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Review

EXPLORING THE COMPLEXITIES OF HEPATIC ENCEPHALOPATHY: PATHOPHYSIOLOGY AND INNOVATIVE THERAPEUTIC OPTIONS

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Abstract

Hepatic encephalopathy is a significant neuropsychiatric complication associated with liver disease, marked by cognitive impairment and changes in mental status. The review discusses the multicomponent pathophysiological mechanisms of disease, focusing on the fundamental role of the gut-brain axis. Recent advances have defined critical contributory elements such as the accumulation of ammonia, neuroinflammation, neurotransmitter imbalance, and microbiome dysregulation. Moreover, understanding the impact of gut microbiota on brain function is essential for developing targeted interventions. Modern treatment strategies have been expanded to include gut-directed therapies, metabolic manipulation, novel molecular therapeutics, new drug delivery systems, and precision medicine significantly improving treatment outcomes. In contrast, artificial intelligence applications revolutionized patient monitoring and therapeutic strategies. These technological advancements have also facilitated personalized approaches to treatment. Furthermore, ongoing research into biomarkers is crucial for early diagnosis and monitoring of disease progression. The identification of specific biomarkers can enhance our understanding of disease severity and guide therapeutic decisions. These advances have improved knowledge of inter-organ system interaction and biomarker-based strategies that have improved the outcomes in these patients and opened new vistas for future therapeutic strategies. Ultimately, a comprehensive approach that integrates these findings will be essential for the effective management and treatment of hepatic encephalopathy.

Keywords: Hyperammonemia, Hepatic Encephalopathy, Vagus Nerve, Blood-Brain Barrier, Neuroinflammation, Cirrhosis

1. Introduction :

Hepatic encephalopathy is a complex brain disorder caused by liver problems, involving a range of neurological and psychiatric symptoms, and can result in severe cognitive impairment, changes in consciousness, and even coma [1]. The gut-brain axis plays a vital role in this complex condition [2]. Our digestive system's relationship with the brain extends beyond simple nutrient processing, with sophisticated communication networks existing through the microbiome-gut-brain axis and vagus nerve gut-brain axis [3]. These networks affect everything from cognitive function to emotional well-being, especially when you have liver disease [4]

Hepatic encephalopathy progressed from the observations of Hippocrates of behaviour change during jaundice (460-370 B.C.) and also marked the chronological first evidence of cirrhosis in its first stage to the 18th century, which was the earliest learned documentation of cirrhotic patients showing altered mental states together with other old age diseases [5], [6]. Contemporary characterization first started to take shape in the second half of the twentieth century around the same period when the term asterixis was coined and portosystemic encephalopathy was defined

with its emphasis on the contribution of the gut in particular substances and hyperammonemia. The term 'hepatic encephalopathy' gained legitimacy in 1957[7], [8].

The onset of hepatic encephalopathy varies based on the specific type of liver disease and the population being studied. An estimated 70% of patients with cirrhosis will experience at least one episode of hepatic encephalopathy during their lifetime [9]. The prevalence is modified by factors such as age, gender, and the presence of precipitating conditions, which include infections, gastrointestinal bleeding, and abnormalities of electrolyte balance [10], [11]. Scientists are developing innovative therapeutic approaches that target these gut-brain connections in hepatic encephalopathy. This review article focuses on exploring the complex pathophysiological mechanisms of hepatic encephalopathy, with special emphasis on the gut-brain axis, current therapeutic strategies, and emerging innovative treatment approaches to improve patient outcomes.

2. Pathophysiological Mechanisms :

The pathophysiological mechanisms of hepatic encephalopathy are highly complex and involve an interaction of metabolic, neurochemical, and inflammatory components [12]. The major factors predisposing to the onset of hepatic encephalopathy are given in Figure 1.

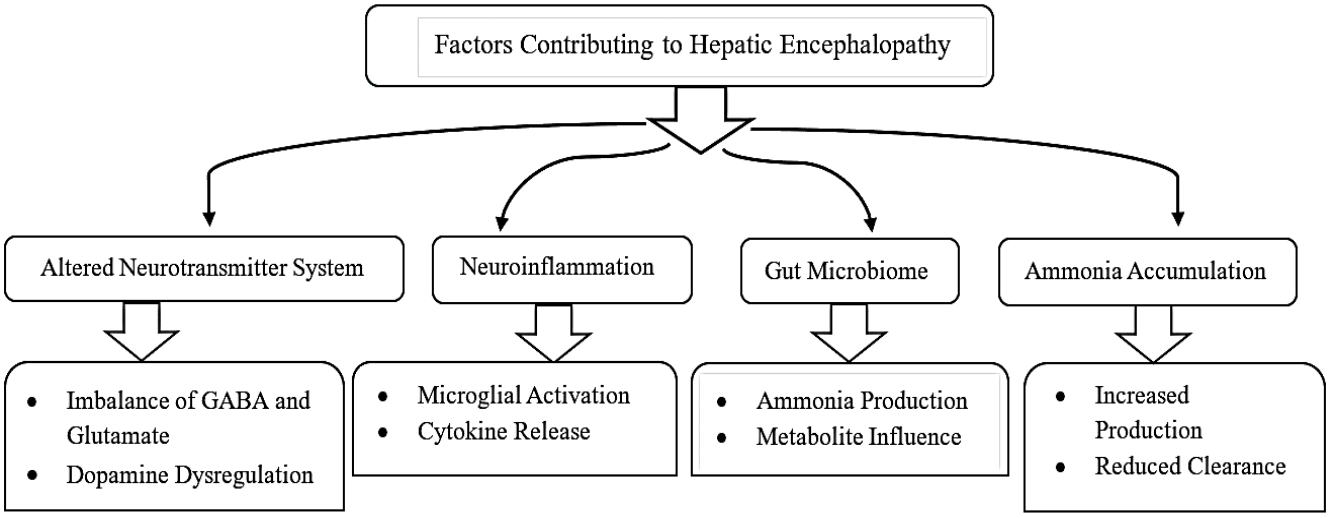

Figure 1: The diagram shows the major factors contributing to hepatic encephalopathy (HE). The condition is influenced by multiple interconnected mechanisms, including alterations in the neurotransmitter system (such as imbalance of GABA and glutamate, and dopamine dysregulation), neuroinflammation (characterized by microglial activation and the release of pro-inflammatory cytokines), disturbances in the gut microbiome (leading to increased ammonia production and metabolite-related effects), and ammonia accumulation (resulting from increased production and reduced hepatic clearance). These factors collectively disrupt normal brain function, leading to the neurological symptoms of HE.

