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Comparison of the Efficacy of Rifaximin-Lactulose Combination with and Without Probiotics in Hepatic Encephalopathy- A Review

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ABSTRACT:
Hepatic Encephalopathy (HE) is a condition that affects the brain function due to liver dysfunction. It typically arises in individuals with advanced liver disease, such as cirrhosis. The liver normally filters toxins from the blood, but when it fails to do so effectively, toxins buildup and affect brain function. Symptoms may vary from mild confusion and forgetfulness to severe disorientation and coma. Early detection and management are crucial to prevent complications and improve outcomes for affected individuals.

Earlier approaches in the treatment of hepatic encephalopathy have primarily focused on reducing the accumulation of toxic substances in the bloodstream, particularly ammonia, which is believed to play a central role in the development of symptoms.

Lactulose is a synthetic sugar with laxative property. It works by promoting the growth of beneficial bacteria in the colon, which helps convert ammonia into a less toxic form that can be excreted from the body through stool.Antibiotics such as neomycin or rifaximin have been used to reduce the population of ammonia-producing bacteria in the gut. By decreasing the bacterial load, these antibiotics aim to lower ammonia levels in the bloodstream.

Probiotics are live microorganisms, primarily bacteria and yeast, that confer health benefits to the host (typically humans) when consumed in adequate amounts. These microorganisms are often referred to as "good" or "friendly" bacteria because they contribute to the balance of the microbial communities in the digestive system and play a role in maintaining overall health.

Keywords: Hepatic Encephalopathy, Rifaximin, Lactulose, Probiotics

I. HEPATIC ENCEPHALOPATHY:

Hepatic encephalopathy (HE) is a complex and serious neurological condition that arises as a consequence of liver dysfunction, particularly in cases of advanced liver disease. The liver, a central organ in metabolism and detoxification, normally processes and removes toxins from the blood[1]. However, when the liver is impaired due to conditions such as cirrhosis, hepatitis, or liver failure, harmful substances, primarily ammonia, accumulate in the bloodstream and eventually affect the brain[2].

HE manifests as a spectrum of neuropsychiatric abnormalities, ranging from subtle cognitive impairments to severe neurological dysfunction[1]. The condition is marked by alterations in mood, personality changes, confusion, and in severe cases, coma. HE is often categorized into two types: overt HE, characterized by noticeable and significant neurological symptoms, and covert HE, which involves more subtle cognitive changes that may not be immediately apparent[3].

The precise mechanisms underlying HE are multifactorial, involving the toxic effects of elevated ammonia levels, inflammation, and the disruption of neurotransmitter balance in the brain[4]. Ammonia, a byproduct of protein metabolism normally detoxified by the liver, becomes neurotoxic when its clearance is compromised[5]. This toxic buildup disrupts neurotransmission, leading to the neurological symptoms observed in HE[6].

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Various precipitating factors can exacerbate HE, including gastrointestinal bleeding, infections, electrolyte imbalances, and certain medications. The diagnosis of HE involves a clinical assessment of neurological symptoms, laboratory tests to evaluate liver function, and sometimes advanced imaging studies[3]. Management strategies focus on addressing the underlying liver disease, reducing ammonia levels, and managing contributing factors[7]. Treatment may involve dietary restrictions, medications, and in severe cases, liver transplantation[8].

HE poses a significant challenge in the clinical management of patients with advanced liver disease, impacting their quality of life and prognosis. Understanding the pathophysiology and triggers of HE is crucial for developing effective therapeutic approaches and improving outcomes for individuals affected by this debilitating condition[9].

PREVALANCE OF HEPATIC ENCEPHALOPATHY:

The worldwide prevalence of hepatic encephalopathy is found to vary from 30%-62%. Studies have shown that India has reported a prevalence of 53%-62%. This prevalence rates can be influenced by etiological factors like liver disease, age, alcoholic etiologic and surgical portosystemic shunts[10].

