Open Access

OBM Hepatology and Gastroenterology

LIDSEN Publishing Inc.

Review

Therapeutic Strategies and Current Management for Hepatic Encephalopathy in Liver Cirrhosis

Kazuyuki Suzuki [1,*], Akinobu Kato [2], Yasuhiro Takikawa [1]

1. Division of Hepatology, Department of Internal Medicine, Iwate Medical University, Morioka, Iwate, Japan; E-Mails: kasuzuki48@hotmail.co.jp, ytakikaw@iwate-med.ac.jp
2. Department of Gastroenterology, Morioka Municipal Hospital, Morioka, Iwate, Japan; E-Mail: nobukato@morioka-city-hosp.jp

* **Correspondence:** Kazuyuki Suzuki; kasuzuki48@hotmail.co.jp

Academic Editor: Tatsuo Kanda

Special Issue: Pathology and Management of Cirrhosis

OBM Hepatology and Gastroenterology
2019, volume 3, issue 3
doi:10.21926/obm.hg.1903027

Received: February 04, 2019
Accepted: July 10, 2019
Published: July 16, 2019

Abstract

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome with a wide spectrum of symptoms and one of the serious complications seen in patients with acute and chronic liver disease or spontaneous portal-systemic shunting. HE is usually classified into three types according to the underlying cause (A, B, and C). Some recent discussions suggest a fourth type (D) to exclusively include HE patients with acute-on-chronic liver failure. HE has also been classified into coma grades I to IV according to the West Haven criteria, while the International Society for Hepatic Encephalopathy and Nitrogen Metabolism has proposed two distinct categories: covert HE (includes minimal HE, which is identified solely through psychometric or neurological tests and coma grade I) and overt HE (coma grade II-IV). Although modern therapeutic approaches based on clinical evidence have gradually improved the outcomes of cirrhotic patients with HE, recurrent or resistant HE is still common and the prognosis in patients with severe liver dysfunction is still poor. In this article, we discuss the therapeutic strategies and current management, except for liver

transplantation and interventional procedures for portal-systemic shunting, in cirrhotic patients with HE.

Keywords
Hepatic encephalopathy; liver cirrhosis; portal-systemic shunting; disaccharides; rifaximin; branched-chain amino acids; zinc; carnitine; ammonia-lowering drugs

1. Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome and one of the serious complications often observed in patients with acute and chronic liver failure or spontaneous portal-systemic shunting (PSS) [1]. HE is classified into three types according to the underlying cause: type A results from acute liver failure; type B results from porta-systemic shunting without liver dysfunction; and type C results from liver cirrhosis (LC) [2, 3]. Further, recent discussions have also proposed the fourth type (type D) to separately include HE patients with acute-on-chronic liver failure (ACLF), because they are different in terms of their clinical, pathophysiological, and prognostic features from those with types A–C [4, 5]. HE shows a wide spectrum of clinical symptoms that include personality change, intellectual impairment, changes in neuromuscular activity (in particular, asterixis), and disturbed consciousness ranging from minor deficits in orientation and coordination to deep coma (grades I-IV according to the West Haven criteria) [1-3]. HE, according to its time course, is also subdivided into episodic, recurrent, and persistent HE [2]. Recently, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) recommended that HE needs to be classified into two more distinct categories: covert HE and overt HE [6, 7]. Covert HE involves minimal HE (MHE) and coma grade I (Figure 1). Although MHE is identified solely through psychometric or neurological tests, a global standard method for the diagnosis of MHE has not been established [7-9]. The therapeutic outcome and final prognosis of HE are mainly affected by the severity of liver damage even when appropriate medical treatments (except liver transplantation) have been performed [10-12].

Although the pathogenesis of HE has not been fully clarified, many neurotoxic substances, such as ammonia, short-chain fatty acids, amines, mercaptan, indoles, phenols, and benzodiazepine-like compounds produced mainly in the gut, have been seen to be closely associated with the onset and recurrence of HE [13-15]. Of these neurotoxic substances, ammonia is the most important factor participating in the pathogenesis of HE. Hyperammonemia finally induces the swelling of astrocytes, which is the only compartment for the detoxification of ammonia released by the synthesis of glutamine (Gln) in the brain, resulting in a disturbance of neurotransmission [16-18]. Many studies, using ^{1}H-magnetic resonance spectroscopy, have supported astrocyte swelling and Gln accumulation in the brain in cirrhotic patients with or without HE [18-20]. Furthermore, some recent studies have also shown that gut dysbiosis is closely associated with the pathogenesis of HE in LC [21-24]. Therefore, fecal microbial transplantation (FMT) has been in focus as an option of treatment in LC patients with HE [25, 26]. However, FMT has still not been confirmed and carries many problems including its indication and method of implication.

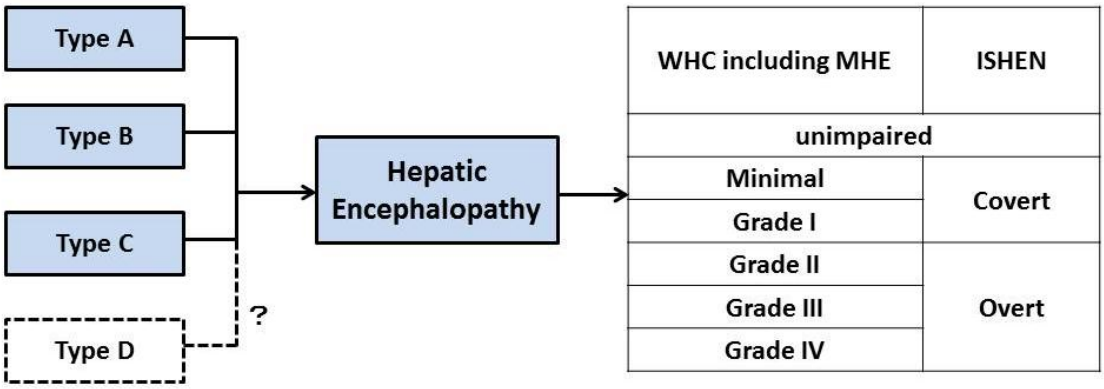

Figure 1 Definition and classification of hepatic encephalopathy.

HE is usually divided into three types (Type A-C), according to the underlying cause: type A results from acute liver failure; type B results from porta-systemic shunting without liver dysfunction; and type C results from liver cirrhosis. Some researchers have proposed, type D resulting from acute-on-chronic liver failure.

WHC, West Haven criteria; MHE, minimal hepatic encephalopathy; ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism.

In this issue, we mainly discuss the therapeutic strategies and current management practices of HE in LC patients (so-called type C HE), except liver transplantation and interventional procedures such as transjugular intrahepatic portosystemic shunt (TIPS) or embolization for PSS.