2.1 Ammonia Accumulation

A cardinal sign of hepatic encephalopathy is blood ammonia accumulation [13]. Ammonia is a by-product of protein metabolism and is produced in the intestinal gut by intestinal microorganisms [14]. Under normal conditions in a healthy individual, ammonia is converted to urea during the urea cycle and excreted by the kidneys. However, in cases where the function of the liver starts being compromised, this system is easily impaired and ammonia levels increase beyond normal [15]. Ammonia causes neurotoxic effects through several pathways which include glutamate and glutamine dysregulation in which ammonia interferes with the balance between the excitatory and inhibitory neurotransmitters within the brain [16]. This disruption increases glutamate into glutamine conversion in astrocytes, resulting in increased intracellular glutamine concentrations. Such changes may result in swelling of the astrocytes leading to failure in neurotransmission [17]. Another contributor that causes neurotoxic effects is altered energy metabolism in which increased ammonia levels can impair mitochondrial function, which results in decreased production of ATP and higher oxidative stress. This energy deficiency can compromise neuronal function and contribute to cognitive impairment [18] Moreover, ammonia may weaken the structural integrity of the blood-brain barrier thereby allowing neurotoxic substances entry into the CNS [19].

2.2 Neuroinflammation :

The underlying cause of hepatic encephalopathy shows significant involvement of neuroinflammation [20].

Liver failure results in the release of pro-inflammatory cytokines, which transverse the blood-brain barrier and initiate activation microglia, which is actually the innate immune cell within the central nervous system [21]. This activation of microglia leads to further production of inflammatory mediators, exacerbating neuronal damage and dysfunction [22]. The main cytokines involved in neuroinflammation within HE are tumour necrosis factor-alpha (TNF-α) whose levels are increased in the patients with HE and are said to be associated with increased neuronal apoptosis [23]. Another pro-inflammatory cytokine is interleukin-6 (IL-6). It plays a significant role in neuroinflammation and cognitive impairment within HE [24], [25]. The figure 2 illustrates the key neuroinflammatory mechanisms contributing to HE.

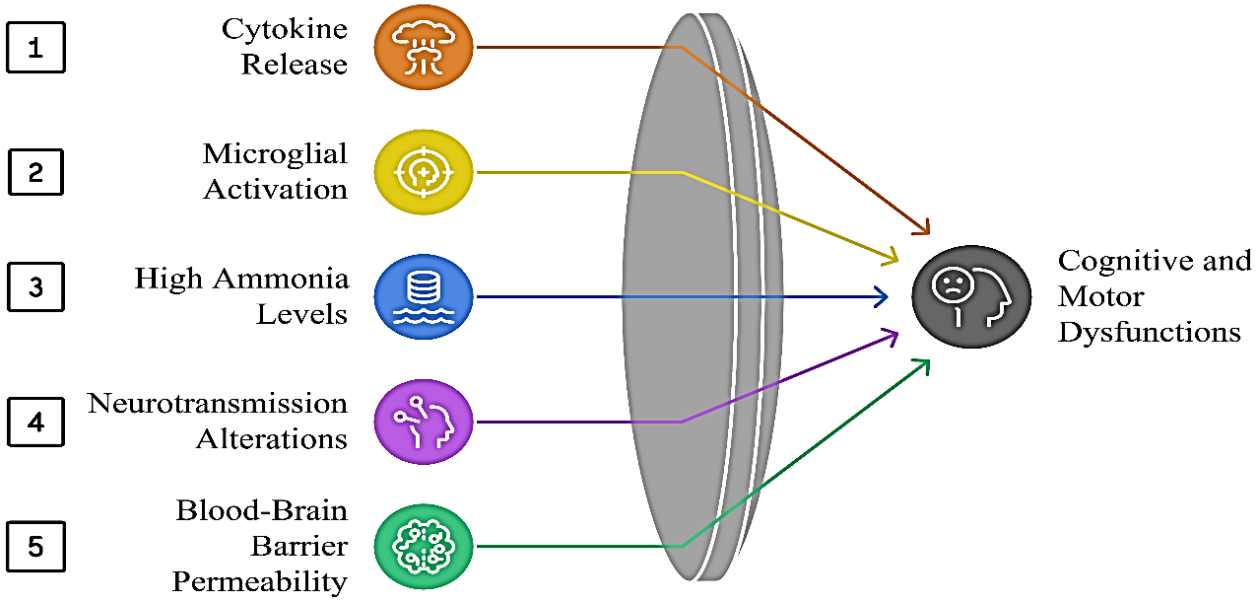

Figure 2: Schematic representation of neuroinflammatory mechanisms contributing to cognitive and motor dysfunctions in hepatic encephalopathy (HE). Key factors include cytokine release, microglial activation, elevated ammonia levels, neurotransmission alterations, and increased blood-brain barrier permeability.

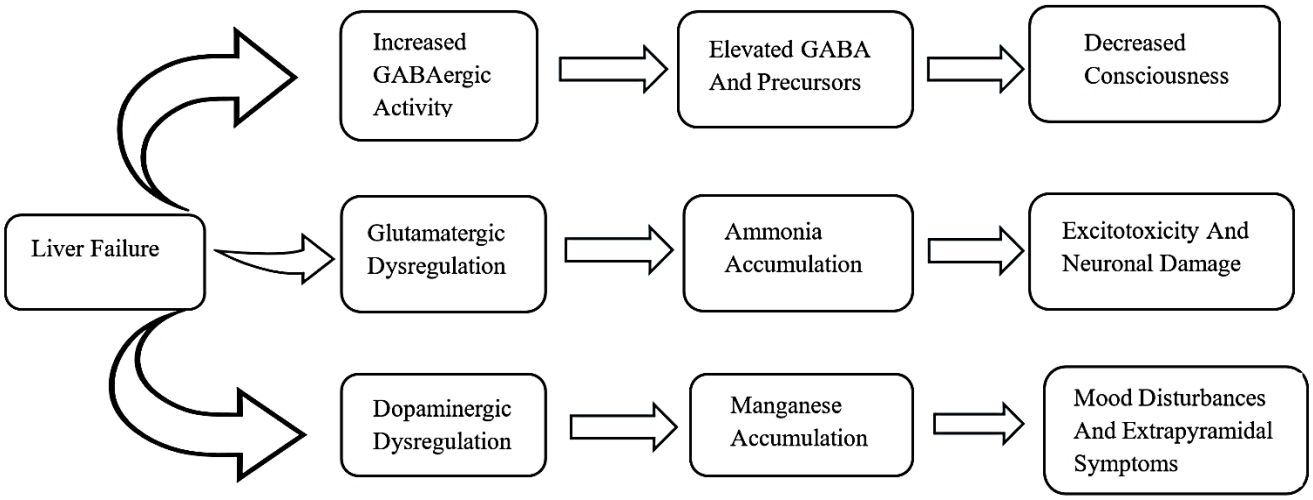

Figure 3: Schematic representation of altered neurotransmitter systems in hepatic encephalopathy. Liver failure leads to increased GABAergic activity, glutamatergic dysregulation, and dopaminergic dysregulation. These alterations result in elevated GABA and its precursors, ammonia accumulation, and manganese accumulation, respectively contributing to decreased consciousness, excitotoxicity and neuronal damage, and mood disturbances with extrapyramidal symptoms.