ETIOLOGY:

The most common cause of HE is cirrhosis, a late stage of scarring of the liver tissue. Cirrhosis can result from chronic liver diseases such as chronic hepatitis, alcoholic liver disease, or non-alcoholic fatty liver disease[11]. The extensive scarring disrupts normal liver function, leading to the accumulation of toxins in the blood[12].

PORTOSYSTEMIC SHUNTING: In cirrhotic livers, blood flow is altered, leading to the development of portosystemic shunts—abnormal connections between the portal vein (which carries blood from the digestive organs to the liver) and the systemic circulation[13]. This bypasses the liver's detoxifying function, allowing toxins like ammonia to reach the brain[14].

IMPAIRED DETOXIFICATION OF AMMONIA:Ammonia is a byproduct of protein metabolism in the gastrointestinal tract. Normally, the liver converts ammonia into urea, that is then excreted via urine[15]. In liver dysfunction, particularly cirrhosis, the liver is unable to efficiently detoxify ammonia, resulting in its accumulation in the bloodstream and subsequent entry into the brain[5].

GASTROINTESTINAL BLEEDING:Gastrointestinal bleeding, often associated with conditions like oesophageal varices in cirrhotic patients, can lead to the sudden release of large amounts of blood into the digestive tract[16]. The breakdown of blood proteins in the gut releases additional ammonia, further contributing to HE[17].

INFECTION:Infections, particularly bacterial infections in the gut, can exacerbate HE. Bacteria in the gut produce ammonia, and infections can increase its production and absorption, overwhelming the impaired detoxification capacity of the damaged liver[18].

ELECTROLYTE IMBALANCES:Imbalances in electrolytes, particularly potassium, can contribute to the development of HE. These imbalances may be exacerbated by conditions such as diuretic use or renal dysfunction, common in advanced liver disease[19].

MEDICATIONS:Certain medications, especially those metabolized by the liver, can contribute to HE. Sedatives, opioids, and benzodiazepines, for example, may have enhanced effects in individuals with compromised liver function[20].

PATHOGENESIS OF HEPATIC ENCEPHALOPATHY:

AMMONIA AND NEUROTOXICITY: The liver normally plays a pivotal role in detoxifying ammonia, a byproduct of protein metabolism in the gastrointestinal tract[5]. In conditions such as cirrhosis, the liver's detoxification capacity is impaired, leading to elevated ammonia levels in the bloodstream. Ammonia is neurotoxic and crosses the blood-brain barrier, where it disrupts neurotransmission and contributes to the neurological symptoms observed in HE[6]. The mechanisms of ammonia neurotoxicity include the alteration of astrocyte function, the inhibition of glutamate uptake, and the modulation of the gamma-aminobutyric acid (GABA)ergic system[21].

PORTOSYSTEMIC SHUNTING:In cirrhosis, the development of portosystemic shunts—abnormal connections between the portal vein and systemic circulation—diverts blood away from the liver's detoxifying pathways[22]. This shunting allows toxins, including ammonia, to bypass the liver and reach the brain directly[23]. The altered blood flow in the presence of portosystemic shunts contributes to the pathogenesis of HE, amplifying the impact of ammonia on neurological function[5].

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INFLAMMATION AND CYTOKINES:Chronic inflammation is a hallmark of advanced liver disease, and the release of pro-inflammatory cytokines contributes to the pathogenesis of HE[23]. Inflammatory mediators can disrupt the blood-brain barrier, allowing toxic substances to enter the brain more readily[25]. Moreover, cytokines can directly affect neurotransmitter systems, influencing cognitive function and contributing to the neuropsychiatric manifestations of HE[26].

ADDITIONAL MECHANISMS AND CONTRIBUTING FACTORS:
MICROBIOTA AND GUT-DERIVED TOXINS:The gut-liver axis plays a crucial role in HE pathogenesis[27]. Changes in the gut microbiota composition, a common occurrence in liver disease, lead to increased production of ammonia and other toxins. Gut-derived toxins, such as short-chain fatty acids and endotoxins, further contribute to neuroinflammation and neuronal dysfunction[28]. The gut-brain axis is an emerging area of research, highlighting the intricate connection between the gastrointestinal system and neurological manifestations in HE[29].

