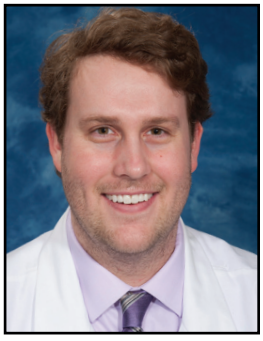
Michael Babich MD, Series Editor

Hepatic Encephalopathy Treatment: Beyond Lactulose and Rifaximin



Vincent Pronesti

Michael Babich

Hepatic encephalopathy (HE) is a devastating consequence of cirrhosis, acute liver failure, or portal hypertension that results in potentially debilitating cognitive impairment that affects patients and their caregivers. HE burdens both the patient and caregivers with substantial physical, emotional, and monetary costs, as well as health care systems with frequent hospitalizations. Understanding of the pathogenesis is limited, and this limited understanding has led to the approval of few effective treatment modalities. Current standard of care treatments include non-absorbable disaccharides (NADs) and rifaximin. Multiple other treatment modalities are gaining support as more data becomes available. Mechanisms of action for these investigational therapies include altering the gut microbiome therefore reducing bacterial production of ammonia, increasing the availability of amino acids in the body, stimulating urea synthesis, decreasing inhibitory neurotransmission, and increasing elimination of ammonia. This article discusses pertinent recent literature regarding development of these newer, non-traditional therapies.

INTRODUCTION

Hepatic encephalopathy (HE) is a frequent complication of liver disease that affects patient morbidity and mortality and quality of life, often resulting in increased caregiver burden. Overt HE will manifest in 30-40% of cirrhotic patients during their lifetimes.[1] Patients with cirrhosis and HE have a 2-fold increase rate of mortality over one year compared to cirrhotic patients without HE. It is also more costly to the health care system, as well as to families paying home caregivers, than other manifestations of cirrhosis, with 110,000 hospitalizations occurring from 2005-2009. Family member caregivers are often negatively affected given the significant time burden, as well as the detrimental emotional effects. The pathogenesis of HE is complex and poorly understood, with many studies being underpowered or containing design flaws that make further elucidation of the etiology difficult.[1] The presentation of HE is also varied and non-specific, making diagnosis and proper classification challenging. Currently, HE is classified by type of underlying disease, time course, severity of manifestations, and precipitating factors.[1] Due

Vincent Pronesti, DO[1] Michael Babich, MD[2] [1]GI Fellow, Allegheny General Hospital. [2]GI Fellowship Program Director, Allegheny General Hospital, Pittsburgh, PA

to the unclear underlying pathogenesis and wide spectrum of presentation, data has been slow to emerge regarding potential treatment options beyond the standard of care. Current approved therapies focus on decreasing serum ammonia levels by reducing gut ammonia formation and absorption, but newer emerging therapies have been considered based on increased understanding of HE pathogenesis. These therapies focus on reduction of ammonia through decreased absorption or increased elimination, replacing anabolic constituents such as amino acids that are decreased in cirrhotic patients with HE, altering the gut microbiome through various methods, or by decreasing the end result of inhibitory neurotransmission. This article is a systematic review and analysis of the most recent and pertinent literature that support or refute the use of these novel therapies in treating HE.

I. Non-Absorbable Disaccharides

Lactulose

Non-absorbable disaccharides (NADs), such as lactulose (beta-galactosidofructose) and lactitol (beta-galactosidosorbitol), have been mainstays of treatment of HE since first described by Johannes Bircher in 1966.[2] NADs reduce the effect of ammonia in induction of hepatic encephalopathy through multiple mechanisms. NADs are fermented in the colon, increasing intraluminal osmolality and reducing pH. Reducing the pH prevents the conversion of ammonium to ammonia. The increase in intraluminal osmolality results in a cathartic effect in the colon. It is also suspected that NADs beneficially affect the colonic microbiota.

A Cochrane review by Gluud et al., published in 2016 included 38 randomized controlled trials (RCTs) that investigated treatment of hepatic encephalopathy using NADs.[2] There was a reduction in mortality in patients presenting with overt HE (RR=0.36, 95% CI 0.14-0.94, NNT=20) but not with minimal HE. Minimal HE was defined as West Haven Criteria grade 1 which can manifest as trivial lack of awareness, change in sleep patterns, and lethargy. There were no differences in effect between lactulose and lactitol. Unfortunately, none of the included RCTs provided details on possible encephalopathy-precipitating factors which may impact the effect of NADs. Adverse events including liver failure, spontaneous bacterial peritonitis, hepatorenal syndrome, variceal bleeding were reduced as a whole with (RR=0.42), 95% CI 0.26-0.69, NNT=50). The direct cost/benefits of NAD treatment were not examined in the individual trials but these substances were felt to be cost-effective. Lactulose is inexpensive and any reduction in hospitalization duration or occurrence would reduce costs associated with HE. An RCT investigated the use of prophylactic lactulose in patients with cirrhosis who had never had an episode of overt HE. The treatment group was given lactulose while the control group was not. The investigators found that lactulose improved minimal hepatic encephalopathy in 66% of patients when measured by psychometry, figure connection test, digital symbol test, serial dot test, line tracing test, and critical flicker frequency testing at inclusion and at 3 months.[3] Despite this finding, AASLD guidelines on hepatic encephalopathy do not recommend primary prophylaxis for prevention of overt HE except "in patients with cirrhosis and a known high risk to develop HE".[1] Recommended dosing is 25mL of lactulose syrup every 1-2 hours until at least two soft or loose bowel movements per day are produced, with continued maintenance of dosing to maintain two to three loose bowel movements per day.[1] This treatment is FDA-approved. Use of lactulose can be limited in a clinical setting, as overuse can lead to dehydration, hypernatremia, perianal skin irritation, and aspiration. Underdosing of lactulose can also lead to breakthrough HE episodes.