2.3 Altered Neurotransmitter Systems :

Hepatic encephalopathy is characterized by alterations in multiple neurotransmitter systems including GABAergic, glutamatergic, and dopaminergic system. GABA is the primary inhibitory neurotransmitter in the central nervous system, crucial for brain function. An increased activity of the GABAergic system has been noted to exist in HE, and effects which conclude in depression of consciousness and cognition. This is at least in part due to heightened levels of GABA and its precursors, such as glutamine [26], [27]. Glutamatergic abnormality includes ammonia-induced dysregulation of glutamate and glutamine which leads to excitotoxicity and neuronal damage [28], [29]. Also, there is altered dopaminergic signaling in HE, which is involved in mood disturbances and behavioral alterations [30], [31]. These interrelated neurotransmitter disruptions are summarized in Figure 3.

2.4 The Gut Microbiome Function :

The intestinal microbiome plays a crucial role in the pathogenesis of hepatic encephalopathy [32]. When the gut microbiota becomes imbalanced, a condition known as dysbiosis, it can produce increased levels of harmful substances, including ammonia and other neurotoxic metabolites. There are some gut flora that produce ammonia; the healthy liver neutralizes this toxin. If the liver fails, then the process fails, and the ammonia remains at even higher concentrations in the blood circulation [33]. The gut-liver axis is a bidirectional communication system in which the gut and liver reciprocally influence each other's functions. Substances from the gut, including toxins and inflammatory mediators, can reach the liver through the portal vein. When liver disease is present, the ability of the organ to remove these harmful substances is compromised. Therefore, the toxins and inflammatory mediators from the gut may cause inflammation in the liver, thereby aggravating liver damage and contributing to the presentation of symptoms of hepatic encephalopathy [34].

3. Understanding the Gut-Brain Axis in Hepatic Encephalopathy

Exploration of the gut-brain axis starts with its basic role in hepatic encephalopathy (HE), a complex neurological condition that stems from the delicate interplay between digestive and nervous systems [35].

3.1 Bidirectional Communication Pathways

The gut-brain axis features sophisticated two-way communication networks that connect the brain's emotional and cognitive centres with peripheral intestinal functions [36]. This communication flows through multiple pathways including neural pathways (vagus nerve and enteric nervous system) involved in endocrine signalling, immune system interactions and humoral links. The vagus nerve acts as a crucial two-way highway. Its afferent fibres send information from the intestine to the central nervous system (CNS). This connection causes the brain to influence intestinal functional cells while gut signals reach the CNS [37].

3.2 Role of Microbiome-Gut-Brain Signaling

Research shows that gut microbiota plays a vital role in this communication network. The microbiome adjusts various neurotransmitters, including GABA, glutamate, acetylcholine, dopamine, and norepinephrine [38], [39]. These bacteria-derived products affect brain function and behavior. The gut microbiota's influence goes beyond neurotransmitter production. It affects the CNS through multiple mechanisms including Regulation of intestinal barrier integrity, modulation of immune responses, production of short-chain fatty acids (SCFAs) and control of microglia function and maturation [40]

3.3 Impact on Cognitive Function:

Cognitive impairment in liver disease shows up through various mechanisms. Liver cirrhosis patients can develop minimal hepatic encephalopathy (MHE) at rates between 20-80% [41]. Several key factors contribute to cognitive dysfunction. The patients of MHE have much higher levels of inflammatory markers, including IL-6 and C-reactive protein [42]. Also, the brain uses 20% of the body's energy while making up only 2% of its weight affecting brain energy metabolism [43]. Changes in glutamatergic and GABAergic systems directly affect cognitive and motor changes thereby disrupting neurotransmission [44]. The gut-liver-brain axis represents a detailed treatment approach to manage cognitive-behavioral disorders in HE [45]. The microbiota and gut-brain axis interact both ways, through neural, endocrine, immune, and humoral links that together shape cognitive function and behavior [36].

4. Microbiome Modulation as a Therapeutic Target

Microbiome modulation has uncovered promising treatment targets for hepatic encephalopathy. The complex connection between gut bacteria and brain function creates several opportunities for treatment intervention [46]. The gut microbiota of cirrhotic patients with HE shows notable changes. Studies reveal a sharp drop in helpful bacteria along with worrying increases in potentially harmful species [47][48]. The decreased beneficial bacteria include *Bacteroidetes, Ruminococcus, Roseburia, Lachnospiraceae* [49]. While there is an elevated level of pathogenic bacteria including *Fusobacteria, Proteobacteria, Enterococcaceae, and Streptococcaceae* [49], [50]. Gut microbiota restoration significantly decreases HE risk. Data from the study indicate that only 13.3% of the incidence of HE occurred in patients who showed better microbiota after TIPS. In contrast, 68.2% of patients whose microbiota deteriorated after TIPS [51]. Faecal microbiota transplantation (FMT) stands out as a promising treatment option. Several ways by which FMT affects HE pathogenesis include Boosted SCFA production, better microbiome community structure, optimized bile acid metabolism and lower ammonia production [52][53]. The work with probiotic treatments shows positive results. Probiotics deliver multiple

benefits as they block harmful bacteria through competition, make intestinal barriers work better and stop bacterial movement across barriers. They also cause a decrease in ammonia production [54] Recent large meta-analysis confirm that probiotics help improve HE symptoms, reverse minimal HE, and reduce overt HE episodes [55]. The VSL#3 probiotic mixture shows particular promise. It reduced serum cytokines (TNF-α, IL-1β, and IL-6) in 24% of patients who completed 24 weeks of treatment [52].The synbiotic approaches that combine probiotics with prebiotics was also looked. This combination therapy helps boost beneficial Lactobacillus species while lowering blood ammonia levels [56]. Standard treatment now combines antibiotics with lactulose [57]. These various treatment strategies and their mechanisms are summarized in Figure 4, highlighting the distinct benefits of FMT, synbiotics, probiotics, and standard therapies in modulating gut microbiota and reducing HE-related complications.