2. Evaluation Associated with the Pathogenesis of HE in LC

A systemic evaluation, including the severity of liver damage, the existence of PSS, participating factors, and other complications such as spontaneous bacterial peritonitis (SBP), must be carried out before the treatment of LC patients with HE (Figure 2). In particular, both the evaluation of the severity of liver damage and clinical characteristics are very important in LC. In fact, LC is classified into two types based on the severity of liver damage: hepatocellular injury-dominant type and shunt-dominant type. The former (including acute-on-chronic type based on LC) usually shows hyperbilirubinemia and low prothrombin time activity, while the latter shows only mild hepatocellular damage. These disease types affect the prognosis of LC. Hyperammonemia is commonly observed in both types. The factors precipitating HE in LC include dietary indiscretion (usually overdose of dietary protein), gastrointestinal bleeding (rupture of gastroesophageal varices and bleeding from portal hypertensive gastropathy), constipation, infection, psychoactive medication (excessive administration of sedative/analgesic drugs), electrolyte disorder due to diuretic overdose, and dehydration [1, 2]. The prevalence of these precipitating factors differs between the episodic type and the recurrent type in LC patients with HE [2]. In addition, it is important to note that intra-abdominal bleeding is caused by the rupture of extrahepatic progressive hepatocellular carcinoma in LC patients with advanced HCC. Certain respiratory and systemic circulatory disturbances (e.g., hypoxemia, hypotension, and congestion) are also associated with exacerbations and the prognosis of HE [12]. In recent time, the cases of HE due to

gastrointestinal bleeding have dramatically decreased, as treatment modalities such as pharmaceutical and interventional therapies for gastroesophageal varices and portal hypertensive gastropathy have advanced. On the other hand, the cases of HE without obvious precipitating factors still occur. A TIPS is useful in the management of the complications of portal hypertension, in particular, gastroesophageal varices, although its insertion precipitates HE [27, 28]. A recent study by Routhu et al. suggested that several factors (in particular, age, pre-TIPS portal venous pressure, serum creatinine, presence of diabetes mellitus, and etiology of portal hypertension) are significantly associated with the development of overt HE after TIPS [29].

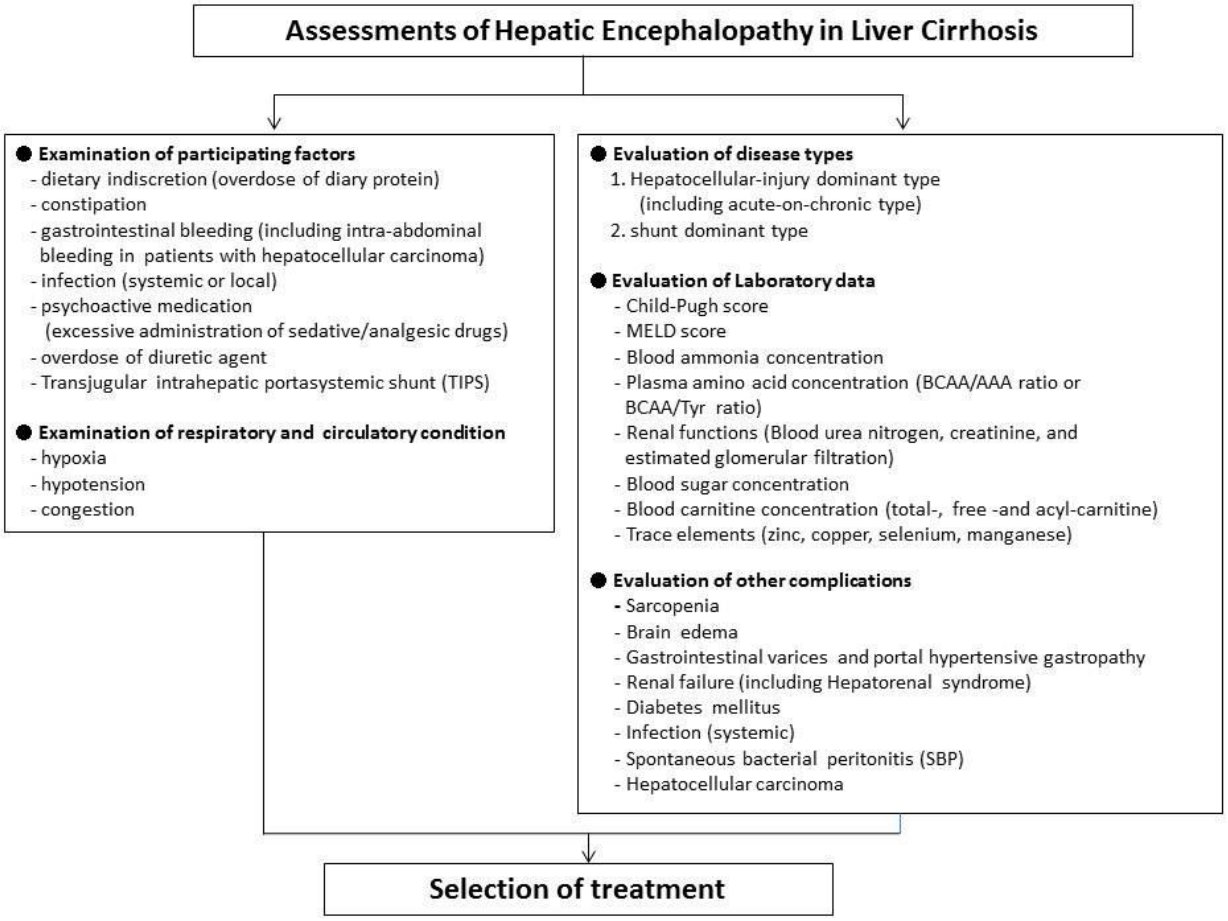

Figure 2 Systemic evaluation of cirrhotic patients with hepatic encephalopathy before treatment.

3. Management

A flow chart of the available pharmacological modalities to treat LC patients with HE is shown in Figure 3. The management of HE in LC patients is classified into two categories (nutritional management and drugs). The goal of the initial management of HE is to improve disturbed consciousness and reduce blood ammonia concentration. First, the coma grade of HE is determined and the possibility of oral administration of nutrients and drugs is explored. The first therapeutic step is the use of non-absorbable disaccharides to improve the hyperammonemic state. Ammonia is metabolized in the liver, digestive organs (stomach, small and large intestines), kidney, muscle, lung, and brain. Since the causes of hyperammonemia in each patient with HE are

complex and diverse, it is very important to understand the ammonia metabolism in various organs and the interactions between them.