II. Antibiotics

Rifaximin

Rifaximin is an oral broad-spectrum antibiotic with very low bioavailability, and antibacterial activity primarily within the colon.[4] It acts on gram-positive and gram-negative aerobic and anaerobic bacteria and modifies the gut microbiome. It is suspected that subtle changes in the microbiome composition, in regards to *Lactobacillus, Streptococcus,* and *Veillonella,* may affect ammonia production and endotoxin release.[4] A favorable microbiome is also suspected to lower the proinflammatory state of the liver by increasing intestinal epithelial homeostasis.[4] A systematic review by Kimer et

al. from 2014 analyzed 19 RCTs, including a total 1370 patients, and found that rifaximin had a beneficial effect on secondary prevention of HE with increased rates of full resolution RR 1.32 (95% CI 1.06-1.65) when compared to control groups including placebo, other antibiotics such as neomycin, and other disaccharides. This full resolution was not significantly different in a subgroup of patients who had undergone TIPS when compared to no treatment (RR 1.27 and 95% CI 1.00-1.53).[5] Rifaximin also increased the proportion of patients who recovered from HE (RR 0.59 and 95% CI 0.46-0.76) and reduced mortality (RR 0.68 and 95% CI 0.48-0.97).[5] The included RCTs had heterogeneity in how they defined recovery from HE. Although the included studies showed no clear benefit of rifaximin after TIPS, the number of patients was small and it was difficult to make definitive conclusions. Multiple studies have shown the effectiveness of adding rifaximin to lactulose for prevention of recurrent HE. Another single-center, retrospective cohort study investigated HE recurrence with rifaximin 600mg BID plus lactulose versus lactulose alone with median follow up 18 months. The rate of HE recurrence was 15.9% for the rifaximin plus lactulose group versus 33.3% for the lactulose monotherapy group.[6] The current AASLD guidelines recommend rifaximin as an effective add-on therapy to lactulose for prevention of an overt HE recurrence.[1] Rifaximin is also an FDA-approved treatment.

Neomycin

Neomycin has been widely used for treatment of HE. It acts to inhibit glutaminase which in turn, decreases ammonia synthesis from glutamine in the intestine.[7] Although it has been widely used from an historical perspective, data supporting its efficacy in comparison to current first-line therapies is lacking. The most recent study from Strauss et al. in 1992 compared 20 patients treated with 6g neomycin qd versus 19 with placebo, and found that the time elapsed between the initiation of the medication and regression to grade zero HE was 39.11+/-23.04 hours for neomycin versus 49.47+/-21.92 for the placebo group, and this did not reach statistical significance.[8] Orlandi et al. compared neomycin to lactulose in an RCT with 173 total patients. Neomycin 1g qid with 30-60g magnesium sulfate purgation were given orally to patients with grade I HE. Neomycin 2g qid with 30-60g magnesium sulfate were given to patients with grade 2 or 3 HE. The lactulose group was treated with 10-35ml of 50% lactulose syrup orally TID. Both groups were treated for 14 days and there was no significant difference between the treatments in regards to improvement in mental status, asterixis score, or ammonia levels. A limitation of this study was that the grading of HE was not standardized compared to more modern trials.[9] Long-term use of neomycin can result in neuro and nephrotoxicity. Use after anesthesia is also associated with neuromuscular blockade with respiratory paralysis. AASLD guidelines state that neomycin has its advocates and can be considered as an alternative choice to treat overt HE.[1] Neomycin is FDA-approved for the treatment of overt HE.

Metronidazole

Metronidazole has been studied as a potential treatment for overt HE. The mechanism of action involves metronidazole's activity against anaerobic gut flora that have urease activity and convert urea to ammonia, thereby reducing serum ammonia levels.[7] In a study from 1982, 11 patients with mild to moderate HE and 7 with severe HE were treated with neomycin 1g qd or metronidazole 0.2g qid for one week, with assessment of mental status scores at end of treatment.[10] The patients were stratified using the West Haven Criteria but the study does not state what constitutes mild, moderate, or severe manifestations. Both the mild/moderate and severe HE groups showed improvement in mental status scores per West Haven Criteria and decrease in asterixis with both drugs. Mean arterial ammonia levels before and after treatment did not show a significant difference. The authors concluded that metronidazole may be just as effective as neomycin in treating overt HE.[10] Long-term use has been limited by concerns of neurotoxicity, including dose-dependent peripheral neuropathy and ototoxicity, and nephrotoxicity.[11] An open-label study by Mekky, et al., in 2018 included 120 patients randomized to rifaximin or metronidazole therapy for treatment of an acute episode of overt HE.[12] The number of patients who showed clinical improvement defined by any favorable change

in the West Haven Criteria was not statistically different between treatment groups (p=0.412) and hospitalization duration was comparable with 4.2+/-2.1 days versus 3.9+/-1.7 days for the metronidazole and rifaximin groups, respectively. This data was obtained at the end of the treatment duration. There was no significant difference in ammonia levels from baseline in either treatment arm (160.77+/-185.mcg/dL versus 207.95+/-218.mcg/dL with p=0.664 and 0.974) in the metronidazole and rifaximin groups, respectively. The authors concluded that these therapies were similar in efficacy.[12] Lactulose was not compared in this study. AASLD guidelines note that the data is not strong enough to warrant use of metronidazole as maintenance therapy over rifaximin, given the potential for side effects, but that it is an alternative option for the treatment of overt HE.[1] Metronidazole is not FDA-approved for treatment of HE.

