Vickey J. Said, MSN, AGACNP-BC
Edith Garcia-Trujillo, MSN, ACNP-BC

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Beyond Lactulose

Treatment Options for Hepatic Encephalopathy

ABSTRACT

Hepatic encephalopathy is a complication of liver failure characterized by neuropsychiatric dysfunction ranging from disorientation to coma. There is a need for more treatment options and preventive care interventions to reduce the incidence of hepatic encephalopathy and mitigate its socioeconomic impact on families and strain on healthcare resources. Currently, there is no consensus on a single pathophysiological mechanism responsible for the development of this neurocognitive disorder. Ammonia toxicity remains a significant factor, but there is now increased recognition that hyperammonemia acts synergistically with systemic inflammation, oxidative stress, and gut microbiota imbalance in the development of hepatic encephalopathy. This article provides an overview of current and emerging therapies that target these factors in the treatment and management of this condition. Because of its complex pathogenesis, a multipronged approach to treating hepatic encephalopathy may be highly beneficial.

Hepatic encephalopathy (HE) is a complication of liver disease characterized by neuropsychiatric dysfunction ranging from poor concentration and forgetfulness to seizures and coma (Vilstrup et al., 2014). Fully symptomatic HE, or overt HE (OHE), occurs in 30%–40% of patients with cirrhosis in the United States, whereas minor cognitive dysfunction, termed "covert or minimal HE (MHE)," occurs in 20%–80% of the same population (Vilstrup et al., 2014). The symptoms of HE can be disabling, interfering with daily activities, and leading to loss of independence. Hepatic encephalopathy has been linked to decreased health-related quality of life attributed to reduced appetite, ascites, and fatigue (Mina, Moran, Ortiz-Olvera, Mera, & Uribe, 2014). It is also associated with poorer employment and financial status for patients and increased socioeconomic burden for caregivers, all of which have a negative impact on medical compliance (Bajaj et al., 2011). On a broader scope, HE has a profound effect on hospital resources and government health subsidies. Between 2005 and 2009, HE accounted for more than 100,000 annual hospitalizations nationwide that averaged 8–9 days per admission, with two thirds of those patients covered by Medicare or Medicaid (Stepanova, Mishra, Venkatesan, & Younossi, 2012).

Treatments of HE have primarily centered on decreasing the intestinal production and systemic accumulation of ammonia to mitigate its neurotoxic effects (Hadjihambi & Jalan, 2015). Current guidelines for the clinical management of HE recommend lactulose as the first-line treatment and rifaximin as an add-on therapy (Vilstrup et al., 2014). The paucity of clinically approved HE therapies may be due to difficulty quantifying highly variable treatment effects in a disorder with such wide-ranging symptoms.

The pathogenesis of HE is not yet fully understood, but it is now thought that various factors contribute to its development. More recently, inflammation, oxidative stress, and changes in the gut microbiome have been implicated as contributing factors in HE (Sheasgreen, Lu, & Patel, 2014; Tranah, Paolino, & Shawcross, 2015). Its

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About the authors: *Vickey J. Said, MSN, AGACNP-BC, is New Graduate, Adult-Gerontology Acute Care Nurse Practitioner Program, California State University, Los Angeles; and Nurse Practitioner, Neurosurgery Unit, Ronald Reagan UCLA Medical Center, Los Angeles, California.*

Edith Garcia-Trujillo, MSN, ACNP-BC, is Clinical Instructor, Adult-Gerontology Acute Care Nurse Practitioner Program, California State University, Los Angeles; and Nurse Practitioner, Liver Transplant Surgery, Ronald Reagan UCLA Medical Center, Los Angeles, California.

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Correspondence to: *Vickey J. Said, MSN, AGACNP-BC, California State University, Los Angeles, School of Nursing, 5151 State University Dr, Los Angeles, CA, 90032 (vsaid@calstatela.edu).*

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multifactorial pathogenesis provides an opportunity for exploring alternative treatment pathways. There is a pressing need for more drug options and preventive care interventions to reduce the incidence of HE, thereby lessening its socioeconomic impact on families and immense burden on healthcare resources (Stepanova et al., 2012). This article provides an overview of current and emerging therapies in the treatment and management of HE in chronic liver disease.

Pathophysiology

There is no consensus on a single pathophysiological mechanism responsible for the development of HE. Ammonia toxicity remains a significant factor, but there is now increased recognition that hyperammonemia acts synergistically with systemic inflammation, oxidative stress, and gut microbiota imbalance in the pathogenesis of HE (Tranah et al., 2015) (Figure 1). In the presence of cirrhosis, the liver is unable to effectively convert ammonia, a nitrogenous waste product of intestinal metabolism, into urea (Hadjihambi & Jalan, 2015). Serum ammonia level rises and crosses the blood–brain barrier due to the shunting of portal blood into the systemic circulation (Tranah et al., 2015). Astrocytes are the most numerous neuroglial cells tasked with maintaining the blood–brain barrier and detoxifying ammonia by rapidly converting it to glutamine (Iwasa & Takei, 2015). An increase in glutamine concentrations leads to astrocyte swelling, morphological changes, and subsequent cell dysfunction (Iwasa & Takei, 2015).