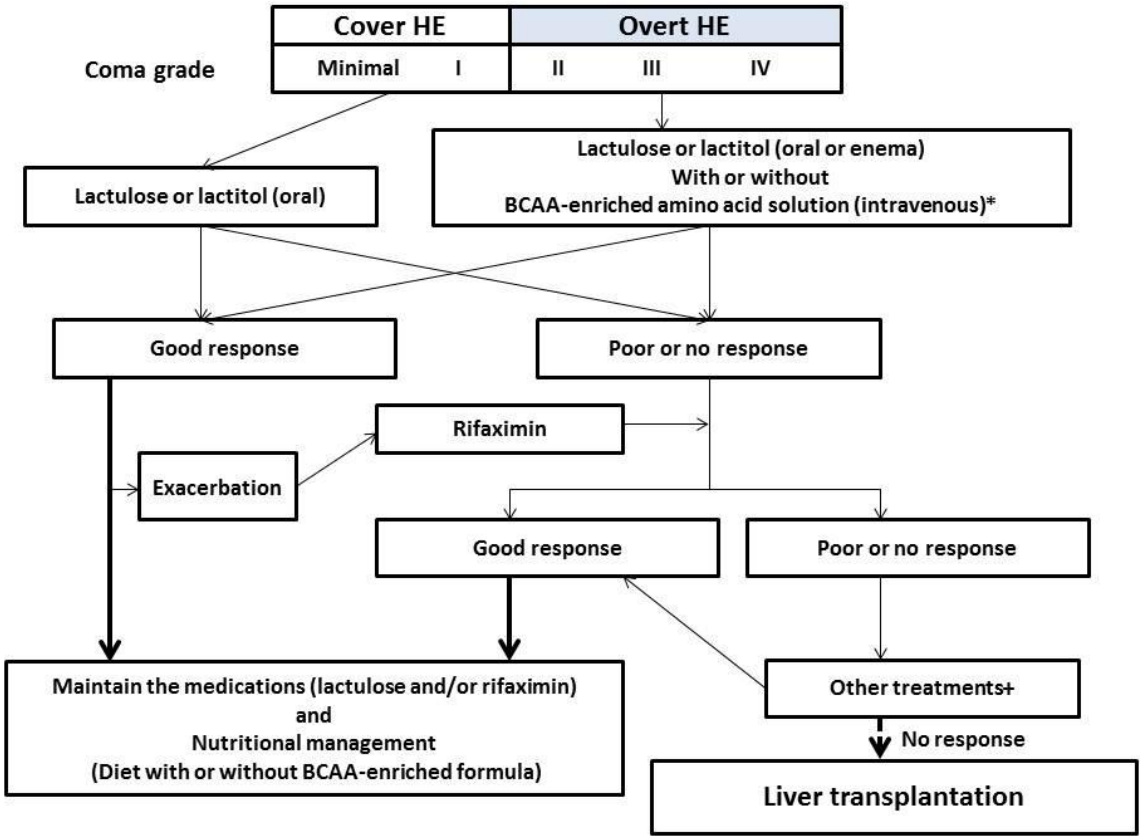

Figure 3 The flow chart of the proposed management for cirrhotic patients with hepatic encephalopathy.

* Infusion therapy of BCAA-enriched amino acid solution has not yet been adopted worldwide;
+ including ammonia-lowering drugs and fecal microbiota transplantation

3.1 Nutritional Management

Nutritional management is fundamental in LC patients, regardless of HE, because the liver is the central organ in nutritional metabolism. In general, LC patients have malnutrition, which is characterized by protein-energy malnutrition (PEM) and is associated with LC prognosis [31-35]. Furthermore, sarcopenia or skeletal muscle atrophy is often observed in LC patients [36]. While muscles play an important role in ammonia detoxification by increasing glutamine synthesis, hyperammonemia may induce muscle dysfunction and contribute to muscle mass loss [37, 38]. Therefore, sarcopenia contributes to survival, health-related quality of life, outcomes after liver transplantation, and severe complications including HE in LC patients [39-43].

In order to formulate nutritional recommendations for LC patients with HE, the practice consensus was proposed by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) [44, 45]. More recently, the European Association for the Study of the Liver (EASL) proposed a clinical practice guideline on the nutrition in chronic liver disease [46], and

described the approaches and treatments for malnutrition (or undernutrition), sarcopenia, obesity, HE, and bone diseases (osteoporosis) in LC patients in detail. In contrast, the guideline on nutritional management of patients with LC of the Japanese Nutritional Study Group for Liver Cirrhosis suggests a restriction on dietary iron intake when LC patients show frequent hyperferritinemia because the excess deposition of iron in the liver causes oxidative stress and promotes hepatocarcinogenesis [47].

In general, since in LC patients with HE and coma over grade III, oral intake is impossible, nutrition is provided by a nasogastric tube or parenterally. However, HE patients with gastrointestinal bleeding (mainly rupture of gastroesophageal varices) and gastrointestinal motility dysfunction should be maintained by intravenous nutritional supplementation. In intravenous supplementation, a solution of glucose and high branched-chain amino acid (BCAA), with low aromatic amino acid (AAA) concentrations is recommended [48, 49]. However, in cases with severe liver dysfunction with hyperbilirubinemia and low prothrombin time activity (i.e., hepatocellular injury-dominant type), the administration of amino acid solutions is mostly contraindicated, because the excess nitrogen load exacerbates hyperammonemia and worsens coma grading [49].

By the middle of the 20th century, it was believed that the daily dosage of dietary protein should be strictly limited in LC patients with HE, as the overdosage of daily protein accelerated the hyperammonemic state as observed in dogs with the Eck fistula [50]. Additionally, a long-term protein-restricted diet results in progressive protein catabolism and exacerbates PEM in LC patients [51]. However, some other studies have shown that the restriction of dietary protein may not be necessary over the short term [52-54]. In addition, recent studies have recommended that the administration of enteral nutrients involving BCAA-enriched formulas is effective in improving the nitrogen balance in LC patients [55-59]. Further, Maharshi et al. reported in a randomized controlled trial that nutritional intervention (30–35 kcal/kg/day, 1.0–1.5 g vegetable protein/kg/day) for six months is effective in the treatment of MHE and health-related quality of life [60]. In an open randomized clinical trial carried on Mexican patients, it was observed that a high-fiber (30 g/day) high-protein (1.2 g/kg) diet, supplemented with BCAA (8.63 g/day involving sachets of 110 grams), over six months, was safe without elevation of blood ammonia and glucose levels and helped in increasing muscle mass [61]. Furthermore, Campollo et al. suggested that stable LC patients can tolerate standard mixed meals (protein intake of 1.2–1.5 g/kg body weight/day) but further study is necessary for decompensated LC patients [62]. Although these results suggest that the type of protein ingested may be important in countries where the use of BCAA-enriched formula is practically feasible, it is better to mildly restrict dietary protein and to add a BCAA-enriched enteral supplement in LC patients with HE and a large PSS.

On the other hand, the nutritional management in HE patients with diabetes mellitus (DM) and/or obesity has not been well established. However, total calorie intake should be carefully limited, even though hypoglycemic drugs and/or insulin are often administered as needed. The recent guidelines for the management of LC patients with DM recommend that a late evening snack (LES) may also ameliorate the hyperglycemic state [46, 47]. Furthermore, it has been reported that acarbose, an α-glucosidase inhibitor, is effective as a therapeutic agent for low-grade HE in LC patients with type 2 DM [63]. Our previous examination (unpublished data) showed that LES with α-glucosidase inhibitors is effective in correcting the energy metabolic abnormalities

using indirect calorimetry in LC patients. The total nutritional management involving the BCAA formula is also useful in patients with MHE diagnosed by neuropsychological tests [64].

3.2 Drugs

3.2.1 Non-Absorbable Disaccharides

Lactulose (β-galactosido-fructose) and lactitol (β-galactosido-sorbitol) are synthetic disaccharides and non-absorbable in the small intestine. These drugs are metabolized by the bacteria in the colon to acetic and lactic acids. This acidification in the colon not only creates a hostile environment for the survival of intestinal bacteria with urease activity involved in the production of ammonia in the gut but also facilitates the conversion of ammonia to non-absorbable ammonium, and, then, by an osmotic laxative effect, it flushes the ammonium ions out [65-67]. Furthermore, it is important to focus on the relationship between the gut microbiome composition and the pathogenesis of HE in LC patients [21-24, 68]. However, this relationship has not been clearly confirmed following lactulose administration [69, 70]. At present, these two drugs are widely used for the initial treatment of covert and overt HE both [1-3]. The effect of the two drugs in improving coma grade and blood ammonia concentration is almost equal. However, since the rate of adverse effects (nausea, vomiting, abdominal pain, flatulence, diarrhea, etc.) is lower with lactitol than that with lactulose, the former is better tolerated, though it is not available in the United States [71]. Both drugs are generally administered by the oral route (three to four times a day), and the dosage is appropriately adjusted according to the stool characteristics and daily frequency after administration. In an emergency condition, an enema using a mixture of lactulose (100 mL) and physiological saline (700 mL) is recommended (usually repeated every 4–6 h) [72, 73]. There have been conducted some randomized controlled trials comparing polyethylene glycol (PEG) and lactulose in LC patients with HE [74, 75]. The results of the trials indicated that an enema using both PEG and lactulose is safe and more effective than lactulose alone in the treatment of HE.