Vancomycin

In addition to the well-established use of vancomycin to treat Gram-positive bacteria, it also reduces the burden of Gram-negative anaerobic rods in the stool, which in turn decreases the amount of urease available to produce ammonia.[7] The mechanism of action is similar to metronidazole in this regard. The data on vancomycin's role in HE treatment is sparse. Tarao et al. published a double blind crossover trial in which 12 patients underwent a two week course of lactulose with titration to 2-4 bowel movements per day and then all were given vancomycin 2g qd for 8 weeks, after which 6 patients discontinued vancomycin and started lactulose while the other 6 were continued on vancomycin for another 8 weeks.[13] The groups then switched medications for another 8 weeks. After this, mental status was assessed using the West Haven Criteria. The grade of HE went from 2 to 0 in vancomycin treated patients with p<0.001 and resolution of HE occurred more quickly with vancomycin than with lactulose. This study was limited by the small number of participants and no clear delineation of grade of improvement with lactulose. There is very little published data on the use of vancomycin and for this reason it is not widely used to treat HE. The AASLD guidelines do not mention vancomycin as a treatment for HE.[1] It is not FDA-approved for this indication.

III. Alternative Therapies

Branched Chain Amino Acids

Branched-chain amino acids (BCAAs) have been investigated as a potential treatment for hepatic encephalopathy, but data is very limited and there are no strong head to head trials. Cirrhotic patients have a general deficiency of circulating amino acids compared to healthy controls as a result of nutritional derangements, and have excess muscle catabolism. This has been documented in prior studies. Skeletal muscle plays an important role in serum ammonia reduction. BCAAs have been postulated to reduce malnutrition and consequent reduction in muscle mass, thereby improving ammonia metabolism.[14] One Cochrane review identified 16 RCTs with 827 participants with cirrhosis treated with BCAAs vs other interventions including no intervention, NADs, antibiotics, or diet. There was no difference in mortality between the BCAA intervention group and the other interventions treated as a group (RR=0.88, 95% CI 0.69-1.11).[14] CAAs were associated with a beneficial effect on HE compared to controls consisting of placebo, diets, lactulose, or neomycin (RR 0.73, 95% CI 0.61-0.88), and on subgroup analysis the benefit was associated with oral but not intravenous (IV) BCAA (oral RR 0.67, 95% CI 0.52-0.88 versus IV RR 0.81, 95% CI 0.61-1.08). The specific beneficial effect was heterogeneous between the trials and reflected the contemporary grading at the time of data publishing, but the West Haven Criteria was predominantly used. The lack of specified benefits could be considered a weakness of this analysis. The benefit was only noted when excluding trials with a lactulose or neomycin control group. AASLD guidelines recommend oral BCAAs as an alternative or additional agent to treat patients who are nonresponsive to conventional therapy.[1] The dosing of BCAA is highly variable and is based on patient weight.

L-ornithine L-aspartate

L-ornithine L-aspartate (LOLA) acts to enhance ammonia detoxification by stimulating urea synthesis in periportal hepatocytes.[15] Ammonia removal by skeletal muscle is also stimulated by LOLA via promotion of ammonia incorporation

(continued on page 25)

(continued from page 17)

with glutamate to form glutamine.[15] One systematic review of LOLA's role in HE treatment included 8 RCTs with 646 patients with cirrhosis and compared LOLA to placebo, lactulose, or probiotics. It demonstrated LOLA was more effective than placebo and equally as effective as lactulose or probiotics for improvement of overt HE and minimal HE.[16] A systematic review and meta-analysis of 15 RCTs with 1023 patients showed benefit of LOLA in acute or chronic episodes of HE but not in minimal HE when compared with placebo, but the body of evidence was small.[17] A subsequent review and meta-analysis pooled data from nine trials assessing the effects of LOLA on mental state improvement, and showed significant benefit with improvement occurring more often using the West Haven criteria (RR=1.36 and 95% CI 1.10-1.69) and by psychometric testing (RR=2.15 and 95% CI 1.48-3.14).[18] A head to head trial by Poo et al. comparing LOLA to lactulose has shown that LOLA is at least equivalent to lactulose in lowering serum ammonia but provided greater improvement in mental state and number connection test scores.[19] There is criticism regarding these studies as they have not used the modern definition of covert HE, instead using minimal HE. LOLA has also not been studied in patients who have undergone a TIPS procedure. Although LOLA is not available in the US, AASLD guidelines suggest IV LOLA can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy.[1] It is not FDA-approved.

Albumin

In cirrhosis, oxidative stress, inflammation, and the susceptibility to bacterial infection can play a role in decompensation and the development of HE. For this reason, substances that reduce oxidative stress and inflammation may have a beneficial effect. Albumin has been shown to reduce oxidative stress and vasodilation and increase oncotic pressure. Published studies, however, have shown inconsistent benefit from the use of IV albumin. A meta-analysis recently investigated the role of albumin in the prevention of HE.[20] In this meta-analysis, 6 studies with 889 patients suggested that, while albumin infusion may reduce risk of overt HE in cirrhosis, the difference was not statistically significant (p value=0.07) when compared to a control without albumin infusion. Sharma et al. investigated albumin plus lactulose versus lactulose alone with the primary endpoint being complete reversal of HE.[21] In this RCT, 120 patients were randomized evenly to lactulose plus albumin (1.5g/kg/day) or standard therapy with lactulose. 75% of patients in the combination group versus 53.3% of the patients in the monotherapy group had complete reversal of HE (p=0.03). Mortality was also lower (18.3% versus 31.6%, respectively). There were also significant decreases in arterial ammonia, IL-6, IL-18, TNF-alpha, and endotoxins, with greater decreases in the combination group. A recently published study in 2021 by China, et al. randomized decompensated, hospitalized cirrhotic patients with a serum albumin level of less than 30g/L to receive either a targeted 20% albumin solution with median 200g albumin per patient for up to 14 days or until discharge, or standard care with median 20g albumin per patient.[22] Primary endpoints were new infection, kidney dysfunction, or death between 3 and 15 days after initiation of treatment. 777 patients underwent randomization. The primary end points did not show significant difference between the groups and, in analyzing supplementary materials, rates of encephalopathy were not appreciably different (OR=0.91, CI 95% 0.44 to 1.86). Given these disparate findings of efficacy, the AASLD guidelines do not recommend albumin infusions for the purposes of HE prevention or treatment.[1] This may change given new data and updated guidelines.