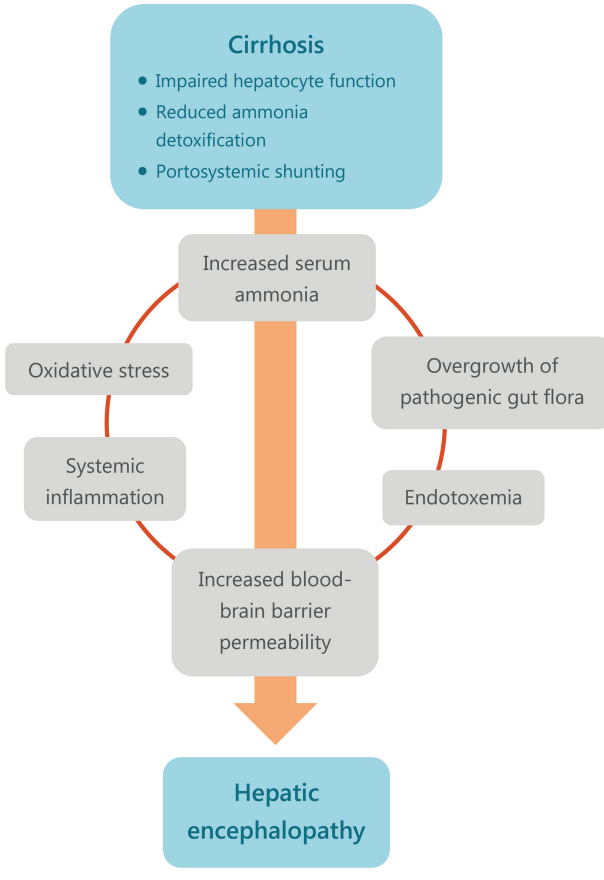

FIGURE 1. Multifactorial pathogenesis of hepatic encephalopathy.

The exposure of astrocytes to ammonia also induces the production of reactive oxygen species, which, in turn, activate the inflammatory cascade (Coltart, Tranah, & Shawcross, 2013; Görg, Schliess, & Häussinger, 2013). Studies have shown that a systemic inflammatory state, often referred to as SIRS (systemic inflammatory response syndrome), in which proinflammatory cytokines are released, can modulate the severity of HE in patients with cirrhosis (Aldridge, Tranah, & Shawcross, 2015).

Proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1), and IL-6 may disrupt the blood–brain barrier, contributing to brain inflammation and edema in HE (Bémeur & Butterworth, 2013; Lv et al., 2010). An association between the level of circulating TNF-α and HE severity has been observed in patients with acute liver failure (ALF) (Bémeur & Butterworth, 2013; Coltart et al., 2013). Furthermore, studies have shown that overgrowth of pathogenic gut flora combined with impaired integrity of the intestinal barrier in patients with cirrhosis can lead to systemic endotoxemia and a resultant inflammatory response (Coltart et al., 2013; Dhiman, 2013).

Treatment Modalities

A multipronged approach to treating HE in patients with advanced liver disease should be considered because of its complex pathogenesis. Therapeutic strategies include decreasing the production and accumulation of ammonia, reducing inflammation, and controlling gut flora (Table 1). Treatment options for HE related to ALF differ from HE therapies for chronic liver disease and are briefly addressed at the end of this review.

Decreasing Ammonia Production

Nonabsorbable Disaccharides

Lactulose, a nonabsorbable disaccharide (NAD), has been deemed a first-line therapy for HE since its use was first publicized in a report in 1966 (Gluud, Vilstrup, & Morgan, 2016). Nonabsorbable disaccharides are osmotic laxatives/prebiotics that reduce intestinal ammonia production by various mechanisms. Colonic metabolism of lactulose results in acidification of the gut, which favors the formation of nonabsorbable ammonium from ammonia as well as exerts a

TABLE 1. Treatment Options for Hepatic Encephalopathy

Treatment	Administration	Class	Mechanism of Action
Nonabsorbable disaccharide	Oral	Osmotic laxative	Acidifies the gut, inhibits intestinal uptake of glutamine, and reduces intestinal transit time
Rifaximin	Oral	Antibiotic	Inhibits growth of ammonia-producing enteric bacteria
Sodium benzoate	Oral, IV	UC disorder treatment agent	Provides alternative pathway for ammonia removal
Glycerol phenylbutyrate	Oral	UC disorder treatment agent	Provides alternative pathway for ammonia removal
L-Ornithine L-aspartate	IV	Hepatoprotectant agent	Increases urea production, activates glutamine synthetase activity in skeletal muscle
L-Ornithine phenylacetate	IV	Hepatoprotectant agent	Increases urea production, activates glutamine synthetase activity in skeletal muscle
Branched-chain amino acids	Oral	Dietary supplement	Increases glutamine synthetase activity and helps maintain muscle mass
Acetyl-L-carnitine	IV	Dietary supplement	Induces urea production
L-Arginine	IV	UC disorder treatment agent	Maximizes ammonia excretion through urea cycle
Probiotics	Oral	Dietary supplement	Acidifies gut to favor non-urease-producing bacteria, decreases endotoxemia, and reduces translocation of pathogenic enteric bacteria
Zinc	Oral	Trace element	Cofactor in urea cycle enzyme activity
Thiamine	IV	Vitamin	Essential coenzyme in intracellular glucose metabolism; prevents oxidative stress
Vegetable- or dairy-based high-protein diet	Oral	N/A	Reduces intestinal ammonia production
Strict diabetes control	N/A	N/A	Reduces systemic inflammation

Note. IV = intravenous; N/A = not applicable; UC = urea cycle.

prebiotic effect on the growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* (Tranah et al., 2015). The cathartic effect of NADs additionally reduces intestinal transit time, leading to increased excretion of nitrogenous waste (Tranah et al., 2015). Nonabsorbable disaccharides also inhibit intestinal uptake of glutamine and its resultant metabolism to ammonia (Gluud et al., 2016). A meta-analysis of 38 randomized controlled trials by Gluud et al. (2016) showed that lactulose compared with placebo or no intervention was beneficial in treating and preventing both MHE and OHE.