3.2.2 Antibiotics

Non-absorbable antibiotics are usually recommended when the treatment using synthetic disaccharides fails to improve hyperammonemia. Although neomycin, kanamycin, polymyxin B, vancomycin, and metronidazole have been used previously [76-78], rifaximin is the first-line antibiotic for the treatment of HE with hyperammonemia worldwide [79-85]. Furthermore, rifaximin shows few adverse effects during long-term use [85]. At present, the indication for rifaximin is HE (covert HE and overt HE) or a hyperammonemic state in chronic liver diseases according to the guidelines of the American Association for the Study of Liver Diseases and EASL [2]. We have recently reported that the efficacy of rifaximin is good and it is well tolerated in Japanese patients with HE and hyperammonemia [86]. In another study, the therapeutic effect of rifaximin on MHE and its effectiveness were reported [85]. Furthermore, rifaximin has been used in LC patients with SBP [87-91]. SBP is considered one of the severe complications in LC patients and is also a participating factor in HE and hepatorenal syndrome. The aforementioned reports suggest that rifaximin is highly promising for the treatment of LC patients with several complications.

3.2.3 BCAA-Enriched Formulas

A BCAA-enriched solution was developed for the purpose of improving intracerebral neurotransmission by correcting the amino acid imbalance in the blood and brain [13]. BCAA-enriched formulas, including an infusion solution, enteral nutritional supplement, and BCAA granules, are used depending on the clinical stage (coma or recovery stage) and the presence or absence of PEM [49, 56-59, 92]. Although the infusion therapy is generally used during the overt coma stage in Japan [49], its use could not be adopted worldwide, because it does not improve the prognosis of patients with HE [2].

Enteral nutrition is usually possible in patients within grade II coma and without abnormalities (bleeding or dysfunction of motility) of the gastrointestinal tract. A BCAA-enriched enteral nutritional supplement and BCAA granules were originally developed to improve the status of HE and are recommended in Japan for PEM [57, 59]. A BCAA-enriched enteral nutritional supplement is also occasionally used as a late evening snack (LES) to improve serum albumin levels and the nonprotein respiratory quotient in patients with LC [56-59]. BCAA granules (at a compounding ratio of approximately 1.2:2:1) were developed to correct the malnutrition status of LC patients with hypoalbuminemia (serum albumin concentration below 3.5 g/dL) in Japan [59]. Regarding the usefulness of long-term administration of BCAA granules to LC patients with malnutrition, the event-free rate (progression of ascites, edema, hepatic encephalopathy, jaundice, rupture of esophagogastric varices, incidence of liver cancer, death due to other causes, etc., during the course of treatment) was significantly lower in a BCAA granule administered group than that in a diet therapy group. Furthermore, it has been shown that male LC patients with both hepatitis C viral infection and a BMI greater than or equal to 25 kg/m^2 have a lower incidence of HCC [93]. Furthermore, some recent studies have indicated that BCAA-enriched formulas prevent carcinogenesis and poor outcomes in patients with LC [94]. Thus, many reports suggest that BCAA supplementation is the fundamental treatment for LC patients with PEM or hypoalbuminemia; however, it is not available in the United States [95].

3.2.4 Other Ammonia-Lowering Drugs

L-ornithine L-aspartate (LOLA): LOLA is a mixture of two amino acids, which metabolizes ammonia in the form of urea and/or glutamine in the liver and muscles [96]. The treatment by LOLA (in oral and intravenous forms) for covert HE and HE has been recently developed in European countries, although it is not available in the United States and Japan. In clinical trials, intravenous administration of LOLA showed a significant effect by reducing HE grade, decreasing venous blood ammonia concentration, and improving psychomotor function in patients with MHE and OHE compared to placebo [97-100]. A large scale study by Sidhu et al. reported that five days of intravenous LOLA (30 g daily), as an add-on therapy with lactulose (30-120 mL through a nasogastric tube or orally and/or lactulose enema) and ceftriaxone (2 g twice daily), can significantly improve the grade of HE over days 1–4, but not on day 5 compared to placebo [98]. It also decreased venous blood ammonia concentration, time until recovery, and length of hospital stay, in the same study. In contrast, Alvares-da-Silva et al. reported no significant differences between oral LOLA administration (for 60 days) and placebo in the mental state and neuropsychological tests in MHE patients [99], but the therapy was useful in preventing further

episodes of OHE. In summary, the administration of LOLA has shown improvement in the mental state and a decrease in the blood ammonia concentration in LC patients with OHE or CHE [100, 101]. However, further studies considering the degree of hepatocellular damage and the stage of HE are necessary.

Zinc: Zinc is an essential trace element that is associated with many metabolic pathways in the liver [102, 103]. Thus, zinc deficiency has frequently been seen in advanced LC patients with decreased dietary intake, decreased absorption from digestive tract, higher urinary excretion, activation of certain zinc transporters, and induction of hepatic metallothionein [104-107]. Zinc is also required for detoxification of ammonia via the urea cycle in the liver and its serum level shows a significant inverse relationship with blood ammonia concentrations in LC patients [108]. Since zinc is closely related to the pathogenesis of HE, several studies have examined the effects of zinc supplementation in patients with HE and hyperammonemia [109-112]. Our research group has recently performed a prolonged, randomized, placebo-controlled, double-blind trial and found that zinc supplementation for three months is effective and safe in treating hyperammonemia in patients with LC [113]. Although a large-scale controlled study examining the dosage of zinc, duration of administration, and basal condition of LC is needed to recommend zinc supplementation as a treatment option for HE patients with hyperammonemia.

Carnitine (CA): CA plays an important role in fat metabolism and energy production in the mitochondria and is also closely associated with the detoxification of ammonia via the urea cycle [114, 115]. It is considered that there is a high prevalence of a secondary CA deficiency state in LC [116, 117]. However, the deficiency of CA caused by the administration of some drugs, e.g., valproate, induces HE with hyperammonemia, and this deficiency can overcome by supplementation with CA [118-120]. At present, the administration of L-carnitine (L-CA) and/or acetyl-L-CA (ALC) is also suggested as an optional therapy for LC patients with covert and overt HE [121, 122]. As a mechanism of the effect of L-CA against hyperammonemia, a previous experimental study suggested that L-CA administration improves ammonia metabolism through energy metabolism in the brain [123]. However, the precise role of L-CA in regulating ammonia metabolism in astrocytes still remains unclear. Recently, our preliminary experimental study indicated that L-CA protects against acute ammonia-induced cytotoxicity in human astrocytes via ameliorating the intracellular amino acid disturbance [124]. Further studies are needed to clarify the mechanism through which L-CA/ALC improves energy metabolism in astrocytes loaded with ammonia.