AST-120

AST-120 is a carbon microsphere adsorbent which was initially approved in Japan in 1991 in order to delay the initiation of dialysis in uremic patients.[23] AST-120 has been shown to reduce oxidative stress and arterial ammonia in rat models by binding to ammonia in the lumen of the gastrointestinal tract and allowing it to be passed from the GI tract.[24] The ASTUTE trial by Bajaj et al. examined the effect of AST-120 on covert HE.[25] This was a multi-center, double-blind, randomized, placebo-controlled trial with cirrhosis patients with MELD less than or equal to 25 and covert HE. Covert HE was defined by a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score below

the 10th percentile, or less than or equal to grade 1 HE defined by the West-Haven criteria. The patients were randomized to 12g, 6g, or placebo daily for 8 weeks. RBANS testing was performed at screening, baseline, 4 weeks, and 8 weeks. 148 patients were enrolled, with primary endpoint being change in the RBANS criteria. There was no change noted at weeks 4 and 8, with a strong learning effect between screening and pre-randomization which confounded results. Venous ammonia levels were decreased from baseline in treatment groups but increased in placebo groups. Due to the lack of robust results, more research is felt to be needed and the AASLD guidelines from 2014 do not recommend AST-120 as a treatment for HE.[1]

Acetyl-L-carnitine

It is hypothesized that acetyl-L-carnitine may benefit HE by increasing urea genesis and decreasing blood and brain ammonia.[26] It also is hypothesized that acetyl-L-carnitine facilitates uptake of acetyl-coenzyme A in brain mitochondria which ultimately stimulates protein synthesis and prevents neuronal death. In 2019 a Cochrane review of five studies investigating this treatment and its role in treating HE was performed.[27] It included 5 Italian studies with a total of 398 patients. No trial in the review reported on rates of all-cause mortality or serious adverse events. Certainty of estimates regarding the effect on quality of life and mental/physical fatigue was low. There was very low quality evidence that blood ammonia levels were reduced but HE was not graded according to a standardized criteria. These studies were felt to be underpowered, with a high risk of bias. More robust studies are needed to validate the use of acetyl-L-carnitine in HE. The AASLD guidelines of 2014 do not recommend the use of acetyl-L-carnitine given paucity of data.[1]

Glycerol Phenylbutyrate

Glycerol phenylbutyrate (GPB) is a tasteless liquid compound that removes nitrogen in the form of urinary phenylacetylglutamine via an alternative pathway for ammonia waste. It is termed an ammonia scavenger. It has primarily been used to treat inherited disorders of hyperammonemia.[28] A multi-center, randomized, placebo-controlled phase II trial to assess the ability of GPB, administered 6mL BID for 16 weeks, to decrease the incidence of HE events in cirrhotic patients who had at least two HE episodes greater than or equal to West Haven grade 2 within the past 6 months.[28] 178 patients were enrolled in total. In the intention to treat groups, 36% of patients taking placebo had an HE event versus 21% in the GPB group ($p<0.05$). Time to first event was longer (HR=0.56, $p<0.05$), total events were fewer (35 versus 57, $p=0.04$), and HE hospitalizations were fewer (13 versus 25, $p=0.06$) in the GPB treatment arm, compared to placebo groups. Plasma ammonia levels were lower in patients on GPB. Of note, patients taking rifaximin were eligible for enrollment if they had been on a stable dose for at least 1 month and had a qualifying HE event while taking lactulose. The results were controlled for the use of rifaximin. A limitation of this study is the low number of enrolled patients, and larger RCTs would be needed in the future to validate these results. The AASLD guidelines do not specify using GPB but are awaiting further clinical studies for an official recommendation.[1]

Flumazenil

In HE, the balance of neurotransmission is predominantly inhibitory due to the effect of hyperammonemia.[29] HE patients are considered to have increased activity of GABA, which is the main inhibitory neurotransmitter in the brain, and may be amenable to GABA/benzodiazepine antagonism. Flumazenil competitively binds to benzodiazepine receptor sites and may modulate inhibitory neurotransmission in this manner.[29] Goh et al. conducted a Cochrane Review in 2017 which included 10 RCTs and 842 participants with an acute episode of overt HE.[30] All RCTs compared IV flumazenil with placebo, with daily dose of flumazenil ranging from 0.2mg to 6.5mg, with total dose between 0.2mg and 19.5mg, and with duration of treatment ranging from 10 minutes to 72 hours. Flumazenil was associated with a beneficial effect on HE (RR=0.75, 95% CI 0.71-0.80). The beneficial effects were heterogeneous among the studies with improvement noted on EEG, subjective alertness, Number Connection Test, or Simple Reaction Time test. The benefit on HE was felt to be short-term, yet there were few

