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REVIEW ARTICLE

Prophylaxis of hepatic encephalopathy: current and future drug targets

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Abstract

Hepatic encephalopathy is described by a broad spectrum of neurological and psychiatric aberrations resulting due to advanced liver dysfunction. It is a neurological disorder due to hepatic insufficiency and/or portosystemic shunts. Its clinical presentation includes neuropsychiatric dysfunction ranging from subclinical changes to comatose state. It is a sign of poor prognosis in cirrhotics with a high 1-year mortality. Each episode of hepatic encephalopathy leads to high hospitalization rate, poor prognosis and raised burden of healthcare. Primary prophylaxis is prevention of initial occurrence and secondary prophylaxis is prevention of reappearance of hepatic encephalopathy in subjects who had prior history. Early detection and management of triggers is very important in the treatment of hepatic encephalopathy. The initial choice of treatment is still lactulose, as it is effective in minimal, overt, and recurrent hepatic encephalopathy. Rifaximin is equally effective as lactulose in managing hepatic encephalopathy and is better tolerated. Branch chain amino acids are beneficial in subjects who are protein intolerant. L-ornithine L-aspartate and probiotics are also useful in the management of hepatic encephalopathy. Rifaximin along with lactulose is effective in managing overt and recurrent hepatic encephalopathy. Large portosystemic shunts embolization and liver transplant is efficacious in certain group of patients. Nutritional therapy and fecal microbiota transplantation are newer therapies for hepatic encephalopathy but the evidences are limited, more research is required to prove their efficacy. Involvement of hospital pharmacists, telemedicine, and providing education are also beneficial in managing hepatic encephalopathy.

Keywords Hepatic encephalopathy · Secondary prophylaxis · Cirrhosis · Portosystemic shunts · Lactulose · Rifaximin · Probiotics · Branch chain amino acids · L-Ornithine L-aspartate · Fecal microbiota transplantation

Introduction

Hepatic encephalopathy (HE) is a syndrome manifested by deterioration in mental state, psychomotor malfunction, reduced memory, disturbed orientation, and coma [1]. HE leads to poor prognosis and reduced quality of life [2]. Preventing the HE episodes is crucial in the management of cirrhotics. Preventing initial episode of HE is defined as primary prophylaxis [3]. Some patients are at increased risk for developing overt HE (OHE) and need primary prophylaxis. Cognitive abnormalities and biomarkers have been shown to predict the first episode of OHE. Tests for minimal HE (MHE), biomarkers, presence of sarcopenia, trans jugular-intrahepatic-portosystemic-shunt (TIPS) and spontaneous portosystemic shunts (SPSS) should be done to identify patients having high risk of OHE [4]. Studies published on primary prophylaxis are described in Table 1. Prevention of the initial episode of OHE is not recommended in all the subjects with cirrhosis. Recurrent HE is observed in 47–57% of patients within 1 year, after first episode of OHE. Each episode of HE leads to high hospitalization rate, poor prognosis and raised burden of healthcare [5–7]. Secondary prophylaxis is prevention of reappearance of HE in subjects who had prior history [5–7]. Data published on secondary prophylaxis are described in Table 2, while efficacy studies on the management of HE in special situations in Table 3. Increased concentration of blood and brain ammonia is

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Table 1 Efficacy studies of treatment for the primary prophylaxis of hepatic encephalopathy

References	Design	Dose and duration	Outcome
Higuera [80]	Double blind RCT Cirrhotic patients with variceal bleed without minimal or overt HE	$N=87$ patients randomized in 4 groups Group A ($n=22$)—lactulose 30 mL 8 hourly Group B ($n=22$)—LOLA 10 g Group C ($n=21$)—Rifaximin 400 mg 8 hourly Group D ($n=22$)—Corresponding placebo Duration 7 days	The frequency of HE development compared to placebo with lactulose was (54.5 vs 27.3%, $p=0.06$), LOLA (54.5 vs 22.7%, $p=0.03$) and with Rifaximin (54.5 vs 23.8%, $p=0.04$) less
Sharma [20]	RCT Cirrhotic patients without prior episode of HE	$N=120$ patients randomized in 2 groups Group L ($n=60$)—lactulose 30–60 mL 2–3 divided doses/day Group NL ($n=60$)—no lactulose Duration 12 months	Incidence of HE development with lactulose (11 vs 28%, $p=0.02$) was less compared to no lactulose
Wen [90]	RCT Cirrhotic patients with upper gastrointestinal bleeding	$N=128$ patients randomized in 2 groups Group A ($n=63$)—lactulose 10–30 mL 2–3 times/day Group B ($n=65$)—no lactulose Duration 6 days	Incidence of HE development with lactulose (3.2 vs 16.9%, $p<0.05$) was less compared to no lactulose
Sharma [91]	RCT Cirrhotic patients with acute variceal bleed without HE	$N=70$ patients randomized in 2 groups Group L ($n=35$)—lactulose 30 mL 3–4 times/day Group P ($n=35$)—no lactulose duration 5 days	Incidence of HE development with lactulose (14 vs 40%, $p=0.03$) was less compared to no lactulose
Rattanasupar [93]	RCT (multicenter) Cirrhotic patients with acute gastrointestinal bleed without HE	$N=46$ patients randomized in 2 groups Lactulose A ($n=22$)—placebo lactulose B ($n=24$)—lactulose 30 mL 2–3 times/day Duration 5 days	Incidence of HE development with lactulose (16.7 vs 22.7%, $p=0.718$) was comparable with placebo
Maharshi [94]	RCT Cirrhotic patients with acute variceal bleed without HE	$N=120$ patients randomized in 2 groups Group L ($n=60$)—lactulose 30 mL 4 times/day Group R ($n=60$)—rifaximin 400 mg 8 hourly Duration 5 days	Incidence of HE development with lactulose (16.6 vs 15%, $p=1.0.$) was comparable to no rifaximin

RCT randomized controlled trial, *HE* hepatic encephalopathy, *L* lactulose, *NL* no lactulose

the main cause of HE in cirrhosis [8]. Lowering the blood ammonia level is the mainstay for prevention of HE in cirrhosis [9].

