	6 months	Rifaximin > placebo

Combination Therapy. Lactulose and rifaximin have shown to be effective in HE, to evaluate the efficacy and safety of lactulose plus rifiximin vs. lactulose alone in the management of HE, Sharma et al conducted a prospective double-blind randomized controlled trial, in this trial, 120 patients were randomized into two groups, group A (lactulose plus rifiximin) and group B (lactulose plus placebo). They found that there was a significant decrease in mortality after treatment with lactulose plus rifaximin vs. lactulose and placebo, and there were more deaths in group B, however, there were no differences in gastrointestinal bleed and hepatorenal syndrome, but it also proved that combination of lactulose plus rifaximin is effective than lactulose alone.[47] To evaluate the effect of rifaximin, lactitol and their combination in treating chronic HE, Loguercio et al randomly assigned forty out-patients in different groups, HE was assessed by considering: mental state, asterixis, number connection test, arterial blood ammonia levels. They concluded that rifaximin in combination with lactitol or sorbitol represents an effective and safe treatment of chronic HE.[48]

In a retrospective study, Mohammad et al conducted a PubMed MEDLINE search, the key words included lactulose,

lactitol, nonabsorbable disaccharide, metronidazole, rifaximin, neomycin, probiotics, and hepatic encephalopathy. They found 6 studies and concluded that the combination of rifaximin and lactulose should be considered in the treatment and prevention of HE.[49] The unfortunate reality is that there are no available clinical studies evaluating dual antibiotic therapy, nonabsorbable disaccharides with probiotics, or antibiotics with probitics.

Probiotics. The effectiveness of lactulose and rifaximin suggest that altering gut flora to a non-urease-producing population may be effective in managing HE.[50] Probiotics alter the intestinal microbiota and reduce the production of ammonia.[51] It has been shown that the administration of probiotics to liver cirrhotic patients resulted in a modulation of the gut flora with a significant reduction of the quantity of several bacterial pathogens in fecal bacteriological analysis.[52]

To assess the effect of probiotic therapies on HE in liver cirrhotic patients, Jun Xu et al collected six randomized controlled trials involving 496 liver cirrhotic patients. The results showed that probiotic therapy significantly reduced the development of overt hepatic encephalopathy (OR [95% CI]: 0.42 [0.26, 0.70], P = 0.0007). However, probiotics did not affect mortality, levels of serum ammonia and constipation (mortality: OR [95% CI]: 0.73 [0.38, 1.41], P = 0.35; serum ammonia: WMD [95% CI]: -3.67 [-15.71, 8.37], P = 0.55; constipation: OR [95% CI]: 0.67 [0.29, 1.56], P = 0.35). [53] While another randomized trial come to the similar conclusions.[54] Before probitics can be endorsed as effective therapy for hepatic encephalopathy, demonstration of unequivocal efficacy is needed.

L-Ornithine L-aspartate. L-Ornithine L-aspartate(LOLA), ornithine and aspartate are substrates of the urea cycle.[55] Even in decompensated cirrhosis, it seems to stimulate the enzyme activity in residual hepatocytes.[56] LOLA decreases ammonia levels by stimulating hepatic urea cycle activity and promoting glutamine synthesis.[57]

As reported in many studies, both oral and intravenous forms of LOLA have the efficacy to decrease ammonia levels and improve HE.[58,59] A meta-analysis of eight randomized controlled trials with 646 patients showed that, compared with placebo/no-intervention control, LOLA benefits both overt and minimal HE patients, and significantly reduced fasting ammonia levels. To critically evaluate the efficacy of the use of LOLA when compared to placebo in the treatment of HE, four studies published between 1993 and 2000 were selected and reviewed, the trials proved the efficacy of LOLA in reducing hyperammonemia of hepatic encephalopathy.[60] A meta-analysis of 217 patients proved the efficacy of LOLA in reducing hyperammonemia of HE again, but they also found that there is no sufficient evidence of a significant beneficial effect of LOLA on patients with HE.[60] So there is a lack of consensus related to the usage of LOLA in HE now.[61]

Branch Chain Amino Acids. Branch Chain Amino Acid(BCAA) preparation is a compound amino acids, it is mainly composed of leucine, isoleucine and valine.[62] The mechanism of BCAA is competitive inhibit the aromatic amino acids to enter in the brain, and reduce the formation of false neurotransmitters.[63,64] The curative effect of BCAA is still controversial.[65] But for malnutrition who intolerance to protein, supply BCAA helps to improve the negative nitrogen balance.[66] Besides, BCAA supplementation may improve albumin synthesis, decrease insulin resistance, decrease hepatocellular carcinoma, and improve immune function.[67] Supplementation can be done via oral or intravenous routes. A double-blind placebo-controlled crossover study indicates that long-term branched-chain amino acid supplementation is well tolerated and effective in the treatment of impaired automobile driving capacity associated with latent HE.[68] While Als-Nielsen et al analyzed eleven randomized trials which involving 556 patients, they found no convincing evidence that BCAA had a significant beneficial effect on patients with hepatic encephalopathy.[69] These contradiction may underlie the difficulty in assessing the clinical effects of BCAAs.