ALTERATIONS IN NEUROTRANSMITTER SYSTEMS:HE disrupts the delicate balance of neurotransmitter systems in the brain. Ammonia affects the synthesis and release of neurotransmitters, including glutamate and GABA[30]. Imbalances in these neurotransmitter systems contribute to excitotoxicity and impaired inhibitory neurotransmission, leading to cognitive and motor disturbances observed in HE patients[31].
CONTRIBUTING FACTORS AND PRECIPITANTS:Various factors can precipitate or exacerbate HE episodes. Gastrointestinal bleeding, infections, electrolyte imbalances, and certain medications can further stress the compromised liver and contribute to the manifestation of HE. Identifying and managing these precipitating factors are crucial components of HE management[6, 32].

AMMONIA AND HEPATIC ENCEPHALOPATHY:

In a healthy liver, ammonia, which is a byproduct of protein metabolism, is converted into urea and then excreted from the body through urine[33]. However, when the liver is damaged or not functioning properly, ammonia levels can rise in the bloodstream[34]. Elevated ammonia levels can have toxic effects on the central nervous system, leading to hepatic encephalopathy[4].

The exact mechanisms by which ammonia contributes to hepatic encephalopathy are not fully understood, but several theories exist:

Neurotoxicity: Ammonia is thought to have direct neurotoxic effects on the brain, affecting neurotransmission and leading to cognitive and neurological impairment[35].
Astrocyte Dysfunction: In the brain, astrocytes play a crucial role in removing excess ammonia. In hepatic encephalopathy, the excessive ammonia can overwhelm the astrocytes, leading to dysfunction and contributing to the neurological symptoms[36].

Inflammation and Oxidative Stress: Ammonia-induced inflammation and oxidative stress may also contribute to the development and progression of hepatic encephalopathy[37].

SIGNS AND SYMPTOMS:

Hepatic encephalopathy can manifest in various ways, including confusion, forgetfulness, personality changes, slurred speech, and impaired coordination. At advanced stages, it can lead to coma or even death. Other symptoms may include jaundice, hand tremors and difficulty with fine motor skills[38].

INVESTIGATION:

It involves a comprehensive approach that integrates clinical evaluation, laboratory tests, imaging studies, and neuropsychological assessments. This multifaceted approach is essential for accurately identifying the condition and ruling out other potential causes of cognitive dysfunction.

Clinical Evaluation:

Physicians begin by conducting a thorough clinical assessment, which involves gathering information about the patient's medical history, symptoms, and any underlying liver disease. They may inquire about recent changes in cognitive function, behaviour, sleep patterns, and motor coordination. Additionally, they assess for signs of liver dysfunction, such as jaundice, ascites, and spider angiomas[39].

Laboratory Tests:

Blood tests are crucial for evaluating liver function and detecting abnormalities that may indicate hepatic encephalopathy. Key laboratory markers include liver function tests (e.g., serum bilirubin, albumin, and international normalized

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ratio), complete blood count, electrolyte levels, and arterial blood gases. Ammonia levels are also measured since elevated ammonia levels in the blood can contribute to the development of hepatic encephalopathy[40].

Imaging Studies:

Imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) scans are utilized to assess the structural integrity of the brain and rule out other neurological conditions. These imaging modalities can help identify any abnormalities such as cerebral edema, atrophy, or lesions that may be associated with hepatic encephalopathy[41].

Neuropsychological Assessments:Neuropsychological testing plays a crucial role in evaluating cognitive function and identifying subtle changes in mental status that may not be evident during a routine clinical examination. These assessments typically include tests of memory, attention, concentration, executive function, and psychomotor speed. Neuropsychological testing helps clinicians quantify the severity of hepatic encephalopathy and monitor changes in cognitive function over time[42].