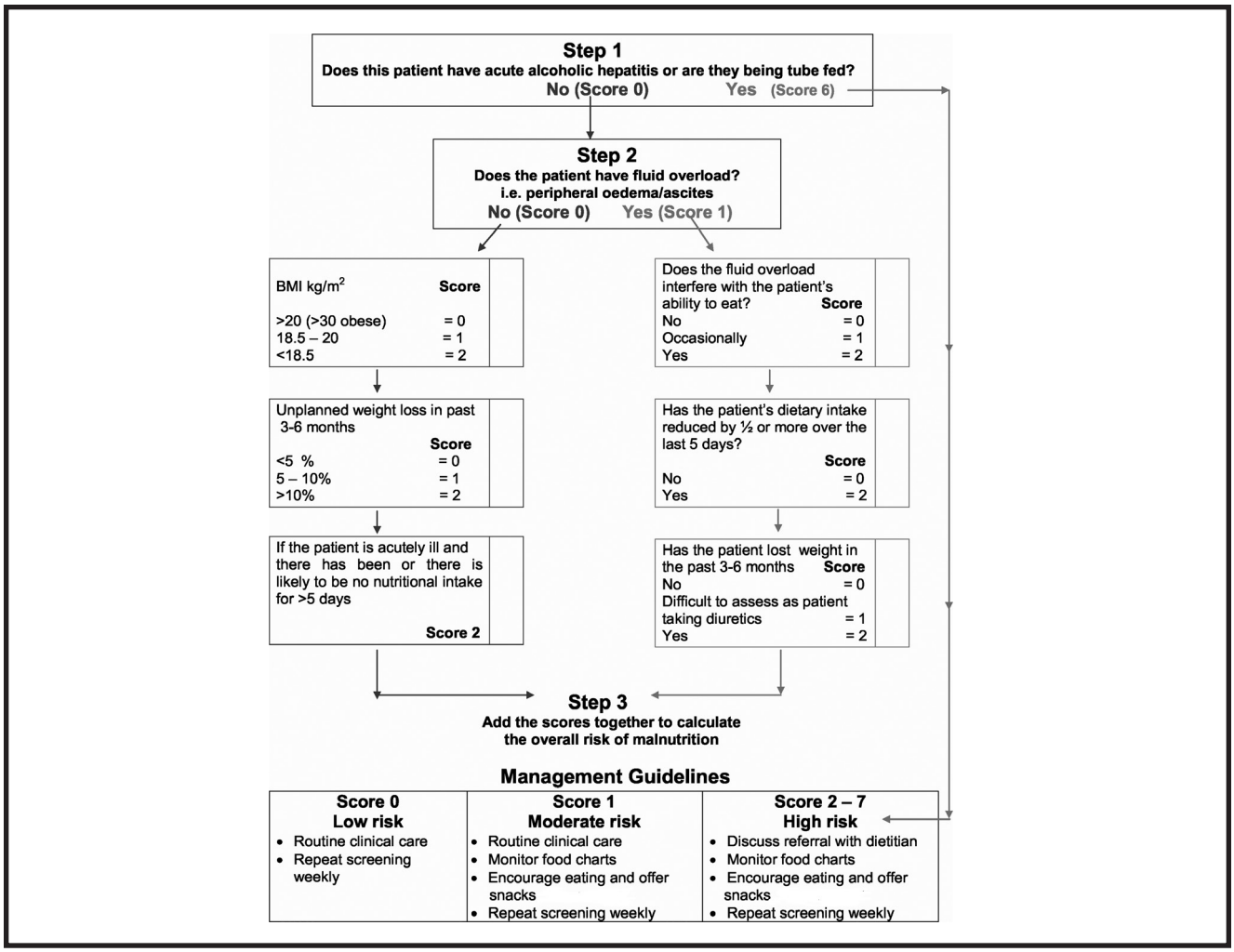
adverse effects. Overall evidence supporting use of flumazenil for treatment of HE was felt to be low. The AASLD guidelines acknowledge this transient improvement in mental status, and mention that it may be most beneficial to avoid assisted ventilation or to differentiate diagnostic situations involving benzodiazepine toxicity.[1]

PEG

Polyethylene glycol (PEG) is postulated to work in ameliorating HE due to it being highly effective as an osmotic laxative to facilitate the removal of fecal nitrogen.[31] Hoilat et al. published a systematic review and meta-analysis to investigate the utility of PEG in comparison to lactulose.[31] The review examined four RCTs with a total of 229 patients. The studies utilized the HE Scoring Algorithm (HESA), which is an adaptation of the West Haven Criteria using both subjective and objective indicators, to gauge the effect of PEG versus lactulose on HE. Two RCTs with a total of 98 patients demonstrated a lower average HESA score at 24 hours post treatment in the PEG group compared to the lactulose group (MD(Mean deviation)= -0.68, 95% CI -1.05 to -0.31, p<0.001). Of these patients, there was also was a higher proportion of patients who had a reduction of HESA score by greater than or equal to 1 at 24 hours post-treatment in the PEG group (RR=1.40, 95% CI 1.17 to 1.67, p<0.001). Two RCTs showed a higher proportion of patients had HESA score of 0 at 24 hours in the PEG group (RR=4.33, 95% CI 2.27 to 8.28, p<0.001). There was no difference between groups in regards to hospital length of stay (MD= -1.00, 95% CI -1.99 to -0.01, p=0.05). Several limitations of this meta-analysis are the inclusion of studies with a small number of patients and the fact that the authors did not perform publication bias analysis. This meta-analysis did not include studies that utilized a treatment arm with both PEG and lactulose. An RCT by Ahmed et al. compared PEG plus lactulose to lactulose alone in regards to HE resolution.[32] 29 patients were randomized to the dual treatment arm and 31 to lactulose monotherapy. There was a shorter median time to HE resolution in the dual therapy arm [4.5(3 to 9) days versus 9(8 to 11) days; p=0.023]. Adverse events included mainly diarrhea. There was also improved survival at 28 days with the dual therapy arm (93.1% versus 67.7%, p=0.010) but the difference was not statistically different at 90 days. The AASLD guidelines from 2014 note that no publications were forthcoming on the use of laxatives in HE at that time.[1] This may change with future guidelines.