Although effective and relatively safe, lactulose has undesirable side effects including nausea, abdominal cramps, and diarrhea that may lead to decreased medication compliance by patients (Iwasa & Takei, 2015). In addition, recurrence of HE caused by lactulose resistance has been noted in cirrhotic patients with unmanaged hyponatremia (Iwasa & Takei, 2015).

Rifaximin

Antibiotics are often used as alternative or add-on therapy to NADs to reduce inflammation and endotoxemia in the setting of HE. Rifaximin, a broad-spectrum antibiotic with specific activity against anaerobic enteric bacteria, is Food and Drug Administration (FDA) approved for the prevention of HE (Patidar & Bajaj, 2013) and recommended as add-on therapy to lactulose in current practice guidelines (Vilstrup et al., 2014).

Rifaximin has been extensively studied and its efficacy well-documented. In a double-blind, randomized

controlled trial, Sharma et al. (2013) demonstrated that a combination of lactulose plus rifaximin was more effective than lactulose alone in the treatment of OHE. In addition, a recent meta-analysis of 20 randomized controlled studies showed that rifaximin effected the greatest reduction in serum ammonia compared with five other interventions (Zhu et al., 2015). Despite its higher cost, rifaximin is increasingly favored over neomycin and metronidazole because of its safer side effect profile and gut specificity, with less than 1% absorbed systemically (Patidar & Bajaj, 2013).

Sodium Benzoate

Widely used as a food preservative, sodium benzoate has been prescribed as an off-label treatment of hyperammonemia since 1979 (Misel, Gish, Patton, & Mendler, 2013). Administered intravenously, it activates an alternative pathway of ammonia elimination through renal excretion in the form of hippuric acid (Misel et al., 2013). Sodium benzoate ultimately reacts with glycine, an ammoniagenic amino acid, thereby preventing its degradation via an ammonia-forming metabolic pathway in the liver, kidney, and brain (Matoori & Leroux, 2015).

A double-blind randomized study found sodium benzoate to be as safe and effective as lactulose in the treatment of acute portosystemic HE (Sushma et al., 1992). Gastrointestinal symptoms including nausea and epigastric discomfort are reported with oral sodium benzoate but can be minimized when taken with a nutritional shake (Misel et al., 2013). Caution must be exercised when giving sodium benzoate to patients with dietary salt restrictions, unmanaged edema, or severe renal dysfunction (Misel et al., 2013).

Glycerol Phenylbutyrate

Glycerol phenylbutyrate (GPB) is an orally administered, odorless, sodium-free liquid that is FDA approved for the treatment of urea cycle disorders (Rockey et al, 2014). It lowers serum ammonia concentration by providing a non-urea cycle pathway for the renal excretion of nitrogenous waste in the form of phenylacetylglutamine (Hadjihambi & Jalan, 2015). Glycerol phenylbutyrate has shown therapeutic potential in the management of HE. In a double-blind, randomized controlled study, Rockey et al (2014) found that GPB reduced HE events as well as significantly lowered ammonia in patients with cirrhosis. Treatment effects of GPB were comparable with rifaximin, and its safety profile is similar to that of placebo (Rockey et al., 2014).

Vegetable- or Dairy-Based High-Protein Diet

For decades, a mainstay of HE management was restricting dietary protein to reduce intestinal ammonia production and prevent HE exacerbations (Nguyen & Morgan, 2014). Clinical guidelines recommended as little as 0.5 g/kg per day for patients with severe HE (Cabral & Burns, 2011). Despite a small sample size and short duration of protein restriction, Córdoba's et al. (2004) study was the first randomized controlled study to demonstrate that normal dietary protein intake did not exacerbate HE in cirrhotic patients whereas a low-protein diet led to increased protein breakdown and amino acid release from skeletal muscle.

Seventy-five percent of patients with HE are moderately to severely malnourished with loss of muscle mass and hepatic reserves (Vilstrup et al., 2014), which can result in reduced ammonia detoxification by skeletal muscle (Sheasgreen et al., 2014). Because of severe muscle wasting, patients with cirrhosis have greater protein requirements than those of healthy individuals (Vilstrup et al., 2014). The American Association for the Study of Liver Disease (AASLD) (2014) currently recommends daily protein intake of 1.2–1.5 g/kg per day for patients with cirrhosis. Temporary protein restriction may be beneficial in cases of medically refractory OHE (Nguyen & Morgan, 2014); however, current practice guidelines recommend substituting dairy-based or vegetable protein for meat protein instead of reducing total protein intake (Vilstrup et al., 2014).