Sodium benzoate: Sodium benzoate has occasionally been used to promote the excretion of ammonia into the urine, but it is mainly used for congenital urea cycle disorders [125].

Benzodiazepine receptor antagonist: Flumazenil has also been reported to show a short-term beneficial effect in HE but exerts no direct effect on hyperammonemia [126, 127].

Acarbose: Acarbose, a hypoglycemic agent acting through the inhibition of glucose absorption in the intestine, is usually used in patients with DM. Gentile et al. demonstrated that acarbose administration (100 mg thrice daily) improved the grade of coma and blood ammonia concentration in mild HE patients [63]. Acarbose may be helpful in treating HE patients with DM.

Probiotics: Probiotics are a mixture of beneficial bacteria. Since the recent studies suggest that the changes in the gut microbiome or dysbiosis in LC patients are associated with the pathogenesis of HE [68-70], probiotics are expected to be used as a long-term treatment in patients with HE.

However, the supremacy of probiotics over lactulose or lactitol in HE is still uncertain [128-130]. High-quality randomized trials are needed to further clarify the efficacy of probiotics.

4. Conclusions

There are multiple factors associated with the risk and prognosis of LC in patients with HE. Furthermore, the causes of hyperammonemia in a patient with HE are complex and diverse. In clinical practices, early detection and appropriately addressing the risk factors are necessary to improve the outcome and reduce mortality in LC patients with HE.

Author Contributions

Dr. Suzuki Kazuyuki planed and wrote this article. Dr. Kato Akinobu and Dr. Takikawa Yasuhiro actively contributed and checked this article.

Competing Interests

All authors have declared that no competing interests exist.

References

1. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy-definition, nomenclature, diagnosis, and quantification. Hepatology. 2002; 35: 716-721.
2. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. 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. 2014; 60: 715-735.
3. Wijdicks EFM. Hepatic encephalopathy. N Engl J Med. 2016; 375: 1660-1670.
4. Romero-Gomez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. J Hepatol. 2015; 62: 437-447.
5. Weissenborn K. Hepatic encephalopathy: Definition, clinical grading and diagnostic principles. Drugs. 2019; 79: 55-59.
6. Bajaj JS, Cordoba J, Mullen KD, Amodio P, Shawcross DL, Butterworth RF, et al. Review article: The design of clinical trials in hepatic encephalopathy-an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement. Aliment Pharmacol Ther. 2011; 33: 739-747.
7. Randolph C, Hilsabeck R, Kato A, Kharbanda P, Li YY, Mapelli D, et al. Neuropsychological assessment of hepatic encephalopathy: ISHEN practice guidelines. Liver Int. 2009; 29: 629-635.
8. Weissenborn K. Diagnosis of minimal hepatic encephalopathy. J Clin Exp Hepatol. 2015; 5: S54-S59.
9. Tapper EB, Parikh ND, Waljee AK, Volk M, Carlozzi NE, Lok AS. Diagnosis of minimal hepatic encephalopathy: A systemic review pf point-of-care diagnostic tests. Am J Gastroenterol. 2018; 113: 529-538.
10. Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. J Hepatol. 1999; 30: 890-895.

11. Arguedas MR, DeLawrence TG, McGuire BM. Influence of hepatic encephalopathy on health-related quality of life in patients with cirrhosis. Dig Dis Sci. 2003; 48: 1622-1626.
12. Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. Liver Transpl. 2007; 13: 1366-1371.
13. Fischer JE, Baldessarini RJ. False neurotransmitters and hepatic failure. Lancet. 1971; 2: 750-780.
14. Butterworth RF. Pathogenesis of hepatic encephalopathy: New insights from neuroimaging and molecular studies. J Hepatol. 2003; 39: 278-285.
15. Atluri DK, Prakash R, Mullen K. Pathogenesis, diagnosis, and treatment of hepatic encephalopathy. J Clin Ex Hepatol. 2011; 1: 77-86.
16. Romero-Gomez M, Jover M, Galan JJ, Ruiz A. Gut ammonia production and its modulation. Metab Brain Dis. 2009; 24: 147-57.
17. Lockwood AH, Yap EW, Wong WH. Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopathy. J Cereb Blood Flow Metab. 1991; 11: 337–341.
18. Häussinger D, Laubenberger J, vom Dahl S, Ernst T, Bayer S, Langer M, et al. Proton-magnetic resonance spectroscopy studies on human brain myoinositol in hypo-osmolality and hepatic encephalopathy. Gastroenterology. 1994; 107: 1475–1480.
19. Laubenberger J, Häussinger D, Bayer S, Gufler H, Hennig J, Langer M. Proton magnetic resonance spectroscopy of the brain in symptomatic and asymptomatic patients with liver cirrhosis. Gastroenterology. 1997; 112: 1610–1616.
20. Kooka Y, Sawara K, Endo R, Kato A, Suzuki K, Takikawa Y. Brain metabolism in minimal hepatic encephalopathy assessed by 3.0-tesla magnetic resonance spectroscopy. Hepatol Res. 2016; 46: 269-276.
21. Dhiman RK. Gut microbiota, inflammation and hepatic encephalopathy: A puzzle with a solution in sight. J Clin Exp Hepatol. 2012; 2: 207-210.
22. Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, et al. The cirrhosis dysbiosis ratio defines changes in the gut microbiome associated with cirrhosis and its complication. J Hepatol. 2014; 60: 940-947.
23. Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature. 2014; 513: 59-64.
24. Rai R, Saraswat VA, Dhiman RK. Gut microbiota: Its role in hepatic encephalopathy. J Clin Exp Hepatol. 2015; 5: s29-36.
25. Kao D, Roach B, Park H, Hotte N, Madsen K, Bain V, et al. Fecal microbiota transplantation in the management of hepatic encephalopathy. Hepatology. 2016; 63: 339-340.
26. Bajaj JS, Kassam Z, Fagan A, Gavis EA, Liu E, Cox IJ, et al. fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. Hepatology. 2017; 66: 1727-1738.
27. Caregaro L, Alberino F, Amodio P, Merkel C, Bolognesi M, Angeli P, et al. Malnutrition in alcoholic and virus-related cirrhosis. Am J Clin Nutr. 1996; 63: 602-609.
28. Riggio O, Angeloni S, Ridola L. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: Still a major problem. Hepatology. 2010; 51: 2237-2238.
29. Pereira K, Carrion AF, Martin P, Vaheesan K, Salsamendi J, Doshi M, et al. Current diagnosis and management of post-transjugular intrahepatic portosystemic shunt refractory hepatic encephalopathy. Liver Int. 2015; 35: 2487-2494.