In the recent past, there are evidences which suggest that inflammation, including systemic inflammation, neuroinflammation and endotoxemia, play a critical role in the pathogenesis of HE, and inflammation is gently being considered an important therapeutic target for HE [10, 11] The studies proved that available therapy for HE, like lactulose, rifaximin, probiotics and the molecular adsorbent recirculating system (MARS), have been found to regulate the inflammatory response and reduce pro-inflammatory markers like tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6 which help to improve and delay the progression of HE [12, 13]. These recent findings revealed the possibility of these therapies in improving inflammation and providing a new treatment alternative for the patients with HE due to liver cirrhosis.

Management or prevention of HE comprises of luminal agents, extraluminal agents, and interventions [3]

1. Luminal agents like non absorbable disaccharides (lactulose and lactitol), rifaximin, and probiotics function by decreasing the nitrogenous load in the intestine in subjects with reduced hepatic functions and portosystemic shunting [3–7].
2. Extraluminal agents including L-ornithine L-aspartate (LOLA), branched chain amino acids (BCAA) and glycerol phenyl butyrate (GPB) etc., decrease ammonia by contributing another routes of metabolism [8, 9, 14].

Table 2 Efficacy studies of treatment for the secondary prophylaxis of hepatic encephalopathy

References	Design	Dose and duration	Outcome
Sharma [5]	RCT Cirrhotic patients recovered from HE	$N=140$ Group 1—HE-L ($n=70$): lactulose (30–60 mL/day in 2 or 3 divided doses) Group 2—HE-NL ($n=70$): no lactulose Duration- 6 months	At the end of 14 months HE developed in 19.6% patients in HE-L vs 46.8% in HE-NL group ($p=0.001$)
Bass [6]	Double blind RCT Cirrhotic patients with recurrent HE (at least 2 overt HE episode in past 6 months)	$N=199$ Group 1—rifaximin ($n=140$): 550 mg 2 times/day Group 2—placebo ($n=159$) ~90% patients received lactulose (average daily dose ~ 30 g) Duration 6 months or until therapy was discontinued	First breakthrough HE episode: 22.1% in rifaximin group vs 45.9% in placebo group ($p<0.001$)
Sanyal [99]	Parallel study with study by Bass [6]		CLDQ scores: significantly higher with rifaximin vs placebo ($p<0.05$) Remission maintained: 74.2% with rifaximin vs 50% with placebo
Les [46]	Double blind RCT Cirrhosis with one HE episode in last 2 months	$N=116$ BCAA group ($n=58$):BCAA supplement 30 g white powder MDX group ($n=58$): Maltodextrin (MDX) supplement All patients received standard diet of 35 kcal/kg and protein 0.7 g/kg per day Duration: 56 weeks	Actuarial risk of remaining free of HE:47% in BCAA group vs 34% in MDX group; $p=0.274$ Two neuropsychological test and midarm muscle circumference (MAMC) significantly improved in BCAA group compared to MDX group $p<0.05$
Agrawal [7]	Open label RCT Patients of liver cirrhosis recovered from HE	$N=235$ Group L ($n=80$): lactulose Group P ($n=77$): probiotics Group N ($n=78$): no therapy Lactulose dose 30–60 mL/day in 2 or 3 divided doses Probiotics 112.5 billion viable lyophilized bacteria per capsule Duration 12 months	At the end of study period the proportion of patients with HE were less in the lactulose and probiotic group compared to no therapy group (26.5% vs. 34.4% vs 56.9%, $p=0.001$)
Dhiman [26]	Double blind RCT Patients of Cirrhosis recovered from HE	$N=130$ Probiotic group ($n=66$): VSL#3 sachet, 9×10^{11} bacteria daily Placebo group ($n=64$): corn flour placebo sachet daily Duration 6 month	Breakthrough HE episode: 34.8% in probiotic group vs 51.6% in placebo group (HR 0.65, 95% CI 0.38–1.11; $p=0.12$) Hospitalization due to HE: 19.7% with probiotic vs 42.2% with placebo (HR 0.45, 95% CI 0.23–0.87; $p=0.02$)
Rockey [45]	Double blind RCT Cirrhosis, ≥ 2 episode of HE in last 6 months	$N=178$ GPB group ($n=90$): glycerol phenylbutyrate (GPB) 6 mL twice daily Placebo ($n=88$): Placebo 6 mL twice daily 59 patients were already on rifaximin Duration 16 weeks	Proportion of patients who developed HE: 21% in GPB group vs 36% in placebo group; $p=0.02$ hospitalizations: 13 in GPB group vs 25 in placebo group; $p=0.06$
Bajaj [54]	RCT Cirrhotic patients with recurrent HE	$N=20$ patients on lactulose/rifaximin were randomized (1:1) FMT group—15 FMT capsule Placebo group—placebo capsule	FMT was associated with improved EncephalApp performance ($p=0.020$) and improved duodenal mucosal diversity ($p=0.01$)

RCT randomized controlled trial, *HE* hepatic encephalopathy, *L* lactulose, *NL* no lactulose, *CLDQ* Chronic Liver Disease Questionnaire, *HE* hepatic encephalopathy, *GPB* glycerol phenyl butyrate, *BCAA* branched chain amino acids, *SPSSs* spontaneous portosystemic shunts, *FMT* fecal microbiota transplantation, *HR* hazard ratio

Table 3 Efficacy studies of treatment for the hepatic encephalopathy in special situations