Increasing Ammonia Removal

L-Ornithine L-Aspartate

As substrates of the urea cycle, the salts L-ornithine L-aspartate (LOLA) have the ability to increase urea production as well as activate the production of glutamine, a nontoxic transport form of ammonia, by stimulating muscular glutamine synthetase activity (Hadjihambi & Jalan, 2015; Matoori & Leroux, 2015). A meta-analysis of eight randomized controlled studies showed that intravenous LOLA was more effective than placebo or no intervention in improving both OHE and MHE by reducing serum ammonia concentration (Bai, Yang, Qi, Fan, & Han, 2013). However, a double-blind randomized trial demonstrated that although oral LOLA was ineffective in treating MHE, it had a prophylactic role in preventing OHE compared with placebo and reported no adverse side effects (Alvares-da-Silva et al., 2014).

L-Ornithine Phenylacetate

L-Ornithine phenylacetate (OP) detoxifies ammonia by providing glutamate as a substrate for glutamine production in muscle, which is then excreted in urine in the form of phenylacetylglutamine (Kristiansen, 2016). The efficacy of OP in lowering plasma ammonia has

been successfully demonstrated in animal models of liver failure (Matoori & Leroux, 2015).

In a single-cohort pilot study involving cirrhotic patients, OP infusions led to a significant decrease in serum ammonia and an increase in urinary phenylacetylglutamine (Ventura-Cots et al., 2013). However, a subsequent trial by Ventura-Cots et al (2016) showed that OP was no better than placebo in lowering ammonia in cirrhotic patients after upper gastrointestinal bleeding. Limitations cited included small sample size, individual variability, and, primarily, too low a dose of OP used (Ventura-Cots et al., 2016). Nonetheless, OP appears to be a well-tolerated and promising drug that warrants further study with higher doses of administration (Ventura-Cots et al., 2016).

Branched-Chain Amino Acids

Branched-chain amino acids (BCAAs) serve as substrates for protein synthesis in skeletal muscle (Dam, Ott, Aagaard, & Vilstrup, 2013). Metabolism of BCAAs can lead to increased glutamine synthetase activity, thereby supporting glutamine formation and subsequent ammonia detoxification (Dam et al., 2013). In a meta-analysis of 16 randomized controlled studies, Gluud et al. (2015) found high-quality evidence that BCAAs had a beneficial effect on HE, though no impact on mortality.

More trials are needed to compare the effects of BCAAs with other interventions such as NADs and rifaximin. As such, current practice guidelines by the AASLD (2014) recommend oral BCAAs as an alternative or add-on therapy for patients with medically refractory HE. Supplementation with BCAAs is also recommended to help improve the nutritional status of cirrhotic patients who are unable to tolerate vegetable- or milk-based proteins (Vilstrup et al., 2014).

Acetyl-L-Carnitine

Acetyl-L-carnitine (ALC), a carnitine ester produced endogenously in mitochondria, is a substrate for cellular energy production (Malaguarnera, 2013). Reviews of randomized controlled trials showed that L-carnitine decreased plasma ammonia levels, improved cognitive function, and improved electroencephalogram scores in patients with cirrhosis (Malaguarnera, 2013; Shores & Keeffe, 2008). No significant side effects were reported.

Acetyl-L-carnitine was found to induce urea formation, which resulted in decreased plasma and brain ammonia levels (Malaguarnera, 2013). Other beneficial effects observed include improved cell energy production, enhanced immune function, and protection of cells from oxidative stress (Malaguarnera, 2013). More randomized controlled studies are needed to evaluate the effect of ALC on HE in cirrhotic patients.

L-Arginine

L-Arginine is an amino acid that functions as a substrate for the urea cycle, allowing for detoxification of ammonia and urinary excretion of nitrogen (Matoori & Leroux, 2015; Wright, Chattree, & Jalan, 2011). Supplementation of L-arginine is currently recommended for urea cycle disorders; however, more clinical studies are needed to evaluate the efficacy of L-arginine in treating HE (Wright et al., 2011). A randomized controlled clinical trial showed that intravenous infusion of L-arginine effectively reduced serum ammonia and prevented HE compared with placebo (Montet et al., 2000), but until more studies are carried out, L-arginine supplementation is currently not recommended in AASLD practice guidelines (Vilstrup et al., 2014).

Zinc

Zinc is a trace mineral that has a role in urea cycle enzyme activity (Mousa et al., 2016). A deficiency of zinc is frequently seen in patients with cirrhosis and may be attributed to poor nutrition, impaired absorption by the digestive tract, and urinary losses secondary to diuretic use (Chavez-Tapia et al., 2013). A meta-analysis of trials on oral zinc supplementation in HE concluded that supplementation improved performance on psychometric tests but found insubstantial evidence that it relieved symptoms of HE (Chavez-Tapia et al., 2013). However, a more recent double-blind randomized trial showed that zinc replacement for 3 months resulted in a reduction of serum ammonia by approximately 30% compared with placebo (Katayama et al., 2014). Because of its low cost, favorable safety profile, and recent promising data, the effect of oral zinc on ammonia metabolism in cirrhotic patients deserves further study.

Reducing Inflammation

Probiotics

The pathogenesis of HE in cirrhotic patients has been linked to deranged gut flora that leads to increased production of ammonia and bacterial endotoxins and a resultant activation of the inflammatory cascade (Dhiman, 2013). Probiotics can treat HE through various mechanisms: (1) lowering pH to favor non-urease-producing bacteria, thereby reducing ammonia production; (2) decreasing endotoxemia, consequently reducing inflammation and oxidative stress; and (3) reducing the translocation of pathogenic bacteria from the gut, therefore preventing systemic infection (Dhiman, 2013; Sharma & Singh, 2016).