FMT

It has been shown that cirrhotic patients with HE have a gut microbiome with a reduced amount of beneficial species, such as *Lachnospiraceae* and *Ruminococcaceae,* with increased amounts of pathogenic species such as *Enterobacteriaceae*.[33,34] This has been postulated to increase systemic inflammation, which in turn can lead to deficits in cognition. Bajaj et al. in 2017 performed an open-label RCT where 20 patients with recurrent HE were randomized to receive FMT from a donor with high amounts of *Lachnospiraceae* and *Ruminococcaceae* versus standard of care (SOC) with lactulose and rifaximin alone.[35] The primary outcome was serious adverse events with secondary outcomes including changes in cognitive function at day 20, and changes in microbiota composition. 80% of SOC participants had adverse events, as compared to 20% of FMT participants, in whom the adverse events were felt to be FMT-unrelated (p=0.02). Events that occurred in the SOC arm include pneumonia, chest pain, portal vein thrombus, anemia, gastroenteritis, and variceal bleeding. Five SOC and zero FMT participants developed recurrent HE during the follow-up period of 150 days (p=0.03). A secondary outcome was improvement in cognition. The FMT arm showed significant improvement in psychometric hepatic encephalopathy score (PHES) and EncephalApp Stroop testing with p=0.003 and p=0.01, respectively. There was a relative increase in beneficial microbial taxa post-FMT relative to patients on SOC. Limitations of this study were small sample size and the lack of a placebo arm. Bajaj et al. subsequently conducted another RCT on a group of 15 patients with HE randomized to FMT capsules or lactulose/rifaximin, with pre- and post-treatment endoscopies performed to obtain duodenal and sigmoid biopsies.[36] Post-FMT duodenal microbial diversity was increased, with higher levels of *Ruminococcaceae* and *Bifidobacteriaceae* with lower *Streptococcaceae* and *Veillonellaceae* (p=0.01). Reduction in



Hepatology, Volume: 58, Issue: 1, Pages: 325-336, First published: 07 March 2013, DOI: (10.1002/hep.26370)

Veillonellaceae was also noted in post-FMT sigmoid biopsies (p=0.04). There was reduction in markers of inflammation, including interleukin-6 and serum LBP in the FMT group. This proved that FMT increased beneficial taxa and decreased pathogenic strains, although no clinical endpoints were assessed in this study. The AASLD guidelines of 2014 do not mention FMT as a treatment for HE but, given emerging data, may appear in future versions.[1]

Probiotics

As noted above, the gut microbiota in patients with liver disease has been shown to be altered to include more pathogenic strains. It has been theorized that probiotics may reduce harmful ammonia-producing bacteria, decrease ammonia absorption by decreasing pH, and decrease intestinal permeability.[37] A Cochrane Review by Dalal et al. in 2017 analyzed 21 trials with 1420 participants comparing probiotics with placebo or lactulose. The most commonly used probiotic product was VSL#3.[37] When compared to placebo, there was no effect on all-cause mortality with probiotics (RR=0.58, 95% CI 0.23-1.44), however failure to improve HE score was lower (RR=0.67, 95% CI 0.56-0.79), adverse events were lower (RR=0.29, 95% CI 0.16-0.51), and plasma ammonia concentration was lower (MD -8.29 micromol/L, 95% CI -13.17 to -3.41). The efficacy data on these items when probiotics were compared to lactulose was unclear due to low quality of evidence. All metrics including all-cause mortality, lack of recovery, and adverse events had large confidence intervals that crossed one. The authors concluded

(continued on page 30)

(continued from page 28)

that there was a high risk of bias and random error with overall low quality of evidence. Probiotics may be considered over no treatment, given their overall safety, although a clear therapeutic benefit has not been established. High-quality RCTs are needed to further investigate the role of probiotics in HE. The AASLD guidelines of 2014 do not specifically recommend for probiotic use but they do not recommend against it.[1]

Diet

Malnutrition is a common complication of cirrhosis and is associated with muscle wasting. The loss of skeletal muscle prevents adequate removal of circulating ammonia and contributes to worsening encephalopathy.[38] This was demonstrated in a study by Nardelli et al. in 2019 which investigated the relationship between skeletal muscle mass and composition and the risk of progression from minimal to overt HE.[38] 64 patients with cirrhosis had computed tomography to analyze skeletal muscle index. Skeletal muscle index was determined using CT to calculate the L3 muscle Hounsfield units (HU) to determine if it was consistent with known ranges for skeletal muscle or if it represented sarcopenia. They found that alteration in muscle composition (myosteatosis) (62.5% versus 12.5%, $p<0.001$) and sarcopenia (84% versus 31%, $p<0.001$) were more frequent in patients who had minimal HE versus no HE. The development of overt HE was independently associated with myosteatosis and sarcopenia. The rationale for this is that skeletal muscle acts to detoxify and metabolize ammonia. A reduction in skeletal muscle results in a reduction in ammonia clearance. Amodio et al. created a consensus document in 2013 to explain methods for investigating sarcopenia in cirrhotic patients.[39] Hand-grip dynamometry was found to be both a sensitive and specific marker for body cell mass depletion and correlated with total protein body stores, but unfortunately is not a strong predictor of outcomes in women. There is a system called the Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT) that can be administered in under 3 minutes and has excellent reproducibility and external validity in assessing nutritional status. It can be carried out by nonspecialist staff in a clinic setting and is noted in Figure 1.