Reference	Design	Dose and duration	Outcome
Cookson [76]	Retrospective case series Cirrhotic post TIPS patients with refractory HE	$N=8$ patients 10 mm self-expandable stent graft and a 5–6 mm diameter balloon expandable stent placed parallel inside the existing TIPS	Clinical improvement in HE observed in 5 (62.5%) and resolution in 4 (50%) patients at median duration of follow up of 137 days
Mukund [16]	Retrospective analysis Cirrhosis with recurrent HE with large portosystemic shunt	Eight session of BRTO with sodium tetradecyl sulfate foam performed in 7 patient	Improvement in HE was seen within 48 h of procedure in 6 of the seven patients (86%) and at the end of 4 months HE was completely resolved in these patients
Laleman [15]	Retrospective cohort study Cirrhotic patients and chronic refractory HE with large spontaneous portosystemic shunts (SPSSs)	$N=37$ patients who underwent embolization (performed using coil, amplatzer plugs or matrix or a combination of these)	On a short-term basis within 100 days after embolization) 59.4% were free of HE ($p<0.001$ vs before embolization) 48.6% of patients remained HE-free over a mean follow-up period of 697 ± 157 days ($p<0.001$ vs before embolization)
Lv [17]	RCT Cirrhotic patients with large SPSS, planed for TIPS	$N=56$ patients were randomized (1:1) TIPS alone—29 TIPS + SPSS embolization—27	The 2 years incidence of HE was significantly lower in TIPS with embolization group (21.2 vs 48.3%, $p=0.043$)

BRTO balloon-occluded retrograde transvenous obliteration, *SPSS* spontaneous portosystemic shunt, *TIPS* trans jugular intrahepatic portosystemic shunts, *RCT* randomized controlled trial, *HE* hepatic encephalopathy)

3. Interventions like embolization of large spontaneous shunts or balloon-occluded retrograde transvenous obliteration (BRTO) of large spontaneous splenorenal shunts decrease portosystemic shunting [15–19].

Drugs used in the management of HE are described in Table 4.

Current drug targets for prophylaxis of HE

Nonabsorbable disaccharides

Nonabsorbable disaccharides like lactulose and lactitol are useful in the management of HE. These agents reduce the ammonia absorption by a purging effect and by changing colonic pH. Lactulose is recommended by the European Association for the Study of the Liver (EASL) for primary and secondary prevention of HE.

In a study which was a randomized controlled trial (RCT), HE recurrence was reduced more with lactulose compared to placebo (19.6 vs 46.8%) as shown in Fig. 1 [5]. Another study evaluated the efficacy of lactulose for the prevention of first episode of HE revealed, lactulose results in MHE reversal and reduced frequency of OHE during the study period (11 vs 28%, $p=0.02$) [20]. Nonabsorbable disaccharides have certain adverse effects like abdominal cramps, abdominal fullness, flatulence and diarrhea which can lead to noncompliance in few patients [21, 22].Therefore dose titration of lactulose to achieve 2–3 stool frequency per day is important. Based on available data, lactulose is effective in the treatment of MHE, OHE and for primary and secondary prophylaxis of HE but side effects like abdominal cramps, flatulence and diarrhea are limitations of long term use.

Antibiotics

Rifaximin is a gastrointestinal tract selective, oral antibiotic which is effective against wide-spectrum organisms like gram-positive, gram-negative aerobic and anaerobic enteric bacteria, has a minimal risk of bacterial resistance and less side effect due to minimum systemic bioavailability [23]. For secondary prophylaxis of HE, a RCT revealed patients on rifaximin had significantly lower first breakthrough HE episodes (22.1 vs 45.9%, $p<0.001$) and first HE related hospital admission (13.6 vs 22.6%, $p=0.01$) compared to placebo with no remarkable difference in the side effects and mortality [6]. Health related quality of life (HRQOL) considerably improved in subjects treated with rifaximin [24]. Prolong (> 24 months) treatment with rifaximin demonstrated reduced hospitalization rate due to HE and other causes, without increasing side effects. Rifaximin results in less adverse effects and reduced hospitalization rate

Table 4 Drugs for the management of hepatic encephalopathy

Drug	Indications	Dosage and administration	Adverse effects	Comments
Non absorbable disaccharides (lactulose and lactitol)	MHE, overt HE and recurrent HE	Oral—lactulose 30–45 mL (20–30 g) two to four times per days to achieve 2–3 soft stools/day Lactitol − 67 to 100 g diluted in 100 mL water represent similar dose Enema—1 to 3 L of a 20 percent solution, if patient unable to take orally	Lactulose can cause crampy abdominal pain, loose motions and flatulence. Lactitol have less adverse effects compared to lactulose	First line drug, cheap, efficacious in the all forms of HE and prevention of recurrence of HE, lactulose is easily available
Rifaximin	Overt HE, recurrent HE, MHE	Oral: 400 mg thrice daily or 550 mg twice daily	No significant adverse effects. Mild nausea and headache	As efficacious as lactulose and better tolerated, Effective as add on therapy to lactulose in recurrent HE, Both the doses are equally effective
BCCA	Overt HE, MHE	Oral and intravenous Dose—10 g/day	No significant adverse effects, Mild nausea, vomiting, diarrhea and headache	Recommended in severely protein-intolerant patients
LOLA	Overt HE, MHE, post TIPS HE	Oral: 9–18 g/day Intravenous—5–40 g/day	No significant side effects. Mild nausea and vomiting	Also efficacious to some extent in post TIPS HE
Probiotics	Overt HE, MHE and recurrent HE	Oral—9×10^{11} CFU /day	No significant adverse effects. Mild nausea, postprandial fullness, flatulence and allergic reaction	Available easily and better tolerated, more data requires to prove efficacy
Metronidazole	HE	Oral: 800–1000 mg/day	Neurotoxicity	Studies are limited, not routinely used
Neomycin	HE	Oral: 4–6 g per day	Nephrotoxicity, ototoxicity and malabsorption	Not routinely used in view of significant adverse effects
FMT	Recurrent HE	Enema, oral capsules	No significant adverse effects	Manipulate gut microbiome, limited studies