Additional Diagnostic Procedures:

In some cases, additional diagnostic procedures may be necessary to confirm the diagnosis or assess the extend of liver damage. These procedures may include liver biopsy, electroencephalography (EEG) to evaluate brain wave patterns, and advanced imaging techniques such as diffusion-weighted MRI or single photon emission computed tomography (SPECT).

Overall, the diagnosis of hepatic encephalopathy requires a comprehensive and interdisciplinary approach, involving collaboration between hepatologists, neurologists, radiologists, and neuropsychologists[43].

EARLIER APPROACHES IN THE TREATMENT OF HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a condition characterized by cognitive and neurological dysfunction due to liver dysfunction. Earlier approaches in the treatment of hepatic encephalopathy have primarily focused on reducing the accumulation of toxic substances in the bloodstream, particularly ammonia, which is believed to play a central role in the development of symptoms[12].

Here are some traditional approaches used in the treatment of hepatic encephalopathy:

1. Dietary Protein Restriction:

Limiting the intake of dietary protein can help reduce the production of ammonia in the gastrointestinal tract. Ammonia is a byproduct of protein metabolism, and reducing protein intake may alleviate symptoms in some cases[39].

2. Lactulose:

Lactulose is a synthetic sugar with a laxative property. It works by promoting the growth of beneficial bacteria in the colon, which helps convert ammonia into a less toxic form that can be excreted from the body through stool[40].

3. Antibiotics:

Antibiotics such as neomycin or rifaximin have been used to reduce the population of ammonia-producing bacteria in the gut. By decreasing the bacterial load, these antibiotics aim to lower ammonia levels in the bloodstream[41]
.

4. L-Ornithine L-Aspartate (LOLA):

LOLA is an amino acid combination that is believed to enhance ammonia detoxification in the liver. It is thought to improve the urea cycle, facilitating the conversion of ammonia into urea for excretion[41].

5. Branched-Chain Amino Acids (BCAAs):

BCAAs, including leucine, isoleucine, and valine, are essential amino acids that have been used in the management of hepatic encephalopathy. They may help improve protein synthesis and promote the formation of neurotransmitters in the brain[42].

6. Zinc Supplementation:

Zinc deficiency is common in liver disease, and zinc supplementation has been suggested to have a positive impact on hepatic encephalopathy. Zinc plays a role in the metabolism of ammonia and neurotransmitters[43].

ROLE OF RIFAXIMIN AND LACTULOSE COMBINATION IN THE TREATMENT OF HEPATIC ENCEPHALOPATHY:

The combination of rifaximin and lactulose is often used in the treatment of hepatic encephalopathy (HE), a neurological complication that can occur in individuals with advanced liver disease, particularly cirrhosis[44]. Both rifaximin and

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lactulose target different aspects of the condition, and their combination is aimed at managing and preventing episodes of hepatic encephalopathy[45].

RIFAXIMIN:

Mechanism of action: Rifaximin is a non-absorbable antibiotic that acts in the gut. It reduces the production of ammonia by decreasing the population of ammonia-producing bacteria in the intestines. Ammonia is a key factor in the development of hepatic encephalopathy[46].

Role in treatment: By lowering intestinal ammonia levels, rifaximin helps to decrease the neurotoxic effects associated with hepatic encephalopathy. It is often used as a maintenance therapy to prevent the recurrence of episodes[47].

LACTULOSE:

Mechanism of action: Lactulose is a synthetic sugar that is not absorbed by the body. It works by promoting the growth of beneficial bacteria in the colon, which convert lactulose into acids. These acids acidify the colonic contents, trapping ammonia in the colon and preventing its absorption into the bloodstream[48].

Role in Treatment: Lactulose is commonly used to treat and prevent hepatic encephalopathy episodes. It helps to reduce ammonia levels and improve the symptoms associated with the condition. Lactulose is also considered a first-line therapy for acute episodes[49].

COMBINATION THERAPY:

Synergistic Effect: The combination of Rifaximin and Lactulose is often considered to have a synergistic effect in managing Hepatic Encephalopathy. While Rifaximin acts to reduce ammonia production in the gut, lactulose works to trap ammonia and eliminate it through bowel movements[(50,51)].