In a meta-analysis of seven randomized trials with a total of 393 patients, treatment with probiotics compared with placebo or lactulose was shown to significantly relieve symptoms of HE (Holte, Krag, & Gluud,

2012). Saab et al.'s (2016) more recent meta-analysis of 14 randomized controlled studies involving 1,152 patients showed that probiotics were more effective than no treatment or placebo in preventing OHE. Probiotics were found to be comparable with that of lactulose in the management of HE but appeared to be better tolerated (Saab et al., 2016). Moreover, rates of hospitalization were decreased, although mortality was not affected (Saab et al., 2016). Probiotics are well tolerated by patients with cirrhosis and may be safely used in conjunction with other therapies in the management of HE (Saab et al., 2016).

Thiamine

Thiamine, or vitamin B_1, is needed for the conversion of carbohydrates to energy as well as the metabolism of amino acids in several important enzyme systems (Gupta et al., 2012). In patients with cirrhosis, thiamine deficiency is commonly the result of depleted hepatic stores, impaired intestinal absorption, and poor dietary intake (Gupta et al., 2012).

Butterworth (2009) describes the synergistic effects of ammonia toxicity and thiamine deficiency on the cerebral manifestations of HE that renders it indistinguishable from Wernicke's encephalopathy, a metabolic brain disorder attributed to thiamine deficiency. The pathophysiological pathways of both disorders lead to the accumulation of lactate in the brain, increased oxidative stress, cellular energy impairment, and the release of proinflammatory cytokines (Butterworth, 2009). Thiamine supplementation in patients with liver disease would appear to be beneficial in the treatment of HE.

Strict Diabetes Control

There is strong evidence linking local and systemic inflammation to Type 2 diabetes mellitus (T2DM) and insulin resistance (Lontchi-Yimagou, Sobngwi, Matsha, & Kengne, 2013). A key inflammatory biomarker in T2DM is TNF-α, which in high concentrations induces insulin resistance (Lontchi-Yimagou et al., 2013). Type 2 diabetes mellitus may contribute to the development of HE by several mechanisms including increased intestinal glutaminase activity, inflammation acting synergistically with ammonia, impaired gut motility due to autonomic neuropathy, and promotion of bacterial overgrowth (Elkrief et al., 2016; Romero-Gómez, Montagnese, & Jalan, 2015).

Cirrhotic patients are functionally immunocompromised and at increased risk for infection (Tranah, Vijay, Ryan, & Shawcross, 2013). Data currently support the association of systemic inflammation and infection with high-grade HE in patients with cirrhosis (Shawcross et al., 2011). The prevalence and severity of HE appear to be higher in cirrhotic patients with diabetes compared with nondiabetic cirrhotic patients (Butt et al., 2013). In one study, analysis of data from three randomized controlled trials found diabetes to be a risk factor for the first-time development of OHE in patients with advanced liver disease (Jepsen, Watson, Andersen, & Vilstrup, 2015). Moreover, diabetic patients developed severe HE *earlier* in their clinical course of cirrhosis than their nondiabetic counterparts (Jepsen et al., 2015).

Diabetes is a prognostic indicator for poor survival and increased risk of complications in patients with cirrhosis (Elkrief et al., 2016). Strict diabetes control may help attenuate the inflammatory process and subsequent development of severe HE.

Treatment Options for HE in Acute Liver Failure

In ALF, intracranial hypertension is the primary cause of morbidity and mortality (Gamal, Abdel Wahab, Eshra, Rashed, & Sharawy, 2014). Central nervous system symptoms such as brain edema and encephalopathy are not effectively managed with ammonia-lowering treatments (Bémeur & Butterworth, 2013). Both systemic inflammation and neuroinflammation are implicated in ALF, with evidence of TNF-α concentrations correlating with HE severity (Bémeur & Butterworth, 2013).

Emerging treatments of brain edema associated with ALF include minocycline and N-acetylcysteine. Minocycline, a lipophilic antibiotic with the ability to cross the blood–brain barrier, has been found to reduce brain edema in animal models by inhibiting microglial activation and proinflammatory cytokine production (Gamal et al., 2014). Minocycline's ability to modulate inflammatory and oxidative changes in the brain may serve as promising therapy for the prevention of cytotoxic brain edema and encephalopathy in patients with acute liver injury (Bémeur & Butterworth, 2013; Gamal et al., 2014).

N-Acetylcysteine (NAC) is another potential therapy in the management of HE in ALF due to its antioxidant and anti-inflammatory properties (Aldridge et al., 2015). In a randomized trial involving 78 patients with non-acetaminophen-induced ALF, Stravitz et al. (2013) found NAC to be effective in attenuating the production of IL-17, a key proinflammatory cytokine implicated in the severity and progression of HE in ALF (Stravitz et al., 2013).

Conclusion

Hepatic encephalopathy is a debilitating complication of liver disease that affects quality of life of patients and places a heavy burden on caregivers and the healthcare system. There is a great need for more treatment options and preventive care interventions to

reduce the incidence of HE, thereby lessening its socioeconomic impact on families and strain on healthcare resources.

Current guidelines for the clinical management of HE recommend lactulose as the first-line treatment and rifaximin as an add-on therapy for lowering ammonia levels in patients with cirrhosis. The reported side effects of lactulose including nausea and diarrhea make the medication intolerable for some patients, which may lead to decreased adherence to therapy. Several emerging treatments that target ammonia production such as LOLA, BCAAs, and zinc have more tolerable side effect profiles and deserve further attention and study.