MHE minimal hepatic encephalopathy, *HE* hepatic encephalopathy, *BCCA* branched chain amino acids, *LOLA* L-ornithine-L-aspartate, *CFU* colony forming units, *TIPS* transjugular intrahepatic portosystemic shunt, *FMT* fecal microbiota transplantation

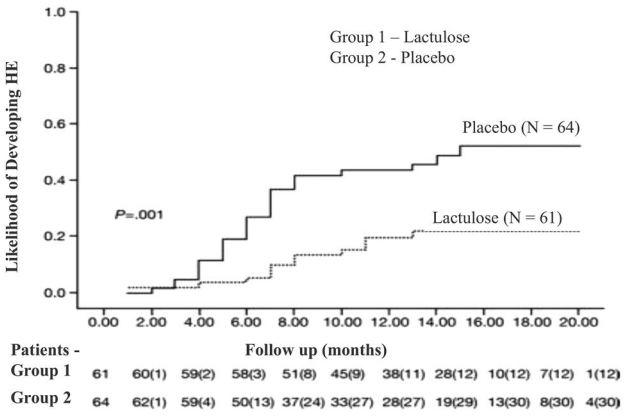

Fig. 1 Likelihood of developing hepatic encephalopathy (HE) in patients receiving lactulose (dotted line) or placebo (continuous line). Figures in parentheses indicate the cumulative number of subjects who developed HE [5]

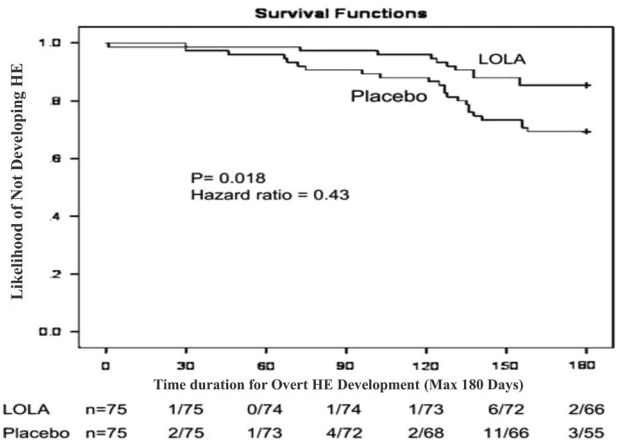

Fig. 2 Likelihood of developing HE in patients receiving probiotics (dotted line) and control group (continuous line) [33]

compared to subjects on lactulose [25, 26]. Effectiveness of earlier rifaximin dose (400 mg three times daily) and recent dose (550 mg twice daily) is similar [27].

A study revealed that rifaximin in the subjects with decompensated cirrhosis remarkably reduced the recurrence of HE compared to controls (31.5 vs 47%, $p=0.03$) [28]. Low dose rifaximin, 400 mg twice a day for 6 months results in significant decrease in the number of patients experiencing episodes of HE [29]. Bacterial resistance to rifaximin is not evaluated yet in the subjects with HE. A study aimed to analyze the bacterial resistance, safety and effectiveness of rifaximin for secondary prevention of HE. In this study, the minimum inhibitory concentration did not change considerably after rifaximin exposure compared with baseline either between the two groups or within the same group [30].

Nitazoxanide has distinct bioavailability in the gut with wide spectrum activity against many anaerobic bacteria and also peripheral and central anti-inflammatory activity. In a RCT, nitazoxanide for 24 weeks was more efficacious than rifaximin in prevention of HE recurrence and decreases serum ammonia, TNF-α, and octopamine levels [31].

There is a lack of data on the preventive effect of rifaximin for initial episode of OHE. Some studies analyzed the efficacy of rifaximin compared to placebo or lactulose in the treatment of MHE; however, these trials did not focus on the prophylaxis of OHE [24, 32]. A study analyzed the efficacy of low-dose rifaximin (400 mg twice daily) for a period of 6 months revealed, rifaximin results in decreased frequency of OHE in subjects without prior history [29].

Addition of rifaximin with lactulose has beneficial effect on patients with recurrent HE who have recurrent episodes of HE despite on lactulose therapy [6]. Thus rifaximin along with lactulose should be considered for preventing the recurrent episodes of HE. With the use of rifaximin as adjunct to lactulose for the prophylaxis of third and further episodes of OHE, cost can be saved from a hospital and healthcare payer's perspective. From a healthcare payer's view, costs raised by adding rifaximin to lactulose is saved due to increased survival with rifaximin causing relatively low drug and liver transplant associated costs [33]. So, rifaximin is effective in both treatment and prophylaxis of HE and is better tolerated than lactulose although cost is an issue, it can be curbed on long term use, both from hospital and patient's perspective.