Molecular Adsorbent Recirculating System. Molecular adsorbent recirculating system (MARS) is a blood detoxification system that removes fat-soluble, water-soluble and albumin-bound toxins by means of albumin recycling system, activated carbon, resin and dialysis.[70,71] This system can remove a part of toxic substances in the blood of patients with hepatic encephalopathy, decrease the concentration of serum bilirubin and improve the prothrombin time, and have a temporary and a certain degree of curative effect to hepatic encephalopathy, at the same time it may be possible to win the time for liver transplantation.[72]

To prove the efficacy, safety, and tolerability of MARS, Hassanein et al conducted a prospective, randomized, controlled, multicenter trial in severe hepatic encephalopathy patients. Patients were randomized to MARS and standard medical therapy (SMT) or SMT alone, the results indicated that the improvement proportion of HE was higher in MARS versus the SMT group and was reached faster and more frequently than in the SMT group, besides, the subjects receiving MARS tolerated treatment well with no unexpected adverse events.[73] Exclusion criteria in this trial included active hemorrhage, active infections, severe cardiopulmonary disease and so on, which will decrease the applicability of MARS.[74] The insufficient of this study was not designed to examine the impact of MARS on survival, a full assessment of the role of albumin dialysis awaits the results of additional controlled trials.[75]

Zinc. Zinc is a critical cofactor in the metabolism of ammonia, zinc deficiency is associated with the down-regulation of muscle glutamine synthetase, which leads to hyperammonemia.[76] A study aim to assess serum zinc levels in a cohort of healthy subjects and cirrhotic patients, they

found that in cirrhotic patients zinc serum levels were significantly lower than in healthy subjects, and a stepwise decline in serum zinc with worsening Child class.[77] Reding et al conducted a double-blind randomized trial in which 22 cirrhotic patients with HE were given oral zinc supplementation or placebo. In the group which received zinc acetate 600mg/day for 7 days, serum zinc had been restored to normal by day 8. On day 8, HE was improved in the supplemented group but not in the placebo group. Besides, blood urea nitrogen was also significant increase in the supplemented group.[78,79] But the duration of this improvement requires further investigation.[80-82] A meta-analysis of 233 patients revealed that oral zinc supplementation improved performance on the number connection test, but there was no evidence about other clinical or biochemical outcomes.[83] Therefore more trials are needed to evaluate the efficacy of oral zinc acetate in the patients with liver cirrhosis and hepatic encephalopathy.

Sodium Benzoate. Sodium benzoate is thought to activate a non-urea cycle pathway for ammonia removal.[84] To evaluate the efficacy of sodium benzoate in the management of HE, Sushma et al conducted a prospective randomized double-blind study, the patients were randomized to receive sodium benzoate (5 gm twice daily) or lactulose (dose adjusted for 2 or 3 semiformed stools/day), the results showed that sodium benzoate is a safe and effective alternative to lactulose in the treatment of acute HE.[85] Given the need for intravenous administration, and the dose-dependent sodium content in this therapy, it may not be useful in treating HE.[86]

SUMMARY

Hepatic encephalopathy (HE) is one of the most serious complications of chronic or fulminant liver failure, and encompasses a spectrum of neuropsychiatric symptoms and signs. Due to differences in etiology and severity, as well as heterogeneity of manifestations, the diagnosis and management of HE remain a difficult challenge for physicians and medical professionals. Several factors have been implicated in pathogenesis, with ammonia considered to have a central role, thus prompt reduce the level of ammonia can be potentially lifesaving. Identification and correction of precipitating factors remains the cornerstone of treatment. Lactulose and rifaximin are the two most effective therapeutic agents available now, and we believe that lactulose plus rifaximin will obtain a better treatment effect. While in clinical practice, to reduce morbidity and mortality, we also combination with other agents, probiotics, L-Ornithine L-aspartate, Branch Chain Amino Acid and so on, although there are no enough evidences to prove the effectiveness of these drugs. It is clear that little progress has been made in developing new therapeutic options over the last 20 years, so study the mechanism of HE and find new drugs are very important now. Overall, when we meet in clinical patients with hepatic encephalopathy, prompt correction of precipitating factors, decrease blood and cerebral ammonia levels quickly, use antibiotics properly and apply molecular adsorbent recirculating system when necessary. If these are not work, liver transplant may be a choice.

CONFLICT OF INTEREST
The authors have no conflict of interest to disclose.

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