Cirrhotic patients have increased resting energy expenditure, due to reductions in hepatic glycogen. As a result, there is increased use of amino acids which must be offset by daily intake of 1.2-1.5g protein/kg body weight to maintain nitrogen balance.[40] Daily energy intake should be 35-40kcal/kg body weight. Fasting for longer than 3-6 hours should be avoided by eating small, frequent meals throughout the day, including a protein-based bedtime snack. The authors did not identify any high quality studies demonstrating the impact of diet intervention on hepatic encephalopathy.

CONCLUSION

The standard of care in treating hepatic encephalopathy has been non-absorbable disaccharides and rifaximin but there are newer therapies that are emerging that seek to modify multiple targets in the complex pathogenesis pathway leading to hepatic encephalopathy. Many of these therapies are supported by data that is not robust or has been subject to bias, but some have increasing support in the literature. This support may continue to grow as we better understand the underlying factors precipitating hepatic encephalopathy. Moving forward, larger clinical trials with robust methodology and minimization of inherent bias will be needed to support the addition of these therapeutic options to the treatment of hepatic encephalopathy. ■

References

1. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen K, Weissenborn K, and Wong P. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European association for the study of the liver and the American association for the study of liver diseases. J Hepatol 2014;61:642-659. Doi: 10.1016/j.jhep.2014.05.042.
2. Gluud LL, Vilstrup H, Morgan MY. Nonabsorbable disaccharides for hepatic encephalopathy: A systematic review and meta-analysis. Hepatology. 2016 Sep;64(3):908-22. doi: 10.1002/hep.28598. Epub 2016 May 20. PMID: 27081787.
3. Sharma P, Sharma B, Agrawal A, Sarin S. Primary prophylaxis of overt hepatic encephalopathy in patients with cirrhosis: An open labeled randomized controlled trial of lactulose versus no lactulose. J. Gastroenterol. Hepatol. 2012;27(8):1329-1335.
4. Caraceni P, et al. The Use of Rifaximin in Patients With Cirrhosis. Hepatology. 2021, 74(3):1660-1673.
5. Kimer N, Krag A, Moller S, Bendtsen L, Gluud L. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. Aliment Pharmacol Ther. 2014;40(2): 123-132.
6. Kang SH, Lee YB, Lee JH, Nam JY, Chang Y, Cho H, et al. Rifaximin treatment is associated with reduced risk of cirrhotic complications and prolonged overall survival in patients experiencing hepatic encephalopathy. Aliment Pharmacol Ther