Preventive Approach: The combination is often used for long-term maintenance therapy to prevent the recurrence of hepatic encephalopathy episodes in individuals with a history of the condition[(52,53)].

PROBIOTICS:

Probiotics are live microorganisms, primarily bacteria and yeast, that confer health benefits to the host (typically humans) when consumed in adequate amounts. These microorganisms are often referred to as "good" or "friendly" bacteria because they contribute to the balance of the microbial communities in the digestive system and play a role in maintaining overall health[(54,55,56)].

EFFICIENCY OF PROBIOTICS ALONG WITH THE RIFAXIMIN- LACTULOSE COMBINATION:

Studies have shown that the combination of rifaximin and lactulose is effective in managing hepatic encephalopathy by reducing ammonia levels and improving symptoms. The addition of probiotics to the rifaximin and lactulose regimen may provide additional benefits by promoting a healthier gut microbiota. Probiotics may contribute to the stability and diversity of the gut flora. The combination with probiotics may enhance patient tolerance by potentially reducing side effects associated with antibiotic use. Probiotics are generally considered safe, and their inclusion may improve overall gastrointestinal well-being. The response to treatment can vary among individuals. Factors such as the severity of hepatic encephalopathy, patient comorbidities, and other medications being taken can influence the effectiveness of the treatment regimen [(57,58,59)].

SIGNIFICANCE:

Rifaximin and Lactulose are taken as the first line therapy in the treatment of hepatic encephalopathy although probiotics also has effectiveness in the treatment of the same. This review points out the effectiveness and benefits of including probiotics to the rifaximin-lactulose combination during the treatment of hepatic encephalopathy.

II. DISCUSSION:

Hepatic encephalopathy is a serious and neuropsychological condition that occurs during advanced liver diseases. Traditional approaches for the treatment of hepatic encephalopathy included rifaximin, lactulose, LOLA, BCAAs, and zinc supplementation. This can be supported by dietary restriction of protein. The main aim is to lower the ammonia level and improve the quality of life of the patient. Studies are emerging that focus on the alternate therapies for the treatment of hepatic encephalopathy, among which probiotics has shown its effect contributing to the treatment of the condition. In an era of antibiotic resistance, probiotics have shown to eliminate bad bacteria in the intestine which reduces ammonia production without causing any resistance scenarios. Including probiotics and other alternatives broadens the dimensions for further discovery of mechanisms

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underlying in the pathophysiology of hepatic encephalopathy.

III. CONCLUSION:

Hepatic encephalopathy (HE) is a complex and serious neurological condition that arises as a consequence of liver dysfunction, particularly in cases of advanced liver disease.Hepatic encephalopathy can manifest in various ways, including confusion, forgetfulness, personality changes, slurred speech, and impaired coordination. At advanced stages, it can lead to coma or even death. Earlier approaches in the treatment of hepatic encephalopathy included dietary approaches, antibiotics, lactulose and zinc supplements that have primarily focused on reducing the accumulation of toxic substances in the bloodstream, particularly ammonia, which is believed to play a central role in the development of symptoms.Probiotics are live microorganisms that have shown to contribute to the balance of microbial communities in digestive system and thus has the ability to reduce the production of ammonia by bacterial colonies. The overall goal of treatment for hepatic encephalopathy is to reduce the ammonia production. Thus, probiotics also contributes to this goal along with rifaximin and lactulose and shown effectiveness in many studies. It is safe, economical, and clinically proven drug.

REFERENCES:

[1]. Kumar G, Taneja A, Kandiah PA. Brain and the Liver: Cerebral Edema, Hepatic Encephalopathy and Beyond. Hepatic Critical Care. 2017:83–103.

[2]. Aldridge DR, Tranah EJ, Shawcross DL. Pathogenesis of hepatic encephalopathy: role of ammonia and systemic inflammation. Journal of Clinical and Experimental Hepatology. 2015;(5):S7-20.

[3]. Ferenci P. Hepatic encephalopathy. Gastroenterology Report (oxford academy). 2017;5(2):138-47.