30. Routhu M, Safka V, Routhu SK, Fejfar T, Jirkovsky V, Krajina A, et al. Observational cohort study of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt (TIPS). Ann Hepatol. 2017; 16: 140-148.
31. Campillo B, Richardet JP, Scherman E, Bories PN. Evaluation of nutritional practice in hospitalized cirrhotic patients: Results of a prospective study. Nutrition. 2003; 19: 515-521.
32. McCullough AR, Raguso C. Effect of cirrhosis on energy expenditure. Am J Clin Nutr. 1999; 69: 1066-1068.
33. Alberino F, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, et al. Nutrition and survival in patients with liver cirrhosis. Nutrition. 2001; 17: 445-450.
34. Tajika M, Kato, Mohri H, Miwa Y, Kato T, Ohnishi H, et al. Prognostic value of energy metabolism in patients with viral liver cirrhosis. Nutrition. 2002; 18: 229-234.
35. Huisman EJ, Trip EJ, Siersema PD, van Hoek B, van Erpecum KJ. Protein energy malnutrition predicts complications in liver cirrhosis. Eur J Gastroenterol Hepatol. 2011; 23: 982-989.
36. Anand AC. Nutrition and muscle in cirrhosis. J Clin Exp Hepatol. 2017; 7: 340-357.
37. McDaniel J, Davuluri G, Hill EA, Moyer M, Runkana A, Prayson R, et al. Hyperammonemia results in reduced muscle function independent of muscle mass. Am J Physiol Gastrointest Liver Physiol. 2016; 310: G163-G170.
38. Kumar A, Davuluri G, Englelen MP, Ten Have GA, Prayson R, Deutz NE, et al. Ammonia lowering reverses sarcopenia of cirrhosis by restoring skeletal muscle proteostasis. Hepatology. 2017; 65: 2045-2058.
39. Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: A systemic review and meta-analysis. PloS one. 2017; 12: e0186990.
40. Kaido T, Tamai Y, Hamaguchi Y, Okumura S, Kobayashi A, Shirai H, et al. Effects of pretransplant sarcopenia and sequential changes in sarcopenic parameters after living donor liver transplantation. Nutrition. 2017; 33: 195-198.
41. Harimoto N, Yoshizumi T, Izumi T, Motomura T, Harada N, Itoh S, et al. Clinical outcomes of liver transplantation according to the presence of sarcopenia as defined by skeletal muscle mass, hand grip, and gait speed. Transplant Proc. 2017; 49: 2144-2152.
42. Chae MS, Moon KU, Jung JY, Choi HJ, Chung HS, Park CS, et al. Perioperative loss of psoas muscle is associated with patient survival in living donor liver transplantation. Liver Transpl. 2018; 24: 623-633.
43. Hanai T, Shiraki M, Watanabe S, Kochi T, Imai K, Suetsugu A, et al. Sarcopenia predicts minimal hepatic encephalopathy in patients with liver cirrhosis. Hepatol Res. 2017; 47: 1359-1367.
44. Amodio P, Bemeur C, Butterworth RF, Cordoba J, Kato A, Montagnese S, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. Hepatology. 2013; 58: 325-336.
45. Bemeur C, Butterworth RF. Nutrition in the management of cirrhosis and its neurological complications. J Clin Exp Hepatol. 2014; 4: 141-150.
46. European Association for the Study of the Liver. EASL clinical practice guidelines on nutrition in chronic liver disease. J Hepatol. 2019; 70: 172-193.
47. Suzuki K, Endo R, Kohgo Y, Ohtake T, Ueno Y, Kato A, et al. Guidelines of nutritional management in Japanese patients with liver cirrhosis from the perspective of preventing hepatocellular carcinoma. Hepatol Res. 2012; 42: 621-626.

48. Fischer JE, Rosen HM, Ebeid AM, James JH, Keane JM, Soeters PB. The effect of normalization of plasma amino acids on hepatic encephalopathy. Surgery. 1976; 80: 77-91.
49. Suzuki K, Kato A, Iwai M. branched-chain amino acid treatment in patients with liver cirrhosis. Hepatol Res. 2004; 30S: S25-S29.
50. Thompson J, Schafer D, Haun J, Schafer G. Adequate diet prevents hepatic coma in dogs with Eck fistulas. Surg Gynecol Obstetr. 1986; 162: 126-130.
51. Schwartz R, Phillips GB, Seegmiller JE, Gabuzda Jr GJ, Davidson CS. Dietary protein in the genesis of hepatic coma. N Engl J Med. 1954; 251: 685-689.
52. Córdoba J, López-Hellin J, Planas M, Sabin P, Sanpedro F, Castro F, et al. Normal protein diet for episodic hepatic encephalopathy: Results of a randomized study. J Hepatol. 2004; 41: 38-43.
53. Cabral CM, Burns DL. Low-protein diets for hepatic encephalopathy: Let them eat steak. Nutr Clin Pract. 2011; 26: 155-159.
54. Amodio P, Canesso F, Montagnese S. Dietary management of hepatic encephalopathy revised. Curr Opin Clin Nutr Metab Care. 2014; 17: 448-452.
55. Fialla AD, Israelsen M, Hamberg O, Krag A, Gluud LL. Nutritional therapy in cirrhosis or alcoholic hepatitis: A systemic review and meta-analysis. Liver Int. 2015; 35: 2072-2078.
56. Moriwaki H, Miwa Y, Tajika M, Kato M, Fukushima H, Shiraki M. Branched-chain amino acids as a protein- and energy-source in liver cirrhosis. Biochem Biophys Res Commun. 2004; 313: 405-409.
57. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol. 2005; 3: 705-713.
58. Marchesini G, Bianchi G, Merli M, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis. A double blind, randomized trial. Gastroenterology. 2003; 124: 1792-1801.
59. Nakaya Y, Okita K, Suzuki K, Moriwaki H, Kato A, Miwa Y, et al. BCAA- enriched snack improves nutritional state of cirrhosis. Nutrition. 2007; 23: 113-120.
60. Maharshi S, Sharma BC, Sachdeva S, Srivastava S, Sharma O. Efficacy of nutritional therapy for patients with cirrhosis and minimal hepatic encephalopathy in a randomized trial. Clin Gastroenterol Hepatol. 2016; 14: 454-460.
61. Ruiz-Margáin A, Macias-Rodriguez RU, Rios-Torres SL, Román-Calleja BM, Mendez-Guerrero O, Rodriguez-Cordova P, et al. Effect of a high-protein, high-fiber diet plus supplementation with branched-chain amino acids on the nutritional status of patients with cirrhosis. Revista de Gastroenterologia de Mexico. 2018; 83: 9-15.
62. Campollo O, Sprengers D, Dam G, Vilstrup H, McIntyre N. protein tolerance to standard and high protein meals in patients with liver cirrhosis. World J Hepatol. 2017; 18: 667-676.
63. Gentile S, Guarino G, Romano M, Alagia IA, Fierro M, Annunziata S, et al. A randomized controlled trial of acarbose in hepatic encephalopathy. Clin Gastroenterol Hepatol. 2005; 3: 1834-1191.
64. Kato A, Tanaka H, Kawaguchi T, Kanazawa H, Iwasa M, Sakaida I, et al. Nutritional management contributes to improvement in minimal hepatic encephalopathy and quality of life in patients with liver cirrhosis: A preliminary, prospective, open-labeled study. Hepatol Res. 2013: 43: 452-458.