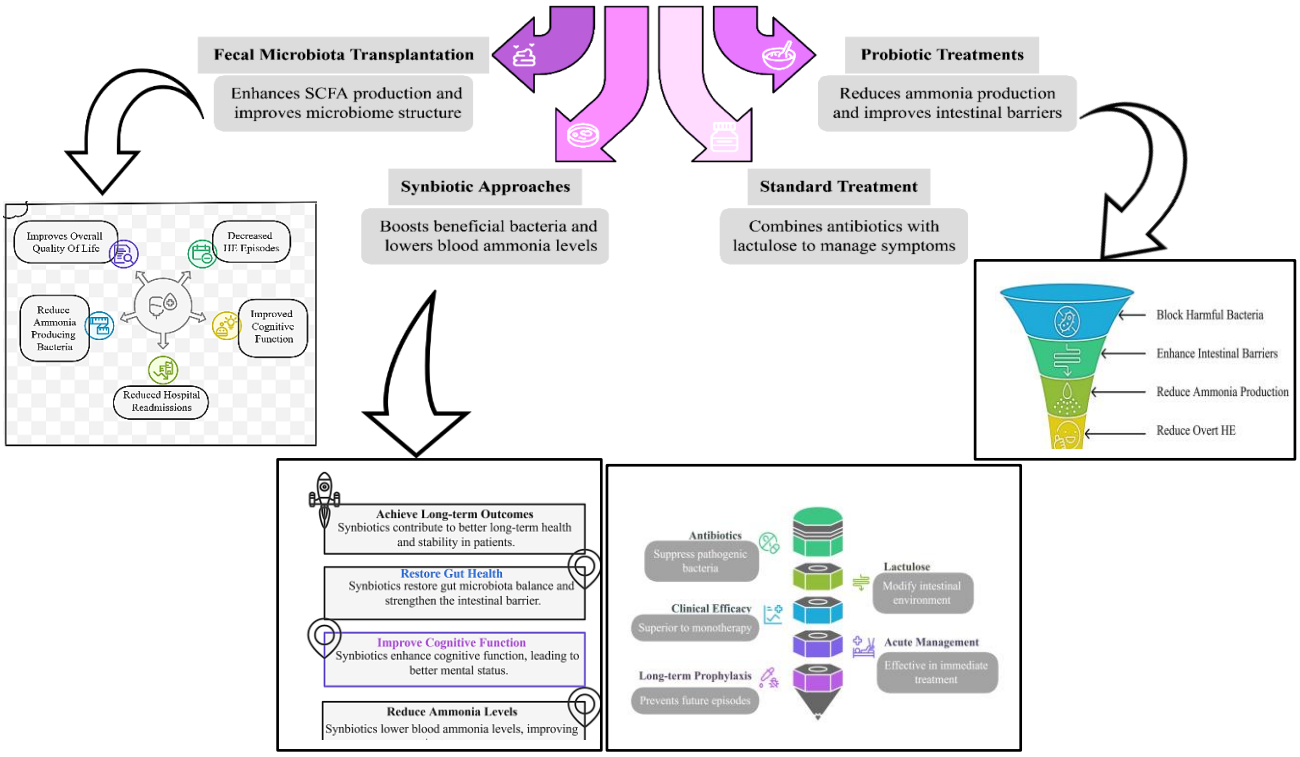

Figure 4: Overview of microbiome-modulating strategies in hepatic encephalopathy (HE). Fecal microbiota transplantation (FMT), synbiotic, probiotic, and standard antibiotic-lactulose therapies contribute to HE management through different mechanisms such as enhancing short-chain fatty acid (SCFA) production, blocking harmful bacteria, restoring gut health, reducing ammonia production, and improving cognitive function and patient outcomes.

5. Innovative Metabolic Interventions

Research into hepatic encephalopathy treatments has found important breakthroughs in metabolic interventions [58]. Ammonia-lowering treatments work through two main mechanisms to treat hepatic encephalopathy which involves inhibiting ammonia production or by increasing ammonia removal [59] .Lactulose works through multiple mechanisms and creates an acidic pH environment. This converts ammonia (NH_3) to ammonium (NH_4^+) and reduces bloodstream diffusion [60]. Rifaximin effectively reduces ammonia production by targeting ammonia-producing bacteria. It does this through DNA-dependent RNA polymerase inhibition [61].

The clinical trials show remarkable progress with amino acid interventions. L-ornithine-L-aspartate (LOLA) looks especially promising. It effectively lowers blood and brain ammonia levels by stimulating hepatic urea synthesis, improving glutamine synthesis in muscle tissue [62].Branched-chain amino acids (BCAAs) show significant therapeutic potential. Studies reveal that BCAA supplements improve mental status in patients with end-stage liver disease [59]. The process involves improved protein synthesis and reduced catabolism. Leucine plays a vital role in muscle protein synthesis [63].Investigations have shown that targeting nutrient-sensing pathways through precision medicine-based strategies, like nanotechnologies, might improve bioavailability and increase efficacy. These interventions address impaired mitochondrial energy metabolism and insulin-glucose metabolism. The results show improved cognitive function [64]. The mechanisms and therapeutic target of these ammonia-lowering strategies are summarized in Figure 5.

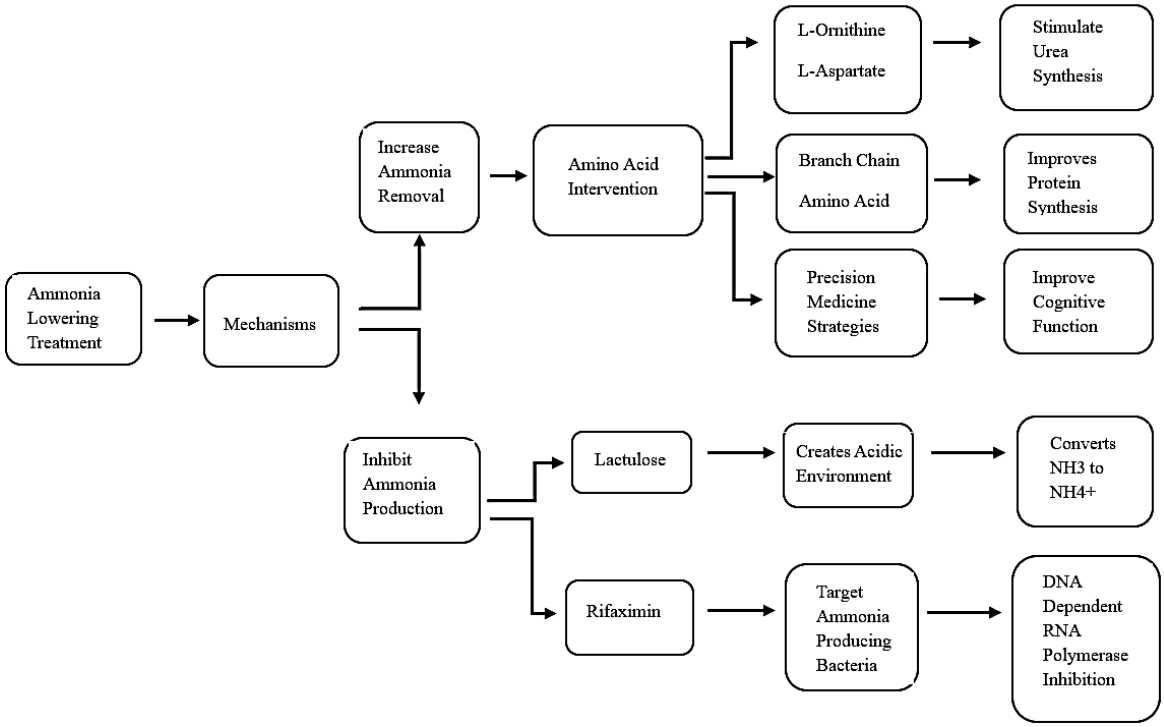

Figure 5: Mechanisms of innovative metabolic interventions for hepatic encephalopathy. Ammonia-lowering treatments act via two primary pathways: increasing ammonia removal (through amino acid interventions like L-ornithine L-aspartate and BCAAs, and precision strategies) or inhibiting ammonia production (through agents like lactulose and rifaximin). These strategies contribute to improved cognitive function, protein synthesis, and reduced systemic ammonia levels.