[4]. Jayakumar AR, Norenberg MD. Hyperammonemia in Hepatic Encephalopathy. Journal of Clinical and Experimental Hepatology. 2018;8(3):272-80.

[5]. Aldridge DR, Tranah EJ, Shawcross DL. Pathogenesis of hepatic encephalopathy: role of ammonia and systemic inflammation. Journal of Clinical and Experimental Hepatology. 2015;(5):S7-20.

[6]. Teleanu RI, Niculescu AG, Roza E, Vladâcenco O, Grumezescu AM, Teleanu DM. Neurotransmitters-Key Factors in Neurological and Neurodegenerative Disorders of the Central Nervous System. International Journal of Molecular Sciences. 2022;23(11):5954.

[7]. Aamann L, Tandon P, Bémeur C. Role of Exercise in the Management of Hepatic Encephalopathy: Experience from Animal and Human Studies. Journal of Clinical and Experimental Hepatology. 2019;9(1):131-36.

[8]. Hammad A, Kaido T, Aliyev V, Mandato C, Uemoto S. Nutritional Therapy in Liver Transplantation. Nutrients. 2017;9(10):1126.

[9]. Kaplan A, Rosenblatt R. Symptom Management in Patients with Cirrhosis: A Practical Guide. Current Treatment Options in Gastroenterology. 2022;20(2):144-59.

[10]. Rathi S, Chopra M, Chouduri G, Sharma P, Madan K, Chhabra M, Rai RR, Govil A, Konar A, Goenka M, Agarwal M, Mukherjee J, Thorat V, Salunkhe S, Abraham P, Nagral A, Jhaveri A, Bhat N, Varghese J, R S A, Ravishankar, Reddy DC, Dhiman RK. Prevalence of Minimal Hepatic encephalopathy in Patients with Liver Cirrhosis: A Cross- Sectional Clinicoepidemiological, Multicentre, Nationwide Study in India: The Predict Study. Journal of Clinical and Experimental Hepatology. 2019;9(4):476-83.

[11]. Pouwels S, Sakran N, Graham Y, Leal A, Pintar T, Yang W, Kassir R, Singhal R, Mahawar K, Ramnarain D. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. BMC Endocrine Disorder. 2022;22(1):63.

[12]. Friedman SL. Scarring in alcoholic liver disease: new insights and emerging therapies. Alcohol Health and Research World. 1997;21(4):310-6.

[13]. Nardelli S, Riggio O, Gioia S, Puzzono M, Pelle G, Ridola L. Spontaneous porto-systemic shunts in liver cirrhosis: Clinical and therapeutical aspects. World Journal of Gastroenterology. 2020;26(15):1726-32.

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Volume 9, Issue 3 May-June 2024, pp: 1065-1073 www.ijprajournal.com ISSN: 2456-4494