65. Bircher J, Muller J, Guggenheim P, Haemmerli VP. Treatment of chronic portal-systemic encephalopathy with lactulose. Lancet. 1966; 1: 890-893.
66. Lanthier PL, Morgan MY. Lactitol in the treatment of chronic encephalopathy: An open comparison with lactulose. Gut. 1985; 26: 415-420.
67. Morgan MY. Current state of knowledge of hepatic encephalopathy (part III): Non-absorbable disaccharides. Metab Brain Dis. 2016; 31: 1361-1364.
68. Baja JS, Betrapally NS, Hylemon PB, Heuman DM, Daita K, White MB, et al. Salivary microbiota reflects changes in gut microbiota in cirrhosis with hepatic encephalopathy. Hepatology. 2015; 62: 1260-1271.
69. Rai R, Saraswat VA, Dhiman RK. Gut microbiota: Its role in hepatic encephalopathy. J Clin Exp Hepatol. 2015; 5: S29-S36.
70. Sarangi AN, Goel A, Singh A, Sasi A, Aggarwal R. Faecal bacterial microbiota in patients with cirrhosis and the effect of lactulose administration. BMC Gastroenterology. 2017: 17: 125.
71. Acharya CA, Bajaj JS. Current management of hepatic encephalopathy. Am J Gastroenterol. 2018. DOI: 10.1038/s41395-018-0179-4.
72. Kersh ES, Rifkin H. Lactulose enemas. Am Int Med. 1973; 78: 81-84.
73. Uribe M, Campollo O, Vargas F, Ravelli GP, Mundo F, Zapata L, et al. Acidifying enemas (lactitol and lactulose) vs. nonacidifying enemas (tap water) to treat portal-systemic encephalopathy: A double-blind, randomized clinical trial. Hepatology. 1987; 7: 639-643.
74. Naderian M, Akbari H, Saeedi M, Sohrabpour AA. Polyethylene glycol and lactulose versus lactulose alone in the treatment of hepatic encephalopathy in patients with cirrhosis: A non-inferiority randomized controlled trial. Meddle East J Dig Dis. 2017; 9: 12-19.
75. Shehata HH, Elfert AA, Abdin AA, Soliman SM, Elkhouly RA, Hawash NI, et al. Randomized controlled trial of polyethylene glycol versus lactulose for the treatment of overt hepatic encephalopathy. Eur J Gastroenterol Hepatol. 2018; 30: 1476-1481.
76. Tarao K, Ikeda T, Hayashi K, Sakurai A, Okada T, Ito T, et al. Successful use of vancomycin hydrochloride in the treatment of lactulose resistant chronic hepatic encephalopathy. Gut. 1990; 31: 702-706.
77. Blei AT, Córdoba J. Hepatic encephalopathy. Am J Gastroenterol. 2001; 96: 70-80.
78. Morgan MY, Blei A, Grüngreiff K, Jalan R, Kircheis G, Marchesini G, et al. The treatment of hepatic encephalopathy. Metab Brain Dis. 2007; 22: 389-405.
79. De Marco F, Santamaria AP, D'arienzo A. Rifaximin in collateral treatment of portal-systemic encephalopathy: A preliminary report. Current Ther Res. 1984; 36: 668-674.
80. Giacomo F, Francesco A, Michele N, Oronzo S, Antonella F. Rifaximin in the treatment of hepatic encephalopathy. Eur J Clin Res. 1993; 4: 57-66.
81. Festi D, Mazella G, Orsini M, Sottili S, Sangermano A, Li Bassi S. Rifaximin in the treatment of chronic hepatic encephalopathy: Results of a multicenter study of efficacy and safety. Curr Ther Res. 1993; 54: 598-609.
82. Mas A, Rodes J, Sunyer L, Rodrigo L, Planas R, Vargas V, et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: Results of a randomized, double-blind, double-dummy, controlled clinical trial. J Hepatol. 2003; 38: 51-58.
83. Miglio F, Valpiani D, Rossellini SR, Ferrieri A. Rifaximin, a non-absorbable rifaximin, for the treatment of hepatic encephalopathy. A double-blind, randomized trial. Current Med Res Opinion. 1997; 13: 593-601.

84. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010; 362: 1071-1081.
85. Kimer N, Krag A, Møller S, Bendtsen F, Gluud LL. Systemic review with meta-analysis: The effects of rifaximin in hepatic encephalopathy. Aliment Pharmacol Ther. 2014: 40: 123-132.
86. Suzuki K, Endo R, Takikawa Y, Moriyasu F, Aoyagi Y, Moriwaki H, et al. Efficacy and safety of rifaximin in Japanese patients with hepatic encephalopathy: A phase II/III, multicenter, randomized, evaluator-blinded, active-controlled trial and a phase III, multicenter, open trial. Hepatol Res. 2018; 48: 411-423.
87. Kalambokis GN, Mouzaki A, Rodi M, Tsianos EV. Rifaximin for the prevention of spontaneous bacterial peritonitis. World J Gastroenterol. 2012; 18: 1700-1702.
88. Hanouneh MA, Hanouneh IA, Hashash JG, Law R, Esfeh JM, Lopez R, et al. The role of rifaximin in the primary prophylaxis of spontaneous bacterial peritonitis in patients with liver cirrhosis. J Clin Gastroenterol. 2012; 46: 709-715.
89. Assem M, Elsabaawy M, Abdelrashed M, Elemam S, Khodeer S, Hamed W, et al. Efficacy and safety of alternating norfloxacin and rifaximin as primary prophylaxis for spontaneous bacterial peritonitis in cirrhotic ascites: A prospective randomized open-label comparative multicenter study. Hepatol Int. 2016; 10: 377-385.
90. Kamal F, Khan MA, Khan Z, Cholankeril G, Hammad TA, Lee WM, et al. Rifaximin for the prevention of spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis: A systemic review and meta-analysis. Eur J Gastroenterol Hepatol. 2017; 29: 1109-1117.
91. Flamm SL, Mullen KD, Heimanson Z, Sanyal AJ. Rifaximin has the potential to prevent complications of cirrhosis. Therap Adv Gastroenterol. 2018; 11: 175628481880030.
92. Kawaguchi T, Izumi N, Charton MR, Sata M. Branched-chain amino acids as pharmaceutical nutrients in chronic liver disease. Hepatology. 2011; 54: 1063-1070.
93. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. Hepatol Res. 2006; 35: 204-214.
94. Kawaguchi T, Shiraishi K, Ito T, Suzuki K, Koreeda C, Ohtake T, et al. Branched-chain amino acids prevent hepatocarcinogenesis and prolong survival of patients with cirrhosis. Clin Gastroenterol Hepatol. 2014; 12: 1012-1018.
95. Ooi PH, Glimour SM, Yap J, Mager DR. Effects of branched chain amino acid supplementation on patient care outcomes in adult and children with liver cirrhosis: A systemic review. Clin Nutr ESPEN. 2018; 28: 41-51.
96. Butterworth RF, Giguere JF, Michaud J, Lavoie J, Layrargues GP. Ammonia: Key factor in the pathogenesis of hepatic encephalopathy. Neurochem Pathol. 1987; 6: 1-12.
97. Stauch S, Kircheis G, Adler G, Beckh K, Ditschuneit H, Gortelmeyer R, et al. Oral-L-ornithine-L-aspartate therapy of chronic hepatic encephalopathy: Results of a placebo-controlled double-blind study. J Hepatol. 1998; 28: 856-864.
98. Sidhu SS, Sharma BC, Goyal O, Kishore H, Kaur N. L-ornithine L-aspartate in bouts of overt hepatic encephalopathy. Hepatology. 2018; 67: 700-710.
99. Alvares-da-Silva MR, de Araujo A, Vicenzi JR, da Silva GV, Oliveira FB, Schacher F, et al. Oral l-ornithine-l-aspartate in minimal hepatic encephalopathy: A randomized, double-blind, placebo-controlled trial. Hepatol Res. 2014; 44: 956-963.