6. Targeting Neuroinflammation

Research into neuroinflammation in hepatic encephalopathy has shown compelling evidence. Chronic, low-grade inflammation causes the immune system to remain activated even when there are no apparent threats [65]. Liver inflammation affects cognitive function through multiple pathways. Liver necroptosis increases inflammation in both the liver and brain. This affects cognitive abilities [66]. Several inflammatory markers that relate to cognitive decline include TNF-α expression in astrocytes, increased IL-1ß and IL-6 levels and higher CXCL1 in cerebrospinal fluid (CSF) [67]

Anti-inflammatory approaches show remarkable neuroprotective effects. These reduce cognitive decline and motor impairments in experimental models [68]. Minocycline, a tetracycline antibiotic, prevents microglial activation in multiple brain regions. The effects show up in the frontal cortex, thalamus, and hippocampus [69].

A study of blood-brain barrier (BBB) integrity showed structural BBB abnormalities. These occur in both acute liver failure and chronic liver insufficiency. BBB disruption mainly affects junctional proteins' structures, including tight junction proteins and integrins [70]. BBB dysfunction happens because of the decomposition of structural elements, uncontrolled influx of substances along increased permeability [71]Changes in BBB permeability might happen before tight junction disruption. This suggests a complex progression of barrier breakdown [72]. The studies of glial cell function show that astrocytes and microglia are important for CNS homeostasis. These cells serve important functions as they provide defence against pathogens. Synaptic plasticity and elimination of toxic substances is also major work performed by these cells. They are also involved in Physiological neurodegeneration [68].

Astrocytes respond to brain tissue derangement through astrogliosis. This involves GFAP overexpression and cell body enlargement. Inflammation contributes by a lot to astrocyte swelling, especially with elevated ammonia levels [73].The microglial response shows these cells become active in both Type A and Type C HE. They produce cytokines and generate oxidative stress. Post-mortem studies of cortical brain tissue from cirrhotic patients with overt HE reveals something interesting. The microglial marker IBA1 shows higher levels compared to cirrhotic patients that do not have HE [74]. Key neuroinflammatory targets in HE are highlighted in figure 6.

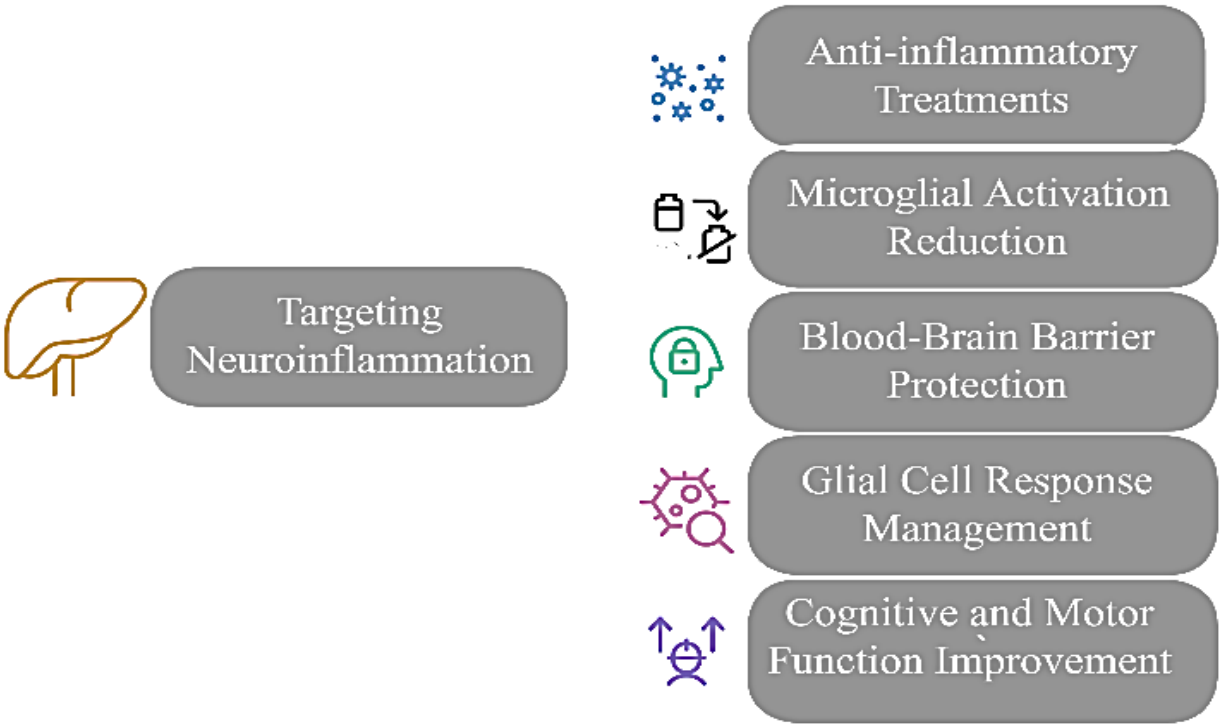

Figure 6: Therapeutic strategies targeting neuroinflammation in hepatic encephalopathy. Key approaches include anti-inflammatory treatments, suppression of microglial activation, protection of the blood-brain barrier, and regulation of glial cell activity. These interventions aim to restore neurological function and reduce cognitive and motor impairments associated with HE.

7. Emerging Molecular Therapeutics

Molecular biology breakthroughs have transformed how we treat hepatic encephalopathy with targeted interventions at genetic and cellular levels [75]. Scientists have made remarkable progress in creating precision therapies that address why this complex condition happens. The liver's unique regenerative capacity makes it perfect for gene editing interventions. The liver absorbs almost all foreign molecules, which makes it especially receptive to genetic modifications [76]. Researchers discovered that there existed a single-gene defect responsible for all but one of these 100 hepatopathies, with the exception of carbamoyl phosphate synthetase (CPS1) deficiency, where the gene size exceeds standard adeno associated virus (AAV) vector capacity. This creates clear targets for therapeutic intervention [77]. Research shows that ex-vivo gene editing brings several benefits as patient-derived cells trigger minimal immune response. And scientists can screen and remove cells with unexpected edits as well as the process allows precise control over cell selection for reinjection [78]. RNA interference

(RNAi) has emerged as a powerful therapeutic tool. RNA therapy can effectively change gene expression without altering DNA sequences [79]. These RNA-based treatments work by target silencing (using ASOs, siRNAs, and miRNAs) and protein expression modulation (primarily through mRNAs) [80].