L-Ornithine L-aspartate

L-ornithine L-aspartate reduces ammonia in HE subjects with distinct mechanism including optimization of liver metabolism pathways for ammonia elimination and direct liver protective effect including the liberation of glutathione and nitric oxide with favorable effect on liver microcirculation. It also reduces sarcopenia in cirrhotics, that leads to increased capacity of skeletal muscles for ammonia elimination [34]. In a double blind RCT, subjects with cirrhosis who had improved from OHE were randomized to get LOLA or placebo for 6 months. HE recurrence was less common in subjects treated with LOLA (12.3 vs 27.7%, $p=0.02$) as shown in Fig. 2, with similar mortality in both the groups (6.8 vs 13.8%, $p=0.18$) [35]. Systemic review with meta-analysis demonstrates that LOLA is efficacious for significant reduction in the risk of progression in MHE subjects to OHE. Both intravenous and oral formulation of LOLA were found efficacious [36]. The published meta-analysis on LOLA has few concerns, first, efficacy of LOLA using modern definition of HE (like covert HE including MHE with grade I HE) has not been established. Second, to establish the efficacy in pre and post TIPS prophylaxis, further large RCTs with sufficient power is required. A recently published meta-analysis revealed that oral LOLA was no more

efficacious as compared to lactulose or rifaximin for the prophylaxis of OHE [37]. The meta-analyses analyzing primary or secondary prophylaxis revealed favorable effect on mortality. The nonabsorbable disaccharides also had favorable effects on the prophylaxis of HE [38]. In spite of all the benefits, RCTs on LOLA endures multiple biases related with improper blinding, pharmaceutical funding, inadequate data and selection bias. The data on the efficacy of LOLA on prophylaxis of a first OHE episode is currently scarce. Another study revealed that subjects treated with LOLA had considerably less OHE episodes in 6 months in comparison to placebo (5 vs. 37.9%, $p=0.016$) [39]. A study compared the efficacy of LOLA, lactulose, probiotics, or no therapy with the primary aim of evaluating MHE reversal, reported on OHE episodes during the study period. In this study one subject in the lactulose arm, two subjects in the probiotic arm, two subjects in the LOLA arm, and four subjects in the no-therapy arm developed OHE ($n=40$ patients in each arm). The low frequency of episodes prohibits sufficient statistical comparison [40]. Therefore, based on available data, LOLA is also effective in the treatment and prophylaxis of HE.

Future or novel drugs and other targets

Probiotics

Alterations of the gut microbiota with non-urease-producing microbes are achieved by probiotics. It results in reduced production and absorption of ammonia because of decreased intraluminal pH. Probiotics also improve nutritional level of intestinal epithelium, resulting in reduced gut permeability, inflammation, and oxidative stress in the hepatocyte leading to raised clearance of ammonia from the liver [41, 42]. In a study, the number of cirrhotics with HE were significantly less in the lactulose and probiotic group in comparison to those with no treatment (26.5% vs 34.4% vs 56.9% $p=0.001$) [7]. Another study revealed a reduction trend in the occurrence of breakthrough HE (34.8 vs 51.6%), decrease in hospital admissions due to HE (19.7 vs 42.2%) and reduced cirrhosis complications (24.2 vs 45.3%) in subjects who received probiotics in comparison to placebo [26].

In a RCT, probiotic therapy leads to considerable improvement in the arterial ammonia level and overt HE developed in 8.8% patients in probiotic group compared to 20.3% in no therapy group as shown in Fig. 3. In cirrhotics with MHE, number needed to treat was 4.2 and absolute risk reduction was 23.8% [43]. Thus, probiotics are efficacious in the management of MHE, HE and prophylaxis of HE along with reduced HE related hospitalizations and cirrhotic complications.

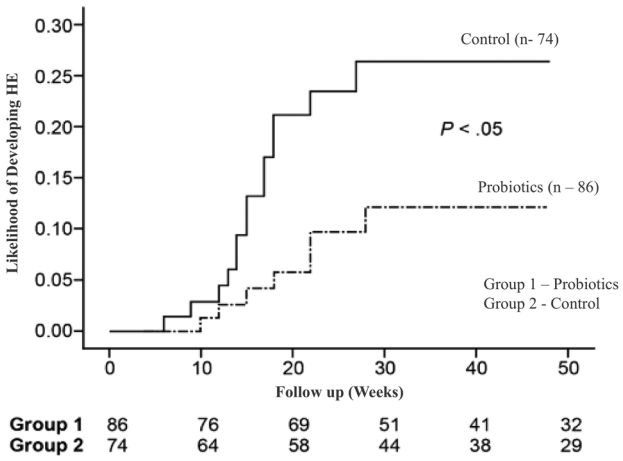

Fig. 3 Kaplan–Meier analysis for recurrence of HE between L-ornithine L-aspartate (LOLA) group and placebo group [35]

Glycerol phenyl butyrate

Glycerol phenylbutyrate decreases ammonia levels by the formation of phenylacetyl glutamine in muscles, which is eliminated in urine [44]. Oral GPB in the dose of 6 mL two times a day, decreased the further episodes of HE (21 vs 36%; $p=0.02$), time to first episode (hazard ratio [HR] = 0.56; $p<0.05$), total episodes (35 vs 57; $p=0.04$), and HE-associated hospital admissions (13 vs 25; $p=0.06$) in comparison to placebo [45].

Branched chain amino acids

In cirrhotics, the level of branched chain amino acids (BCAA) decreases and aromatic amino acids (AAAs) level increases. The BCAAs are a root of glutamate that helps ammonia metabolism in skeletal muscles. In patients with history of prior HE episode, on comparing BCAAs with maltodextrin, no considerable difference in the recurrence of HE was seen, but BCAAs improve MHE and skeletal muscle mass [46]. In patients with insufficient oral intake, BCAAs treatment has been shown to ameliorate symptoms and decrease recurrent episodes of OHE [43]. A meta-analysis including 16 RCT showed, oral BCAA decreased the recurrent episode of OHE, but there was no survival difference [47]. Despite all the favorable effects, RCTs on BCAA encounters bias related with improper blinding of participant and outcome assessment and selection. The BCCA helps in muscle building in all cirrhotic patients with sarcopenia along with favorable effects on HE which led to improvement in the quality of life.