100. Goh ET, Stokes CS, Sidhu SS, Vilstrup H, Gluud LL, Morgan MY. L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis. Cochrane Database Syst Rev. 2018; 15; 5:CD012410.
101. Butterworth RF, Kircheis G, Hilger N, McPhail MJW. Efficacy of l-ornithine l-aspartate for the treatment of hepatic encephalopathy and hyperammonemia in cirrhosis: Systemic review and meta-analysis of randomized controlled trials. J Clin Exp Hepatol. 2018: 8: 301-313.
102. Vallee BL, Wacker WEC, Batholomay AF, Robin ED. Zinc metabolism in hepatic dysfunction, I: Serum zinc concentrations in Laennec's cirrhosis and their validation by sequential analysis. N Engl J Med. 1956; 255: 403-408.
103. Vallee BL, Wacker WEC, Batholomay AF, Hoch FL. Zinc metabolism in hepatic dysfunction, II: Correlation of metabolic patterns with biochemical findings. N Engl J Med. 1956; 257: 1056-1065.
104. Grungreiff K, Reinhold D, Wedemeyer H. The role of zinc in liver cirrhosis. Ann Hepatol. 2016; 15: 7-16.
105. Mohammad MK, Zhou Z, Cave M, Barve A, McClain CJ. Zinc and liver disease. Nutr Clin Pract. 2012; 27: 8-20.
106. Chiba M, Katayama K, Takeda R, Morita R, Iwahashi K, Onishi Y, et al. Diuretics aggravate zinc deficiency in patients with liver cirrhosis by increasing zinc excretion in urine. Hepatol Res. 2013; 43: 365-373.
107. Katayama K, Kawaguchi T, Shiraishi K, Ito T, Suzuki K, Koreeda C, et al. The prevalence and implication of zinc deficiency in patients with chronic liver disease. J Clin Med Res. 2018; 10: 437-444.
108. Reding P, Duchateau J, Bataille C. Oral zinc supplementation improves hepatic encephalopathy: Results of a randomized controlled trial. Lancet. 1984; 2: 493-495.
109. Riggio O, Ariosto F, Merli M, Caschera M, Zullo A, Balducci G, et al. Short-term oral zinc supplementation does not improve chronic hepatic encephalopathy. Result of a double-blind crossover trial. Dig Dis Sci. 1991; 36: 1204-1208.
110. Bresci G, Parisi G, Banti S, Management of hepatic encephalopathy with oral zinc supplementation: A long-term treatment. Eur J Med. 1993; 2: 414-416.
111. Chavez-Tapia NC, Cesar –Arce A, Barrientos-Gutierrez T, Villegas-Lopez FA, Mendez-Sanchez N, Uribe M. A systematic review and meta-analysis of the use of oral zinc in the treatment of hepatic encephalopathy. Nutr J. 2013; 12: 74.
112. Mousa N, Abdel-Razik A, Zaher A, Hamed M, Shiha G, Effat N, et al. The role of antioxidants and zinc in minimal hepatic encephalopathy: A randomized trial. Ther Adv Gastroenterol. 2016; 9: 684-691.
113. Katayama K, Saito M, Kawaguchi T, Endo R, Sawara K, Nishiguchi S, et al. Effect of zinc on liver cirrhosis with hyperammonemia: A preliminary randomized, placebo-controlled double-blind trial. Nutrition. 2014; 30: 1409-1414.
114. Vaz FM, Wanders RJ. Carnitine biosynthesis in mammals. Biochem J. 2002; 361: 417-429.
115. Krähenbühl S, Brass EP, Hoppel CL. Decreased carnitine biosynthesis in rats with secondary biliary cirrhosis. Hepatology. 2000; 31: 1217-1223.
116. Rudman D, Sewell CW, Ansley JD. Deficiency of carnitine in cachectic cirrhotic patients. J Clin Invest. 1977; 60: 716-723.

117. Amodio P, Angeli P, Merkel C, Menon F, Gatta A. Plasma carnitine levels in liver cirrhosis: Relationship with nutritional status and liver damage. J Clin Chem Clin Biochem. 1990; 28: 619-626.
118. Verrotti A, Trotta D, Morgese G, Chiarelli F. Valproate-induced hyperammonemic encephalopathy. Metab Brain Dis. 2002; 17: 367-373.
119. Limketkai BN, Zucker SD. Hyperammonemic encephalopathy caused by carnitine deficiency. J Gen Intern Med. 2008; 23: 210-213.
120. Rigamonti A, Lauria G, Grimod G, Bianchi G, Salmaggi A. Valproate induced hyperammonemic encephalopathy successfully treated with Levocarnitine. J Clin Neurosci. 2014; 21: 690-691.
121. Malaguarnera M, Pistone G, Elvira R, Leotta C, Scarpello L, Liborio R. Effects of L-carnitine in patients with hepatic encephalopathy. World J Gastroenterol. 2005; 11: 7197-7202.
122. Malaguarnera M. Acetyl-L-carnitine in hepatic encephalopathy. Metab Brain Dis. 2013; 28: 193-199.
123. Therrien G, Rose C, Butterworth RJ, Butterworth RF. Protective effect of L-carnitine in ammonia-precipitated encephalopathy in the portacaval shunted rat. Hepatology. 1997; 25: 551-556.
124. Wang T, Suzuki K, Kakisaka K, Onodera M, Sawara K, Takikawa Y. L-carnitine prevents ammonia-induced cytotoxicity and disturbances in intracellular amino acids levels in human astrocytes. J Gastoenterol Hepatol. 2018. DOI: 10.1111/jgh.14497.
125. Sushma S, Dasarathy S, Tandon RK, Jain S, Gupta S, Bhist MS. Sodium benzoate in the treatment of acute hepatic encephalopathy: A double-blind randomized trial. Hepatology. 1992; 16: 138-144.
126. Ahboucha S, Pomier-Layragues G, Butterworth RJ. Increased brain concentrations of endogenous (non-benzodiazepine) GABA-A receptor ligands in human hepatic encephalopathy. Metab Brain Dis. 2004; 19: 241-251.
127. Goh ET, Anderson ML, Morgan MY, Gluud LL. Flumazenil versus placebo or no intervention for people with cirrhosis and hepatic encephalopathy. Cochrane Database Syst Rev. 2017; 8: CD002798.
128. Sharma BC, Singh J. Probiotics in management of hepatic encephalopathy. Metab Brain Dis. 2016; 31: 1295-1301.
129. Viramontes Hornet D, Avery A, Stow R. The effect of probiotics and symbiotics on risk factors for hepatic encephalopathy: A systemic review. J Clin Gastroenterol. 2017; 51: 312-323.
130. Dalal R, McGee RG, Riordan SM, Webster AC. Probiotics for people with hepatic encephalopathy. Cochrane Database Sys Rev. 2017; 2: CD008716.

Enjoy *OBM Hepatology and Gastroenterology* by:

1. Submitting a manuscript
2. Joining in volunteer reviewer bank
3. Joining Editorial Board
4. Guest editing a special issue

For more details, please visit:
http://www.lidsen.com/journals/hg