The siRNA treatments have proven highly successful, especially in liver-targeted therapies. Four FDA-approved drugs that employ this technology have achieved remarkable results and these include givosiran (2019) for acute hepatic porphyria [81], inclisiran (2020) for hypercholesterolemia [82], lumasiran (2020) for primary hyperoxaluria type-1 [82], and vutrisiran (2022) for hATTR amyloidosis [83], [84].

Table 1: Emerging gene and RNA-based therapeutic strategies for hepatic encephalopathy (HE). This table outlines the mechanisms of action, clinical applications, and supporting evidence for each approach, including gene therapy, ex-vivo gene editing, RNA interference, and FDA-approved siRNA therapies, highlighting their potential in reducing ammonia levels and targeting liver-related genetic and metabolic dysfunctions.

Therapeutic Approach	Mechanism of Action	Applications	Evidence	References

Gene Therapy (Bac-GS)	Delivery of glutamine synthetase gene via baculovirus in order to decrease ammonia levels.	Promising in treatment of hyperammonemia in HE patients.	Gene therapy has been shown to significantly decrease ammonia levels in chronic liver disease models, providing a potential therapy for HE.	[85]
Ex-vivo Gene Editing	Cells from the patient are modified in ex vivo to correct genetic defects.	Potential for precision therapies targeting HE-related genetic issues.	This method ensures that there is minimal immune response and precise control over cell selection, which is useful for liver conditions.	[85]
RNA Interference (RNAi)	It modulates gene expression by siRNA, ASOs (Antisense Oligonucleotides Synthetic single-stranded DNA or RNA), and miRNAs without altering DNA.	It is effective in silencing genes associated with HE.	RNA-based therapies have been successful in targeting liver diseases, showing promise for HE management.	[77], [85]
FDA-Approved siRNA Therapies	It targets specific mRNAs to reduce the protein expression linked to liver diseases.	It includes drugs givosiran, inclisiran, lumasiran, and vutrisiran, which have shown to be effective for related health issues.	These treatments have demonstrated important results in handling problems that might lead to HE.	[85], [86]

8. Novel Drug Delivery Systems

Two primary approaches have shown exceptional promise in delivery platform development. Lipid Nanoparticles (LNPs) are the most advanced RNA delivery platform available. These LNPs achieve selective hepatocyte uptake through ApoE-mediated binding to LDLR surface receptors [87]. Also, GalNAc-RNA conjugates have achieved remarkable clinical success. These are targeted RNA delivery systems where RNA molecules (like siRNAs or antisense oligonucleotides) are chemically linked to N-acetylgalactosamine (GalNAc). GalNAc specifically binds to the asialoglycoprotein receptor (ASGPR), which is highly expressed on the surface of hepatocytes (liver cells). These conjugates provide significant advantages as patients need fewer doses, subcutaneous injection becomes possible and targeting becomes more specific [79].

Clinical trials show that mRNA in LNPs efficiently targets the liver after systemic injection. This approach is valuable because it reduces genotoxicity risks, protects RNA from nuclease-mediated degradation and keeps the payload safe from immune system recognition. These characteristics make molecular therapeutic approaches a great way to get long-term management of hepatic encephalopathy [86].Research into personalized treatment approaches for hepatic encephalopathy shows how important it is to tailor interventions to each patient's profile. A patient's unique characteristics can guide us toward more effective outcomes [88].

9. Biomarker-Based Approach and Genetic Profile Considerations

Several key biomarkers help guide treatment decisions. In a cohort study, patients with cirrhosis were evaluated for metabolic and clinical indicators of minimal hepatic encephalopathy (MHE). All of them have minimal hepatic encephalopathy (MHE), except one who does not [89]. The largest longitudinal study has helped us build a complete biomarker panel that has serum ammonia levels, inflammatory markers (IL-6, C-reactive protein), and neurosteroid metabolites. Also, the blood-brain barrier integrity markers and gut microbiome composition indicators make the biomarker panel more effective. Elevated levels of inflammation markers, especially IL-6 and C-reactive protein, are associated with cognitive decline in MHE patients more than in normal individuals [90]. Genomic analysis becomes crucial for adults with unexplained liver disease, especially those under 40 or those who show multisystemic signs. Genetic information in clinical decision-making has boosted patient outcomes by a lot. Overweight or obese individuals carrying specific genetic variants face a higher risk of progressing to cirrhosis and developing complications [91]

10. Individual Response Monitoring

A sophisticated approach to monitoring treatment responses has developed. MHE affects 20-80% of patients with liver cirrhosis which makes careful tracking of individual responses essential [92]. A complete monitoring protocol has been developed that has regular cognitive function assessments, biomarker

level tracking, microbiome composition analysis, quality of life measurements and treatment adherence evaluation. This personalized approach affects patient outcomes significantly. MHE affects the quality of life and patients' work severely [90]. Early intervention can prevent progression to overt hepatic encephalopathy, which raises mortality rates [93]. Traditional clinical scores work better when combined with genetic information. Variants that affect hepatic lipid accumulation and specific metabolic pathways can improve conventional clinical assessments' accuracy. This merged approach helps predict disease progression and adjust treatment strategies [94].

11. Multi-Organ System Integration

The study of complex interactions between organ systems in hepatic encephalopathy shows that these relationships are vital for developing treatments that work. The liver acts as a metabolic hub that converts dietary macronutrients into usable forms and maintains nutrient levels the brain needs to function [95]. The liver-gut-brain axis works through multiple pathways. The vagus nerve plays a vital role in this axis. It sends signals from the intestine to the brainstem through the left nodose ganglion, which creates a complete gut-liver-brain-gut signalling loop [96]. Hepatorenal syndrome (HRS) affects cognitive function through several mechanisms. HRS-AKI leads to rapid kidney function decline by affecting blood filtration and decreasing the toxin removal capacity. Moreover, renal function decline also happens due to an imbalance of fluid and metabolic waste elimination [97].

Regular creatinine monitoring helps detect problems early. This matters because 50% of patients die within 2 weeks of diagnosis without therapy [98]. Continuous renal replacement therapy (CRRT) can save lives while patients wait for liver transplantation [99].

12. Systemic Treatment Approaches

The complete research has led to multi-targeted treatment strategies. The gut microbiota through the enteric nervous system changes the central nervous system. The vagus nerve controls immunity and inflammation in both the liver and gastrointestinal tract [100]. Successful treatment needs to address three major barriers i.e. intestinal epithelial integrity, normal liver function, and blood-brain barrier stability [96]. Combined approaches have shown great results. Faecal microbiota transplantation rebuilds intestinal barrier integrity and reduces ammonia absorption effectively. On top of that, probiotics improve intestinal barrier function and reduce portal hypertension [57], [101]. The largest longitudinal study shows that cognitive problems from hepatic encephalopathy can reverse within 5 years after liver transplantation. This finding makes transplantation worth thinking about when the Model of End-Stage Liver Disease (MELD) score goes above 15 [102]. The ongoing research keeps improving our understanding of these complex organ system interactions. The gut microbiome might be the best treatment target at any stage of liver disease as it reduces the exposure of intestinal toxins to both liver and nervous system [103].