Nutrition

Insufficient nutrition results in sarcopenia, resulting in impaired ammonia metabolism. Current, guidelines advise a daily energy intake of 35–40 kcal/kg bodyweight and a protein intake of 1–1.5 g/kg bodyweight in subjects with decompensated cirrhosis [48]. Dietary counselling includes the addition of snacks in between meals and before sleep to decrease gluconeogenesis and proteolysis of muscle proteins. Feeding of protein from milk, pulses, cereals along with adequate intake of calorie, micronutrients and increased fiber consumption which has a prebiotic effect, reduces gut transit time and rises gut nitrogen clearance [49]. In a study, cirrhotic patients with MHE were randomized to nutritional therapy (30–35 kcal/kg/day, 1–1.5 g vegetable protein/kg/day) or no nutritional therapy. Amelioration of MHE and improvement in HRQOL were significantly higher in nutritional therapy group. Overt HE occurred in 10% of patients in nutritional therapy group vs 21.7% in no nutritional therapy group ($p = 0.04$) [50]. In a double blind RCT, patients with a recent history of HE, were randomized to nutritional therapy and no nutritional therapy for 6 months. There was considerable reduction in the development of OHE (10 vs 36 $p < 0.001$) and HE-associated hospital admissions (8 vs 24, $p < 0.001$) in the nutritional therapy group [51]. Hence, nutritional therapy is effective in the treatment of MHE and prevention of OHE along with improvement in muscle mass in patients with cirrhosis. However, the data on nutritional therapy are limited, more studies are required to prove these results.

Fecal microbial transplant

Fecal microbiota transplantation (FMT) is also an alternative for decrease in HE recurrence. It directly targets the gut microbiota of the subjects with HE by dispensing the donor fecal matter into the gastrointestinal tract. The FMT was used in the form of enema or oral capsules. Many studies have shown that FMT prevents recurrence of HE, enhance cognition and dysbiosis without serious adverse effects in cirrhotic patients [52–54]. The FMT is an emerging therapy for the management of HE, more studies with large sample size are required to prove these evidences.

Albumin

Intravenous albumin infusion (40 g/week) has been shown to significantly lower the probability of grade 3 or 4 OHE and improve overall survival [55]. In the ANSWER trial, a multicenter RCT on 440 cirrhotic patients with diuretic responsive ascites were included. The intervention group received standard care with albumin and control group received standard care only. The results revealed higher survival rate in the albumin group with reduce rate of hospitalization, severe HE, future requirement of therapeutic paracentesis, and renal dysfunction [54]. An open label RCT and the absence of blinding were the major limitations of this study. Another RCT in 2021 on 777 hospitalized cirrhotic patients with the intervention group receiving 20% albumin till discharge compared to standard medical care, found no significant clinical difference between the two groups. This RCT concluded that targeting the albumin level at > 30 g/L is not beneficial when equated to standard care [56]. Still, albumin is a potential newer therapy in the management of HE and preventing other complication of cirrhosis.

AST-120 (Kremezin)

It is a synthetically activated carbon with a broad area and high adsorptive capacity. Because of restricted intestinal absorption, it can trap organic neuro and hepato-toxic substances of < 10 kDa. A phase II multicentric RCT on 41 patients with low-grade HE with the use of AST- 120 or lactulose for 4 weeks, revealed no significant difference in primary (change in West Haven scale) and secondary (change in hepatic encephalopathy scoring algorithm, ammonia, bile acid, clinical laboratory test, and decrease in itching) outcomes [57]. However, diarrhea and flatulence were less common in patients with AST-120. The ASTUTE, a multicentric, double-blind, RCT on 148 cirrhotic patients, comparing AST-120 and placebo found no significant difference in the neurocognitive status or HE episodes between the two groups at the end of 8 weeks. However, improvement in ammonia level was seen in the intervention group independent of neurocognitive changes [58].

Acetyl-L-carnitine

Carnitine is an essential nutrient which plays an important role in the transfer of fatty acids in the hepatocytes. In patients of liver cirrhosis, reduced metabolism of carnitine is observed. Acetyl-L-carnitine (ALC) is an ester of carnitine, produced within mitochondria and peroxisomes in the liver, brain, and kidney by the enzyme acetyl-L-carnitine transferase. The role of ALC in the management of HE is hypothesized to be related to the decrease in serum ammonia level by increasing ureagenesis. In addition, it decreases neuronal toxicity in patients with HE [59]. An RCT showed that ALC leads to reduction of ammonia level along with improvement in energy level, emotional health, cognitive and neurological functions [60]. A recently published Cochrane review showed no improvement in clinical outcomes or decrease ammonia level with the help of ALC [61]. The adverse effects of ALC were not described, making the potential harm of the drug unknown.

Flumazenil

Flumazenil is a benzodiazepine antagonist with the potential to bind with g-aminobutyric acid (GABA) receptors [62]. Few studies revealed the GABA-A upregulation and augmented GABAergic tone in HE patients [63]. Recently a Cochrane review on 12 RCTs revealed significant improvement in HE, with no difference in mortality. Short duration of follow-up, risk of bias, cross-over design, and limited conclusions were the major limitations of the included trials [64].

Polyethylene glycol

Polyethylene glycol (PEG) is a purgative agent which reduces intestinal transient time for ammonia absorption. The mechanism of action of PEG and lactulose is same but unlike lactulose, PEG does not have a carbohydrate group and is not metabolized by the colonic bacteria [65]. The first RCT, on 50 cirrhotic patients with HE revealed significant improvement in HE outcomes in a shorter median time. However, subjects with PEG experienced more episodes of diarrhea while bloating was more common in the lactulose group [66]. Another RCT evaluated the efficacy of lactulose and PEG combination therapy in 40 cirrhotic patients with HE compared to lactulose monotherapy. It revealed significant improvement in hepatic encephalopathy scoring algorithm (HESA) score within 24 h and shorter hospitalization in combination group [67]. However, non-blinding, small sample size was the major limitation of the trials.