There is mounting evidence that hyperammonemia acts in synergy with systemic inflammation, oxidative stress, and gut microbiota imbalance in the pathogenesis of HE. As such, a multipronged approach targeting ammonia production, systemic inflammation, and gut flora may be highly beneficial in the treatment and prevention of this complex disorder. ✪

REFERENCES

Aldridge, D. R., Tranah, E. J., & Shawcross, D. L. (2015). Pathogenesis of hepatic encephalopathy: Role of ammonia and systemic inflammation. *Journal of Experimental and Clinical Hepatology*, *5*(S1), S7–S20. doi:10.1016/j.jceh.2014.06.004

Alvares-da-Silva, M., Araujo, A., Vicenzi, J., Silva, G., Oliveira, F., Schacher, F., … Fernandes, L. N. (2014). Oral L-ornithine-L-aspartate in minimal hepatic encephalopathy: A randomized, double-blind, placebo-controlled trial. *Hepatology Research*, *44*(9), 956–963. doi:10.1111/hepr.12235

American Association for the Study of Liver Disease (AASLD). (2014). Hepatic encephalopathy in chronic liver disease: 2014 practice guideline. *Journal of Hepatology, 61*, 642–659. doi:10.1016/j.jhep.2014.05.042

Bai, M., Yang, Z., Qi, X., Fan, D., & Han, G. (2013). L-Ornithine-L-aspartate for hepatic encephalopathy in patients with cirrhosis: A meta-analysis of randomized controlled trials. *Journal of Gastroenterology and Hepatology*, *28*(5), 783–792. doi:10.1111/jgh.12142

Bajaj, J., Wade, J., Gibson, D., Heuman, D., Thacker, L., Sterling, R. K., … Sanyal, A. J. (2011). The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *The American Journal of Gastroenterology*, *106*(9), 1646–1653. doi:10.1038/ajg.2011.157

Bémeur, C., & Butterworth, R. (2013). Liver–brain proinflammatory signalling in acute liver failure: Role in the pathogenesis of hepatic encephalopathy and brain edema. *Metabolic Brain Disease*, *28*(2), 145–150. doi:10.1007/s11011-012-9361-3

Butt, Z., Jadoon, N., Salaria, O., Mushtaq, K., Riaz, I., Shahzad, A., … Sarwar, S. (2013). Diabetes mellitus and decompensated cirrhosis: Risk of hepatic encephalopathy in different age groups. *Journal of Diabetes*, *5*(4), 449–455. doi:10.1111/1753–0407.12067

Butterworth, R. (2009). Thiamine deficiency-related brain dysfunction in chronic liver failure. *Metabolic Brain Disease*, *24*(1), 189–196. doi:10.1007/s11011-008-9129-y

Cabral, C., & Burns, D. (2011). Low-protein diets for hepatic encephalopathy debunked: Let them eat steak. *Nutrition in Clinical Practice*, *26*(2), 155–159. doi:10.1177/0884533611400086

Chavez-Tapia, N., Cesar-Arce, A., Barrientos-Gutiérrez, T., Villegas-López, F., Méndez-Sanchez, N., & Uribe, M. (2013). A systematic review and meta-analysis of the use of oral zinc in the treatment of hepatic encephalopathy. *Nutrition Journal*, *12*(1), 74. doi:10.1111/j.1365-2036.2010.04448.x

Coltart, I., Tranah, T., & Shawcross, D. (2013). Inflammation and hepatic encephalopathy. *Archives of Biochemistry and Biophysics*, *536*(2), 189. doi:10.1016/j.abb.2013.03.016

Córdoba, J., López-Hellín, J., Planas, M., Sabín, P., Sanpedro, F., Castro, F., … Guardia, J. (2004). Normal protein diet for episodic hepatic encephalopathy: Results of a randomized study. *Journal of Hepatology*, *41*(1), 38–43. doi:10.1016/j.jhep.2004.03.023

Dam, G., Ott, P., Aagaard, N., & Vilstrup, H. (2013). Branched-chain amino acids and muscle ammonia detoxification in cirrhosis. *Metabolic Brain Disease*, *28*(2), 217–220. doi:10.1007/s11011-013-9377-3

Dhiman, R. (2013). Gut microbiota and hepatic encephalopathy. *Metabolic Brain Disease*, *28*(2), 321–326. doi:10.1007/s11011-013-9388-0

Elkrief, L., Rautou, P., Sarin, S., Valla, D., Paradis, V., & Moreau, R. (2016). Diabetes mellitus in patients with cirrhosis: Clinical implications and management. *Liver International*, *36*(7), 936–948. doi:10.1111/liv.13115

Gamal, M., Abdel Wahab, Z., Eshra, M., Rashed, L., & Sharawy, N. (2014). Comparative neuroprotective effects of dexamethasone and minocycline during hepatic encephalopathy. *Neurology Research International*, *2014*, 1–8. doi:10.1155/2014/254683

Gluud, L., Dam, G., Les, I., Córdoba, J., Marchesini, G., Borre, M., … Vilstrup, H. (2015). Branched-chain amino acids for people with hepatic encephalopathy. *Cochrane Database of Systematic Reviews*, CD001939. doi:10.1002/14651858