[14]. Butterworth RF. Hepatic encephalopathy. Alcohol Research and Health. 2003;27(3):240-6.
[15]. Weiner ID, Mitch WE, Sands JM. Urea and Ammonia Metabolism and the Control of Renal Nitrogen Excretion. Clinical Journal of the American Society of Nephrology. 2015;10(8):1444-58.
[16]. Biecker E. Gastrointestinal Bleeding in Cirrhotic Patients with Portal Hypertension. International Scholarly Research Notices Hepatology. 2013;2013:541836.
[17]. Rai R, Saraswat VA, Dhiman RK. Gut microbiota: its role in hepatic encephalopathy. Journal of Clinical and Experimental Hepatology. 2015;5:S29-36.
[18]. Chen Z, Ruan J, Li D, Wang M, Han Z, Qiu W, Wu G. The Role of Intestinal Bacteria and Gut-Brain Axis in Hepatic Encephalopathy. Frontiers in Cellular and Infection Microbiology. 2021;10:595759.
[19]. Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. Endocrine Connections. 2018;7(4):R135-46.
[20]. Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner Journal. 2013;13(2):214-23.
[21]. Dasarathy S, Mookerjee RP, Rackayova V, Rangroo Thrane V, Vairappan B, Ott P, Rose CF. Ammonia toxicity: from head to toe.Metabolic Brain Disorder. 2017;32(2):529-38.
[22]. Nardelli S, Riggio O, Gioia S, Puzzono M, Pelle G, Ridola L. Spontaneous porto-systemic shunts in liver cirrhosis: Clinical and therapeutical aspects. World Journal of Gastroenterology. 2020;26(15):1726-32.
[23]. Cichoż-Lach H, Michalak A. Current pathogenetic aspects of hepatic encephalopathy and noncirrhotic hyperammonemic encephalopathy. World Journal of Gastroenterology. 2013;19(1):26-34.
[24]. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017;9(6):7204-18.
[25]. Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. Nature Medicine. 2013;19(12):1584-96.
[26]. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience. 2013;246:199-229.
[27]. Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: Pathophysiological basis for therapy. Journal of Hepatology. 2020;72(3):558-77.
[28]. Llorente C, Schnabl B. The gut microbiota and liver disease. Cellular and Molecular Gastroenterology and Hepatology. 2015;1(3):275-84.
[29]. Solanki R, Karande A, Ranganathan P. Emerging role of gut microbiota dysbiosis in neuroinflammation and neurodegeneration. Frontiers in Neurology. 2023;14: 1149618.
[30]. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Annals of Gastroenterology. 2015;28(2):203-9.
[31]. Limón ID, Angulo-Cruz I, Sánchez-Abdon L, Patricio-Martínez A. Disturbance of the Glutamate-Glutamine Cycle, Secondary to Hepatic Damage, Compromises Memory Function. Frontiers in Neuroscience. 2021;15:578922.
[32]. Frederick RT. Current concepts in the pathophysiology and management of hepatic encephalopathy. Gastroenterology and Hepatology. 2011;7(4):222-33.
[33]. Weiner ID, Mitch WE, Sands JM. Urea and Ammonia Metabolism and the control of Renal nitrogen excretion. Clinical Journal of the American Society of Nephrology. 2015;10(8): 1444-58.
[34]. Deutsch-Link S, Moon AM, Jiang Y, Barrit AS 4th, Tapper EB. Serum Ammonia in Cirrhosis: Clinical Impact of Hyperammonaemia, Utility of Testing, and National Testing Trends. Clinical Therapeutics. 2022;44(3): e45-57.
[35]. Ciecko-Michalska I, Szczepanek M, Slowik A, Mach T. Pathogenesis of Hepatic Encephalopathy. Gastroenterology Research and Practical. 2012;2012: 642108.