13. Future Therapeutic Directions

The future of hepatic encephalopathy treatment looks promising. Groundbreaking developments have been found that will transform patient care through new technologies and therapeutic approaches. Research shows an exciting merger of artificial intelligence, new drug development, and combination therapies [104], [105].AI has made remarkable strides in hepatic encephalopathy management. Our studies show that AI algorithms now analyze complex clinical datasets better than physicians in specific areas [106], [107]. AI implementation in hepatology helps boost clinical decision support that includes automated image analysis, up-to-the-minute patient monitoring, and predictive analytics for complications. Treatment Optimization includes individual-specific dosing recommendations, drug interaction predictions and treatment response forecasting [108]. The CirrohCare trial helped us develop a sophisticated remote monitoring system that merges smart devices with AI analytics. The system has smartphones, watches, and other monitoring devices that track vital signs and cognitive function [109]. This technology helps identify complications earlier, which reduces hospital admissions and improves patient outcomes [110]. Combination therapies often yield better results than monotherapy. Patients receiving combination therapy experienced shorter hospital stays and fewer hospitalizations compared to those on lactulose monotherapy [111]. Combination approaches have been found which include microbiome modulation and metabolic interventions. Microbiome modulation involves combining probiotics with traditional treatments and shows better efficacy in reducing ammonia production, improving cognitive function and preventing recurrence [112], [113]. Metabolic interventions combine metabolic activators with standard treatments to improve cognitive performance, ammonia clearance and overall patient outcomes [111]

The molecular adsorbent recirculating system (MARS) shows particular promise. This extracorporeal hepatic support system merges dialysis, ultrafiltration, and adsorption mechanisms. Larger randomized controlled trials are still needed, but original findings suggest significant potential [114], [115]. The research continues to explore AI applications to optimize combination therapy selection. Machine learning algorithms predict treatment responses more accurately as more data becomes available. AI will boost physician performance while decreasing the documentation burden, leading to more individual-specific and effective treatment approaches [116]. The future of hepatic encephalopathy treatment lies in merging multiple therapeutic modalities. Successful outcomes often depend on coordinating various treatment

approaches [117]. Figure 7 summarizes these future therapeutic directions and their clinical impact.

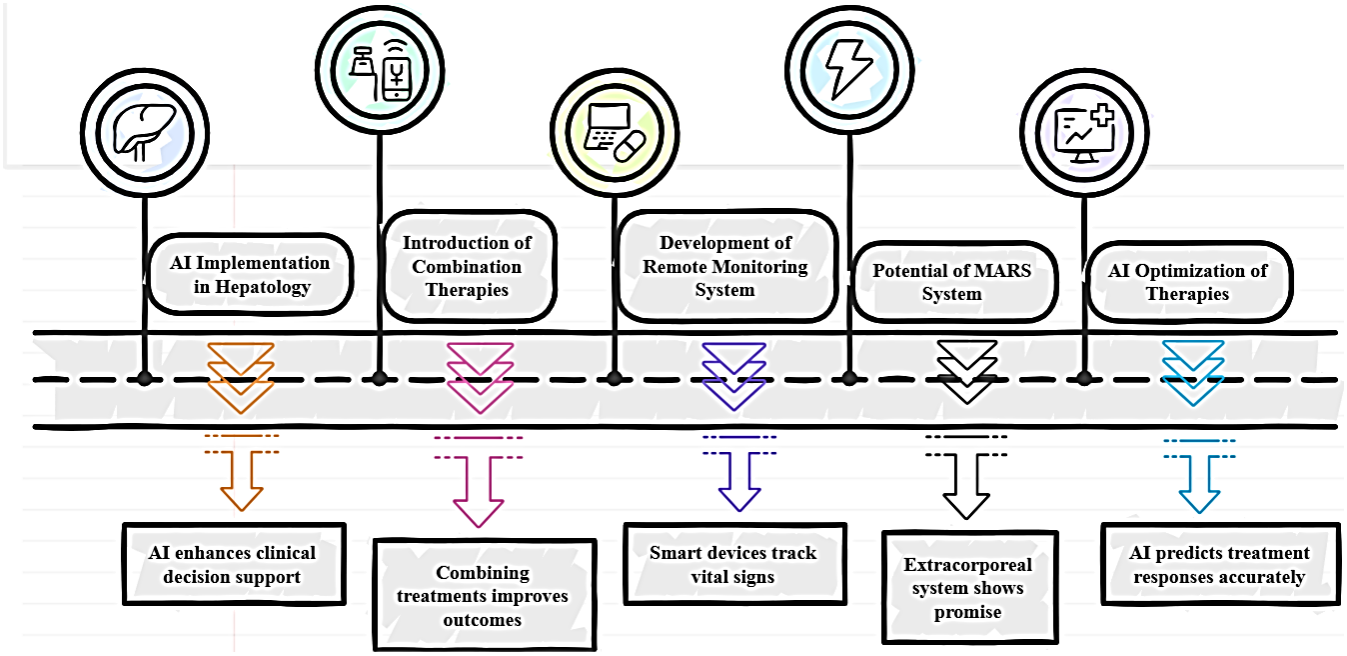

Figure 7: The figure illustrates five key areas expected to transform hepatic encephalopathy management: AI implementation in hepatology, combination therapy approaches, remote monitoring systems, the MARS extracorporeal support system, and AI-based treatment optimization. Each area is aligned with its corresponding clinical benefit, reflecting a comprehensive approach to improve patient outcomes.

Conclusion

Our detailed review of hepatic encephalopathy shows remarkable progress in understanding and treating this complex condition. The gut-brain axis plays a key role in disease pathogenesis. Microbiome modulation shows promising therapeutic potential. Treatment approaches that are customized to each patient's genetic profile and biomarkers produce better outcomes than standard protocols. RNA-based interventions and novel drug delivery systems have made exciting breakthroughs in molecular therapeutics. Furthermore, the identification of specific biomarkers can enhance early diagnosis and inform treatment strategies, leading to more effective management of the condition. These advances give us new opportunities to develop better therapeutic strategies as we learn more about how different organ systems interact with each other. Incorporating insights from ongoing research into patient care will be crucial for refining treatment protocols. The combination of new approaches with traditional treatments will make outcomes for hepatic encephalopathy patients dramatically better.

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References

[1] H. Vilstrup *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*, vol. 60, no. 2, pp. 715–735, Aug. 2014, doi: 10.1002/hep.27210.

[2] A. Mancini, F. Campagna, P. Amodio, and K. M. Tuohy, "Gut : liver : brain axis: the microbial challenge in the hepatic encephalopathy," *Food Funct*, vol. 9, no. 3, pp. 1373–1388, 2018, doi: 10.1039/C7FO01528C.