Gluud, L., Vilstrup, H., & Morgan, M. (2016). Nonabsorbable disaccharides for hepatic encephalopathy: A systematic review and meta-analysis. *Hepatology*, *64*(3), 908–922. doi:10.1002/hep.28598

Görg, B., Schliess, F., & Häussinger, D. (2013). Osmotic and oxidative/nitrosative stress in ammonia toxicity and hepatic encephalopathy. *Archives of Biochemistry and Biophysics*, *536*(2), 158–163. doi:10.1016/j.abb.2013.03.010

Gupta, R., Yadav, S., Saraswat, V., Rangan, M., Srivastava, A., Yadav, A., … Rathore, R. K. (2012). Thiamine deficiency related microstructural brain changes in acute and acute-on-chronic liver failure of non-alcoholic etiology. *Clinical Nutrition (Edinburgh, Scotland)*, *31*(3), 422. doi:10.1016/j.clnu.2011.11.018

Hadjihambi, A., & Jalan, R. (2015). Hepatic encephalopathy: New treatments. *Clinical Liver Disease*, *5*(5), 109–111. doi:10.1002/cld.468.109

Holte, K., Krag, A., & Gluud, L. (2012). Systematic review and meta-analysis of randomized trials on probiotics for hepatic encephalopathy. *Hepatology Research*, *42*(10), 1008–1015. doi:10.1111/j.1872-034X.2012.01015.x

Iwasa, M., & Takei, Y. (2015). Pathophysiology and management of hepatic encephalopathy 2014 update: Ammonia toxicity and hyponatremia: Management of hepatic encephalopathy. *Hepatology Research*, *45*(12), 1155–1162. doi:10.1111/hepr.12495

Jepsen, P., Watson, H., Andersen, P., & Vilstrup, H. (2015). Diabetes as a risk factor for hepatic encephalopathy in cirrhosis patients.

Journal of Hepatology, *63*(5), 1133–1138. doi:10.1016/j.jhep.2015.07.007

Katayama, K., Saito, M., Kawaguchi, T., Endo, R., Sawara, K., Nishiguchi, S., … Suzuki, K. (2014). Effect of zinc on liver cirrhosis with hyperammonemia: A preliminary randomized, placebo-controlled double-blind trial. *Nutrition*, *30*(11–12), 1409–1414. doi:10.1016/j.nut.2014.04.018

Kristiansen, R. (2016). Current state of knowledge of hepatic encephalopathy (Part I): Newer treatment strategies for hyperammonemia in liver failure. *Metabolic Brain Disease*, *31*(6), 1357–1358. doi:10.1007/s11011-016-9908-9

Lontchi-Yimagou, E., Sobngwi, E., Matsha, T., & Kengne, A. (2013). Diabetes mellitus and inflammation. *Current Diabetes Reports*, *13*(3), 435–444. doi:10.1007/s11892-013-0375-y

Lunia, M., Sharma, B., Sharma, P., Sachdeva, S., & Srivastava, S. (2014). Probiotics prevent hepatic encephalopathy in patients with cirrhosis: A randomized controlled trial. *Clinical Gastroenterology and Hepatology*, *12*(6), 1003.e1–1008.e1. doi:10.1016/j.cgh.2013.11.006

Lv, S., Song, H., Zhou, Y., Li, L., Cui, W., Wang, W., & Liu, P. (2010). Tumour necrosis factor-alpha affects blood-brain barrier permeability and tight junction-associated occludin in acute liver failure. *Liver International*, *30*(8), 1198–1210. doi:10.1111/j.1478-3231.2010.02211.x

Malaguarnera, M. (2013). Acetyl-L-carnitine in hepatic encephalopathy. *Metabolic Brain Disease*, *28*(2), 193–199. doi:10.3748/wjg.v11.i45.7197

Matoori, S., & Leroux, J. (2015). Recent advances in the treatment of hyperammonemia. *Advanced Drug Delivery Reviews*, *90*, 55. doi:10.1016/j.addr.2015.04.009

Mina, A., Moran, S., Ortiz-Olvera, N., Mera, R., & Uribe, M. (2014). Prevalence of minimal hepatic encephalopathy and quality of life in patients with decompensated cirrhosis: Quality of life in hepatic encephalopathy. *Hepatology Research*, *44*(10), E92–E99.

Misel, M. L., Gish, R. G., Patton, H., & Mendler, M. (2013). Sodium benzoate for treatment of hepatic encephalopathy. *Gastroenterology & Hepatology*, *9*(4), 219–227.

Montet, J.-C, Salmon, L., Caroli-Bosc, F. X., Demarquay, J. F., Montet, A. M., & Delmont, J. P. (2000). L-Arginine infusion protects against hyperammonemia and hepatic encephalopathy in cirrhotic patients with variceal haemorrhage. *Gastroenterology*, *118*(4), A978.