Naloxone

Naloxone is an opioid receptor antagonist with a higher affinity for the Mu opioids receptor. In both acute and chronic liver failure patients, plasma opioid peptides concentration was found to be elevated, which in turn can modulate the effect of various neurotransmitters [68]. A meta-analysis on 17 RCTs revealed a significant improvement in HE [69]. Limited study design details, randomization technique, and blinding of outcome assessment were the major limitations of the included studies.

Anti-inflammatory drugs

Some preliminary studies suggest inflammation as a potential therapeutic target for the management of HE [10, 11]. The available drugs like lactulose, rifaximin, probiotics and the molecular adsorbent recirculating system (MARS), have been found to regulate the inflammatory response and reduce TNF-α, IL-1β and IL-6 which help to improve and delay the progression of HE [12, 13]. Several anti-inflammatory drugs like ibuprofen, minocycline and anti TNF agents have been studied in the management of HE [70]. Further studies are required to prove the efficacy of these drugs.

Interventions and other future targets

Embolization of large spontaneous shunt and balloon-occluded retrograde transvenous obliteration

Spontaneous portosystemic shunts, including splenorenal shunts are associated with recurrent HE, deteriorating liver functions and raised number of death in cirrhotic patients [18, 19]. In patients with recurrent HE, embolization of SPSS, prevented recurrence of HE in 59.4% patients ($p < 0.001$) [15]. Embolization of SPSS, prevented recurrent HE for a duration of 2 years in comparison to standard medical treatment (39.9 vs. 79.9%; $p = 0.02$) with similar survival rate at the end of 2 years (64.7 vs. 53.4%; $p = 0.98$) [17]. In subjects of large spontaneous splenorenal shunt with recurrent HE, management with BRTO has shown significant improvement in HE in 86% subjects with reduced arterial ammonia levels [16]. So, obliteration of splenorenal shunts may be useful for prophylaxis of HE recurrence.

Post TIPS

Hepatic encephalopathy is more frequently observed after TIPS, especially during the first month. After TIPS, 3–7% of patients develop refractory HE [71]. Majority of patients improved with standard medical treatment [71, 72]. The incidence of HE in 1 month and the number of episodes of severe HE (grade III–IV) were comparable with lactitol, rifaximin and no therapy in a RCT on post TIPS patients [25]. In a double blind RCT, an episode of OHE occurred in 34% in rifaximin group and 53% in the control group during post TIPS periods, odds ratio 0.48 (95% CI 0.27–0.87). Incidence of adverse effects and transplant free survival were considerably different in the two groups [73]. Subject selection for TIPS needs careful examination of risk factors for HE. Prior history of HE has been considered as relative contraindication for TIPS placement [74]. Other mechanical features like stent size of TIPS, decrease of portosystemic pressure gradient during the method and use of adjuvant variceal coil embolization may yield a role [71–75]. Recurrence of HE in post TIPS patients may be prevented by decreasing the diameter of stent or by blocking the shunt. However, this might increase problems associated to portal hypertension like variceal bleed and refractory ascites [77]. When endovascular treatment stop working, investigate for accompanying SPSS leading to HE and if identified these shunts should be embolized. The 2-year incidence of OHE was considerably less in the TIPS with SPSS embolization group in

comparison to TIPS group (21.2 vs 48.3%; $p = 0.043$) [78]. Simultaneous large SPSS embolization should therefore be thought of for the prevention of post TIPS HE. The incidence of HE was more in patients undergoing TIPS (51.7 vs 22%) compared to TIPS with spontaneous portosystemic shunts embolization [79]. Sometimes all these treatment modalities fail and patient may require liver transplantation for recurrent HE [80].

Artificial liver support system

The primary aim of artificial and bioartificial liver support systems is to bridge the liver failure patients to transplantation or recovery. The MARS is one of the artificial liver support systems and has been extensively studied in patients with acute liver failure. The use of extracorporeal albumin dialysis by the MARS has been shown to remove protein-bound substances including toxins and decrease the plasma concentrations of bilirubin, ammonium, and creatinine in patients with acute on chronic liver failure. In a RCT on 70 patients, the use of albumin dialysis was associated with an earlier and more frequent improvement of HE [81]. The RELIEF trial showed the use of MARS results in a non-significant improvement in HE compared to standard medical therapy [82].

Hospital pharmacists and telemedicine

Including pharmacists in the hospital discharge proceeding has been shown to have favorable impact on the results, including hospital re-admissions [83]. Involvement of telemedicine and pharmacists in managing cirrhotic patients with HE receiving rifaximin enhanced adherence and results at the end of 6 months [25, 52, 84].

Telemedicine can improve care of cirrhotic patients with HE by monitoring of medicine adherence, sodium consumption, body weight, cognition, orientation, providing alerts associated to altered mental status and preventing HE related hospital admissions [84, 85].

Education

The education of subjects and their attendants which includes the therapeutic benefits and adverse effects of drugs, strict compliance, early symptoms, and sign of OHE recurrence has been showed to enhance patients adherence to preventive therapy and decrease re-admission due to HE [51]. In a RCT, 15 min education session decreased the risk of OHE-related hospitalizations [86]. In addition, physical exercise may be an emerging target to prevent HE, as sarcopenia is an established risk factor for the development of HE [87].

Treatment of underlying cause of cirrhosis may decrease or regress the progression of disease and avoidance of precipitating factors may be useful for primary prophylaxis of HE, like alcohol abstention in alcohol misuse, antiviral therapy in virus related cirrhosis and adequate nutrition in malnourished patients [28].

Sustained viral response (SVR) to direct acting antivirals (DAA) treatment have been shown to decrease the risk of incidence of HE in patients of HCV related liver cirrhosis. Elimination of HCV infection with DAA was associated with a 59% decrease in the chances of developing HE. The incidence of HE was less in subjects who achieved SVR in comparison to who did not achieve it [88]. The interactive algorithm for the management of HE is described in Fig. 4.