[36]. Jaeger V, DeMorrow S, McMillin M. The Direct Contribution of Astrocytes and Microglia to the Pathogenesis of Hepatic Encephalopathy. Journal of Clinical and Translational Hepatology. 2019;7(4): 352-61.
[37]. Ochoa-Sanchez R, Rose CF. Pathogenesis of Hepatic Encephalopathy in Chronic Liver Disease. Journal of Clinical and Experimental Hepatology. 2018;8(3): 262-71.
[38]. Toris GT, Bikis CN, Tsourouflis GS, Theocharis SE. Hepatic encephalopathy: an updated approach from pathogenesis to treatment. Medical Science Monitor. 2011;17(2):RA53-63.
[39]. Ridola L, Faccioli J, Nardelli S, Gioia S, Riggio O. Hepatic Encephalopathy: Diagnosis and Management. Journal of Translational Internal Medicine. 2020;8(4):210-9.
[40]. Weissenborn K. Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles. Drugs. 2019;79:5-9.
[41]. Harvey PD. Clinical applications of neuropsychological assessment. Dialogues in Clinical Neuroscience. 2012;14(1):91-9.
[42]. Taouli B, Ehman RL, Reeder SB. Advanced MRI methods for assessment of chronic liver disease.American Journal of Roentgenology. 2009;193(1):14-27.
[43]. Aderinto N, Olatunji D, Abdulbasit M, Edun M. The essential role of neuroimaging in diagnosing and managing cerebrovascular disease in Africa: a review. Annals of Medicine. 2023;55(2):2251490.
[44]. Nguyen DL, Morgan T. Protein restriction in hepatic encephalopathy is appropriate for selected patients: a point of view. Hepatology International. 2014 S;8(2):447-51.
[45]. Chu N, Ling J, Jie H, Leung K, Poon E. The potential role of lactulose pharmacotherapy in the treatment and prevention of diabetes. Frontiers in Endocrinology. 2022;13: 956203.
[46]. Ladevaia MD, Prete AD, Cesaro C, Gaeta L, Zulli C, Loguercio C. Rifaximin in the treatment of hepatic encephalopathy. Hepatic Medicine. 2011;3: 109-17.
[47]. Sidhu SS. L-Ornithine L-Aspartate is Effective and Safe for the Treatment of Hepatic Encephalopathy in Cirrhosis. Journal of Clinical and Experimental Hepatology. 2018;8(3):219-21.
[48]. Mohammad MK, Zhou Z, Cave M, Barve A, McClain CJ. Zinc and liver disease. Nutrition in Clinical Practice. 2012;27(1):8-20.
[49]. Paik YH, Lee KS, Han KH, Song KH, Kim MH, Moon BS, Ahn SH, Lee SJ, Park HJ, Lee DK, Chon CY, Lee SI, Moon YM. Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. Yonsei Medical Journal. 2005;46(3):399-407.
[50]. Wang Z, Chu P, Wang W. Combination of rifaximin and lactulose improves clinicalefficacy and mortality in patients with hepatic encephalopathy. Drug Design, Development Therapy. 2018 Dec 17;13:1-11.
[51]. Flamm SL. Rifaximin treatment for reduction of risk of overt hepatic encephalopathy recurrence. Therapeutic Advances in Gastroenterology. 2011;4(3):199-206.
[52]. Felipo V. Hepatic encephalopathy: effects of liver failure on brain function. Nature Reviews Neuroscience. 2013;14(12):851-8.
[53]. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, Sigal S, Sheikh MY, Beavers K, Frederick T, Teperman L, Hillebrand D, Huang S, Merchant K, Shaw A, Bortey E, Forbes WP. Rifaximin treatment in hepatic encephalopathy. The New England Journal of Medicine. 2010;362(12): 1071-81.
[54]. Karakan T, Tuohy KM, Janssen-van Solingen G. Low-Dose Lactulose as a Prebiotic for Improved Gut Health and Enhanced Mineral Absorption. Frontiers in Nutrition. 2021;8: 672925.
[55]. Bloom PP, Tapper EB. Lactulose in cirrhosis: Current understanding of efficacy, mechanism, and practical considerations. Hepatology Communications. 2023;7(11): e0295.
[56]. Yong-Han Paik, Kwan Sik Lee, Kwang-Hyub Han, Kun Hoon Song, Myoung Hwan Kim, Byung Soo Moon, Sang Hoon Ahn, Se Joon Lee, Hyo Jin Park, Dong Ki Lee, Chae Yoon Chon, Sang In Lee, and Young Myoung Moon. Comparison of Rifaximin and Lactulose for the Treatment

of Hepatic Encephalopathy: A Prospective Randomized Study. Yonsei Medical Journal. 2005;46(3): 399-407.

[57]. Amara AA, Shibl A. Role of Probiotics in health improvement, infection control and disease treatment and management. Saudi Pharmaceutical Journal. 2015;23(2):107-14.

[58]. Wang MW, Ma WJ, Wang Y, Ma XH, Xue YF, Guan J, Chen X. Comparison of the effects of probiotics, rifaximin, and lactulose in the treatment of minimal hepatic encephalopathy and gut microbiota. Frontiers in Microbiology. 2023;14: 1091167.

[59]. Markowiak P, Śliżewska K. Effects of Probiotics, Prebiotics, and Synbiotics on Human Health. Nutrients. 2017;9(9):1021.