Mousa, N., Abdel-Razik, A., Zaher, A., Hamed, M., Shiha, G., Effat, N., … Eldars, W. (2016). The role of antioxidants and zinc in minimal hepatic encephalopathy: A randomized trial. *Therapeutic Advances in Gastroenterology*, *9*(5), 684–691. doi:10.1177/1756283X16645049

Nguyen, D., & Morgan, T. (2014). Protein restriction in hepatic encephalopathy is appropriate for selected patients: A point of view. *Hepatology International*, *8*(S2), 447–451. doi:10.1007/s12072-013-9497-1

Patidar, K., & Bajaj, J. (2013). Antibiotics for the treatment of hepatic encephalopathy. *Metabolic Brain Disease*, *28*(2), 307–312. doi:10.1007/s11011-013-9383-5

Rockey, D., Vierling, J., Mantry, P., Ghabril, M., Brown, R., Alexeeva, O., … HALT-HE Study Group. (2014). Randomized, double-blind, controlled study of glycerol phenylbutyrate in hepatic encephalopathy. *Hepatology*, *59*(3), 1073–1083. doi:10.1002/hep.26611

Romero-Gómez, M., Montagnese, S., & Jalan, R. (2015). Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. *Journal of Hepatology*, *62*(2), 437–447. doi:10.1016/j.jhep.2014.09.005

Saab, S., Suraweera, D., Au, J., Saab, E., Alper, T., & Tong, M. J. (2016). Probiotics are helpful in hepatic encephalopathy: A meta-analysis of randomized trials. *Liver International*, *36*(7), 986–993. doi:10.1111/liv.13005

Sharma, B., Sharma, P., Lunia, M., Srivastava, S., Goyal, R., & Sarin, S. K. (2013). A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *The American Journal of Gastroenterology*, *108*(9), 1458. doi:10.1038/ajg.2013.219

Sharma, B., & Singh, J. (2016). Probiotics in management of hepatic encephalopathy. *Metabolic Brain Disease*, *31*(6), 1295–1301. doi:10.1007/s11011-016-9826-x

Shawcross, D., Sharifi, Y., Canavan, J., Yeoman, A., Abeles, R., Taylor, N. J., … Wendon, J. A. (2011). Infection and systemic inflammation, not ammonia, are associated with grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. *Journal of Hepatology*, *54*(4), 640–649. doi:10.1016/j.jhep.2010.07.045

Sheasgreen, C., Lu, L., & Patel, A. (2014). Pathophysiology, diagnosis, and management of hepatic encephalopathy. *Inflammopharmacology*, *22*(6), 319–326. doi:10.1007/s10787-014-0217-9

Shores, N., & Keeffe, E. (2008). Is oral L-acyl-carnitine an effective therapy for hepatic encephalopathy? Review of the literature. *Digestive Diseases and Sciences*, *53*(9), 2330–2333. doi:10.1007/s10620-007-0183-9

Stepanova, M., Mishra, A., Venkatesan, C., & Younossi, Z. (2012). In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. *Clinical Gastroenterology and Hepatology*, *10*(9), 1034. doi:10.1016/j.cgh.2012.05.016

Stravitz, R., Sanyal, A., Reisch, J., Bajaj, J., Mirshahi, F., Cheng, J., … Acute Liver Failure Study Group. (2013). Effects of *N*-acetylcysteine on cytokines in non-acetaminophen acute liver failure: Potential mechanism of improvement in transplant-free survival. *Liver International*, *33*(9), 1324–1331. doi:10.1111/liv.12214

Sushma, S., Dasarathy, S., Tandon, R., Jain, S., Gupta, S., & Bhist, M. (1992). Sodium benzoate in the treatment of acute hepatic encephalopathy: A double-blind randomized trial. *Hepatology*, *16*(1), 138–144. doi:10.1002/hep.1840160123

Tranah, T., Paolino, A., & Shawcross, D. (2015). Pathophysiological mechanisms of hepatic encephalopathy: Pathophysiological mechanisms. *Clinical Liver Disease*, *5*(3), 59–63. doi:10.1002/cld.445

Tranah, T., Vijay, G., Ryan, J., & Shawcross, D. (2013). Systemic inflammation and ammonia in hepatic encephalopathy. *Metabolic Brain Disease*, *28*(1), 1–5. doi:10.1007/s11011-012-9370-2

Ventura-Cots, M., Arranz, J., Simón-Talero, M., Torrens, M., Blanco, A., Riudor, E., … Córdoba, J. (2013). Safety of ornithine phenylacetate in cirrhotic decompensated patients: An open-label, dose-escalating, single-cohort study. *Journal Clinical Gastroenterology*, *47*(10):881–887. doi:10.1097/MCG.0b013e318299c789

Ventura-Cots, M., Concepción, M., Arranz, J., Simón-Talero, M., Torrens, M., Blanco-Grau, A., … Córdoba, J. (2016). Impact of ornithine phenylacetate (OCR-002) in lowering plasma ammonia after upper gastrointestinal bleeding in cirrhotic

patients. *Therapeutic Advances in Gastroenterology*, *9*(6), 823–835. doi:10.1177/1756283X16658252

Vilstrup, H., Amodio, P., Bajaj, J., Cordoba, J., Ferenci, P., Mullen, K. D., … Wong, P. (2014). Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*, *60*(2), 715–735. doi:10.1016/j.jhep.2014.05.042

Wright, G., Chattree, A., & Jalan, R (2011). Management of hepatic encephalopathy. *International Journal of Hepatology*, *2011*, 841407. doi:10.4061/2011/841407

Zhu, G., Shi, K., Huang, S., Wang, L., Lin, Y., Huang, G. Q., … Zheng, M. H. (2015). Systematic review with network meta-analysis: The comparative effectiveness and safety of interventions in patients with overt hepatic encephalopathy. *Alimentary Pharmacology & Therapeutics*, *41*(7), 624–635. doi:10.1111/apt.13122

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