Specific situations

Variceal bleeding

Variceal bleeding is a well-known precipitating element for the occurrence of OHE because of considerable increase in serum ammonia level [89]. So, a quick removal of blood from the gut is advised to prevent the OHE occurrence in subjects with variceal bleeding [78, 88, 89]. Lactulose therapy in subjects with liver cirrhosis with upper gastrointestinal bleed decreases the development of HE [79, 90–92]. In another study, lactulose therapy for 5 days was not effective for the prevention of HE in subjects of liver cirrhosis with upper gastrointestinal bleed [93]. Lactulose and rifaximin were equally efficacious in the prophylaxis of HE subsequent to upper gastrointestinal bleed in cirrhotic patients [94]. The LOLA is also efficacious for secondary (RR 0.389, 95%, CI 0.174–0.870, $p < 0.002$) and primary prophylaxis (RR 0.42, 95% CI 0.16–0.98 $p < 0.003$) of OHE after acute variceal bleed and for prevention of OHE after TIPS (RR: 0.30, 95% CI 0.03–2.66) in comparison to no treatment [38]. Therefore lactulose, rifaximin and LOLA are effective in prevention and treatment of HE developed after variceal bleeding.

Minimal hepatic encephalopathy

Patients with MHE have diminished HRQOL, poor driving ability and increase burden on caregivers [95]. Once the subject suffers of MHE, there is an increased risk of progression to OHE [96]. In view of practical limitations of testing every cirrhotic for MHE using neuropsychometry and neurophysiological tests, it may be beneficial to think about prophylactic therapy for HE in cirrhotics which will prevent the development of MHE or OHE [25, 94, 97, 98].

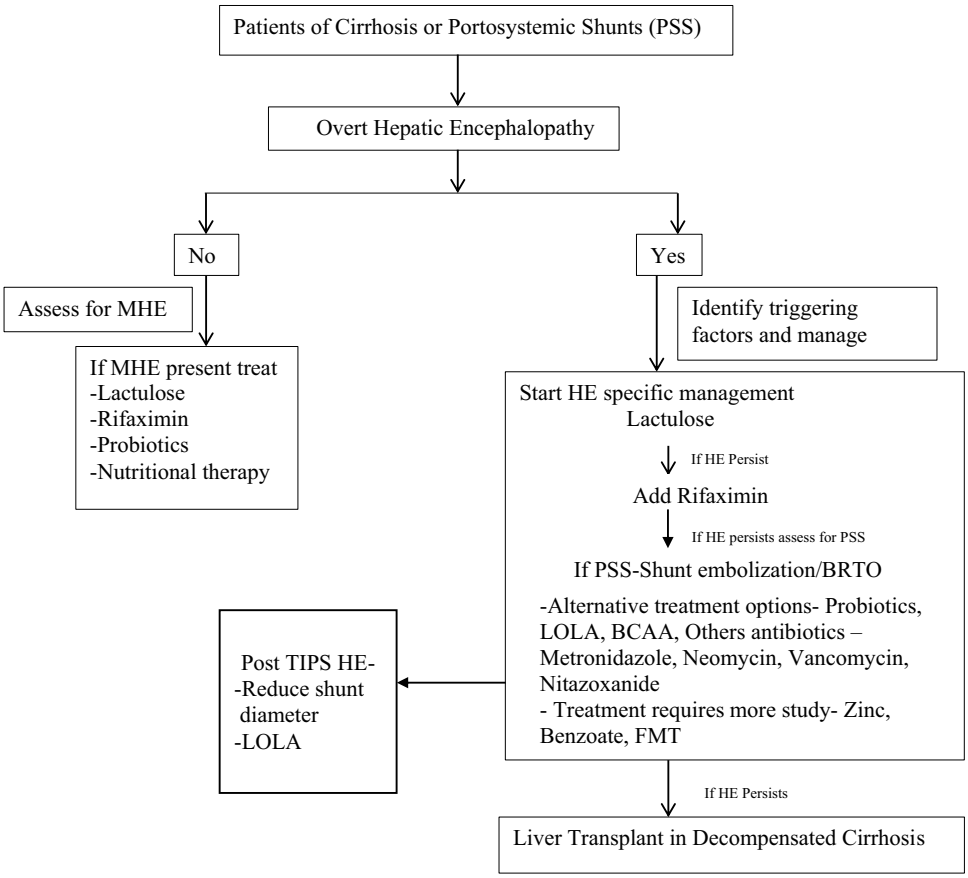

Fig. 4 Management algorithm for hepatic encephalopathy. *PSS* portosystemic shunts, *HE* hepatic encephalopathy, *MHE* minimal hepatic encephalopathy, *BRTO* balloon occluded retrograde transvenous obliteration, *LOLA* L-ornithine L-aspartate, *BCCA* branch-chain amino acids, *FMT* fecal microbiota transplantation, *TIPS* transjugular intrahepatic portosystemic shunt

Conclusion

Preventive measures for first and further episodes of HE should be taken in each subject as each episode of HE is related to raised healthcare cost, poor prognosis and fatality. Early detection and rectification of precipitating factors is crucial in the treatment of HE. The first line treatment is still lactulose which is efficacious in MHE, OHE and recurrent HE. Rifaximin is equally efficacious to lactulose in the treatment of HE and is better tolerated. The BCAA are beneficial in protein intolerant subjects. Probiotics and LOLA are also useful in treating HE. Combination of rifaximin and lactulose is effective in the treatment of overt and recurrent HE. Large PSSs embolization and liver transplantation are effective in certain groups of patients. Nutritional therapy, FMT, albumin, AST-120, ALC, flumazenil, PEG, glycerol phenyl-butyrate and naloxone are emerging therapies for HE but the evidences are limited, more data are required to prove their efficacy.

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