2017; 46:845-855.
7. Jawaro T, Yang A. Dixit D, Bridgeman MB. Management of Hepatic Encephalopathy: A Primer. Annals of Pharmacotherapy. 2016;50(7):569-577. Doi: 10.1177/1060028016645826.
8. Strauss E, Tramote R, Silva EP, Caly WR, Honain NZ, Maffei RA, de Sá MF. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepatogastroenterology. 1992 Dec;39(6):542-5. PMID: 1483668.
9. Orlandi F, Freddara U, Candelaresi MT, et al. Comparison between neomycin and lactulose in 173 patients with hepatic encephalopathy: a randomized clinical study. Dig Dis Sci 1981;26:498–506.
10. Morgan M, Read A, Speller D. Treatment of hepatic encephalopathy with metronidazole. Gut, 1982,23,1-7.
11. Phonsamran, P.V., Kim J.W., Abbott, J.C. et al. Pharmacotherapy for Hepatic Encephalopathy. Drugs 70,1131-1148 (2010). https://doi.org/10/2165/10898630-000000000-00000.
12. Mekky M, Riad A, Gaber M, Abdel-Malek M, Swifee Y. Rifaximin versus metronidazole in management of acute episode of hepatic encephalopathy: An open labeled randomized clinical trial. Arab Journal of Gastroenterology. June 2018;19(2):76-79.
13. Tarao K, Ikeda T, Hayashi K, et al. Successful use of vancomycin hydrochloride in the treatment of lactulose resistant chronic hepatic encephalopathy. Gut 1990;31:702–6.
14. Gluud LL, Dam G, Les I, et al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev. 2017;5(5):CD001939. Published 2017 May 18. Doi; 10.1002/14651858. CD001939.pub4.
15. Butterworth, R.F., McPhail, M.J.W. L-Ornithine L-Aspartate (LOLA) for Hepatic Encephalopathy in Cirrhosis: Results of Randomized Controlled Trials and Meta-Analyses. Drugs. 2019;79:31-37. https://doi.org/10/1007/s40265-018-1024-1.
16. Bai M, Yang Z, Qi X, Fan D, Han G. L-Ornithine L-aspartate for hepatic encephalopathy in patients with cirrhosis: a meta-analysis of randomized controlled trials. J Gastroenterol Hepatol. 2013;28:783-92.
17. Goh ET, Stokes CS, Vilstrup H, GluudLL, Morgan MY. L-Ornithine L-aspartate for hepatic encephalopathy: a systematic review with meta-analysis of randomized controlled trials. J Hepatol. 2017;66;131.
18. Butterworth RF, Kircheis G, Hilger N, McPhail MJW. Efficacy of L-ornithine L-aspartate for the treatment of hepatic encephalopathy and hyperammonemia in cirrhosis: a systematic review and meta-analysis of randomized controlled trials. J Clin Exp Hepatol. 2018;8:301-3. https://doi.org/10/1016/j.jceh.2018,05.004.
19. Poo JL, Gongora J, Sanchez-Avila F, Aguilar-Castillo S, Garcia-Ramos G, Fernandez-Zertuche M, et al. Efficacy of oral L-ornithine L-aspartate in cirrhotic patients with hyperammonemic hepatic encephalopathy. Results of a randomized, lactulose-controlled study. Ann Hepatol. 2006;5:281-8.
20. Bai Z, Bernardi M, Yoshida E, Li H, Guo X, Mendez-Sanchez N, Li Y, Wang R, Deng J, Qi X. Albumin infusion may decrease the incidence and severity of overt hepatic encephalopathy in liver cirrhosis. Aging. 2019;11(19):8502-8525. https://doi.org/10.18632/aging.102335.
21. Sharma B, Singh J, Srivastava S, Sangam A, Mantri A, Trehanpati N, Sarin, S. Randomized controlled trial comparing lactulose plus albumin versus lactulose alone for treatment of hepatic encephalopathy. J Gastroenterol. Hepatol. 2017;32(6):1234-1239.
22. China L, et al. A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis. N Engl J Med 2021;384:808-817. DOI: 10.1056/NEJMoa2022166.
23. Rahimi R, Rockey D. Hepatic Encephalopathy: Pharmacological Therapies Targeting Ammonia. Semin Liver Dis 2016;36(01):48-55. DOI: 10/1055/s-0036-1571298.
24. Bosoi CR, Parent-Robitaille C, Anderson K, Tremblay M, Rose CF. AST-120 (spherical carbon adsorbent) lowers ammonia levels and attenuates brain edema in bile duct-ligated rats. Hepatology 2011;53(6):1995-2002.
25. Bajaj J, et al. AST-120 (Spherical Carbon Adsorbent) in Covert Hepatic Encephalopathy: Results of the Astute Trial. Su1685. Gastroenterology. 2013;144(5):S-997-S997.
26. Malaguarnera M. Acetyl-L-carnitine in hepatic encephalopathy. Metabolic Brain Disease. 2013;28(2):193-9. PUBMED: 23389620.
27. Marti-Carvajal AJ, Gluud C, Arevalo-Rodriguez I, Marti-Amarista CE. Acetyl-L-Carnitine for patients with hepatic encephalopathy. Cochrane Database of Systematic Reviews 2019, Issue 1. Art. No.: CD011451. DOI: 10.1002/14651858. CD011451.pub2. Accessed 11 October 2021.
28. Rockey DC, Vierling JM, Mantry P, et al. HALT-HE Study Group. Randomized, double-blind, controlled study of glycerol phenylbutyrate in hepatic encephalopathy. Hepatology 2014;59(3):1073-1083.
29. Alimirah M, Sadiq O, Gordon S. Novel Therapies in Hepatic Encephalopathy. Clinics in Liver Disease, 2020-05-01;23(2):303-315.
30. Goh E, Andersen M, Morgan M, Gluud L. Flumazenil versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No: CD002798. DOI: 10.1002/14651858. CD002798.pub4. Accessed 11 October 2021.
31. Hoilat GJ, Ayas MF, Hoilat JN, et al. Polyethylene glycol versus lactulose in the treatment of hepatic encephalopathy: a systematic review and meta-analysis. BMJ Open Gastroenterology 2021;8:e000648. Doi: 10.1136/bmjgast-2021-000648.
32. Ahmed S, Premkumar M, Dhiman RK, et al. Combined PEG3350 Plus Lactulose Results in Early Resolution of Hepatic Encephalopathy and Improved 28-Day Survival in Acute-on-Chronic Liver Failure. Journal of Clinical Gastroenterology. 2020 Oct. DOI: 10.1097/mcg.0000000000001450. PMID: 33060437.
33. Chen Y, Yang F, Lu H, Wang B, Chen Y, Lei D, et al. Characterization of fecal microbial communities in patients with liver cirrhosis. Hepatology 2011;54:562-572.
34. Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 2014;60:940-947.
35. Bajaj J, Kassam Z, Fagan A, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. December 2017; 66(6):1727-1738. Doi: https://doi.org/10.1002/hep.29306.
36. Bajaj J, Salzman N, Acharya C, et al. Fecal Microbial Transplant Capsules are Safe in Hepatic Encephalopathy: A Phase 1, Randomized, Placebo-Controlled Trial. November 2019;70(5):1690-1703. https://doi.org/10.1002/hep.30690.
37. Dalal R, McGee RG, Riordan SM, Webster AC. Probiotics for people with hepatic encephalopathy. Cochrane Database of Systematic Reviews 2017, issue 2. Art. No.: CD008716. DOI: 10.1002/14651858.CD008716.pub3. Accessed 12 October 2021.
38. Nardelli S, Lattanzi B, Merli M, Alessio F, Gioia S, Ridola L, Riggio O. Muscle Alterations Are Associated With Minimal and Overt Hepatic Encephalopathy in Patients With Liver Cirrhosis. Hepatology. November 2019;70(5):1704-1713.
39. Amodio P, Bemeur C, Butterworth R, Cordoba J, Kato A, Montagnese S, Uribe M, Vilstrup H, Morgan M. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International society for hepatic encephalopathy and nitrogen metabolism consensus. July 2013;58(1):325-336.
40. Rakoski MO, McCammon RJ, Piette JD, Iwashyna TJ, Marrero JA, Lok AS, Langa KM, Volk ML. Burden of cirrhosis on older Americans and their families: analysis of the health and retirement study. Hepatology. 2012 Jan;55(1):184-91. Doi: 10.1002/hep.24616. PMID: 21858847.