[3] S. El Aidy, R. Stilling, T. G. Dinan, and J. F. Cryan, "Microbiome to Brain: Unravelling the Multidirectional Axes of Communication," 2016, pp. 301–336. doi: 10.1007/978-3-319-20215-0_15.

[4] M. Kandpal *et al.*, "Dysbiosis of Gut Microbiota from the Perspective of the Gut–Brain Axis: Role in the Provocation of Neurological Disorders," *Metabolites*, vol. 12, no. 11, p. 1064, Nov. 2022, doi: 10.3390/metabo12111064.

[5] M. A. Ellul, S. A. Gholkar, and T. J. Cross, "Hepatic encephalopathy due to liver cirrhosis," *BMJ*, p. h4187, Aug. 2015, doi: 10.1136/bmj.h4187.

[6] N. M. Bass, "A Brief History of Hepatic Encephalopathy," *Clin Liver Dis (Hoboken)*, vol.

18, no. S1, pp. 49–62, Oct. 2021, doi: 10.1002/cld.1119.

[7] R. K. Prakash and K. D. Mullen, "Hepatic Encephalopathy," in *Schiff's Diseases of the Liver*, Wiley, 2011, pp. 421–444. doi: 10.1002/9781119950509.ch18.

[8] N. Dharel and J. S. Bajaj, "Definition and Nomenclature of Hepatic Encephalopathy," *J Clin Exp Hepatol*, vol. 5, pp. S37–S41, Mar. 2015, doi: 10.1016/j.jceh.2014.10.001.

[9] S. L. Flamm, "Complications of Cirrhosis in Primary Care: Recognition and Management of Hepatic Encephalopathy," *Am J Med Sci*, vol. 356, no. 3, pp. 296–303, Sep. 2018, doi: 10.1016/j.amjms.2018.06.008.

[10] H. KHOBRAGADE, T. MANOHAR, and A. SATHAWANE, "Precipitating Factors and Clinico-Endoscopic Study of Patients with Hepatic Encephalopathy Type C," *Journal of Contemporary Medicine*, vol. 12, no. 4, pp. 559–564, Jul. 2022, doi: 10.16899/jcm.979964.

[11] H. M. Singh, L. Romesh Sharma, and M. Bijoy, "PRECIPITATING FACTORS AND OUTCOME OF HEPATIC ENCEPHALOPATHY-A HOSPITAL BASE CROSS SECTIONAL STUDY," *International Journal of Academic Medicine and Pharmacy*, 2017, doi: 10.47009/jamp.2023.5.5.356.

[12] A. Jaffe, J. K. Lim, and S. S. Jakab, "Pathophysiology of Hepatic Encephalopathy," *Clin Liver Dis*, vol. 24, no. 2, pp. 175–188, May 2020, doi: 10.1016/j.cld.2020.01.002.

[13] K. Kroupina, C. Bémeur, and C. F. Rose, "Amino acids, ammonia, and hepatic encephalopathy," *Anal Biochem*, vol. 649, p. 114696, Jul. 2022, doi: 10.1016/j.ab.2022.114696.

[14] D. R. Aldridge, E. J. Tranah, and D. L. Shawcross, "Pathogenesis of Hepatic Encephalopathy: Role of Ammonia and Systemic Inflammation," *J Clin Exp Hepatol*, vol. 5, pp. S7–S20, Mar. 2015, doi: 10.1016/j.jceh.2014.06.004.

[15] S. Matsumoto, J. Häberle, J. Kido, H. Mitsubuchi, F. Endo, and K. Nakamura, "Urea cycle disorders—update," *J Hum Genet*, vol. 64, no. 9, pp. 833–847, Sep. 2019, doi: 10.1038/s10038-019-0614-4.

[16] I. D. Limón, I. Angulo-Cruz, L. Sánchez-Abdon, and A. Patricio-Martínez, "Disturbance of the Glutamate-Glutamine Cycle, Secondary to Hepatic Damage, Compromises Memory Function," *Front Neurosci*, vol. 15, Jan. 2021, doi: 10.3389/fnins.2021.578922.

[17] S. Mahmoud, M. Gharagozloo, C. Simard, and D. Gris, "Astrocytes Maintain Glutamate Homeostasis in the CNS by Controlling the Balance between Glutamate Uptake and Release," *Cells*, vol. 8, no. 2, p. 184, Feb. 2019, doi: 10.3390/cells8020184.

[18] P. R. Angelova, A. J. C. Kerbert, A. Habtesion, A. Hall, A. Y. Abramov, and R. Jalan, "Hyperammonaemia induces mitochondrial dysfunction and neuronal cell death," *JHEP Reports*, vol. 4, no. 8, p. 100510, Aug. 2022, doi: 10.1016/j.jhepr.2022.100510.

[19] S. R. Archie, A. Al Shoyaib, and L. Cucullo, "Blood-Brain Barrier Dysfunction in CNS Disorders and Putative Therapeutic Targets: An Overview," *Pharmaceutics*, vol. 13, no. 11, p. 1779, Oct. 2021, doi: 10.3390/pharmaceutics13111779.

[20] A. R. Jayakumar, K. V. Rama Rao, and M. D. Norenberg, "Neuroinflammation in Hepatic Encephalopathy: Mechanistic Aspects," *J Clin Exp Hepatol*, vol. 5, pp. S21–S28, Mar. 2015, doi: 10.1016/j.jceh.2014.07.006.

[21] A. Srivastava, S. K. Yadav, S. K. Yachha, M. A. Thomas, V. A. Saraswat, and R. K. Gupta, "Pro-inflammatory cytokines are raised in extrahepatic portal venous obstruction, with minimal hepatic encephalopathy," *J Gastroenterol Hepatol*, vol. 26, no. 6, pp. 979–986, Jun. 2011, doi: 10.1111/j.1440-1746.2011.06706.x.

[22] V. Jaeger, S. DeMorrow, and M. McMillin, "The Direct Contribution of Astrocytes and Microglia to the Pathogenesis of Hepatic Encephalopathy," *J Clin Transl Hepatol*, vol. 7, no. X, pp. 1–10, Dec. 2019, doi: 10.14218/JCTH.2019.00025.

[23] W. M. Elzefzafy, A. Abou lEla, and M. H. Maabady, "Role of Tumor Necrosis Factor Alpha , Ghrelin , Evoked Potentials in Hepatic Encephalopathy," *Egypt J Hosp Med*, vol. 53, pp. 846–854, Oct. 2013, doi: 10.12816/0001647.

[24] C. Labenz *et al.*, "Raised serum Interleukin-6 identifies patients with liver cirrhosis at high risk for overt hepatic encephalopathy," *Aliment Pharmacol Ther*, vol. 50, no. 10, pp. 1112–1119, Nov. 2019, doi: 10.1111/apt.15515.

[25] M. Luo, L. Li, E. Yang, and W. Cao, "Relationship between interleukin-6 and ammonia in patients with minimal hepatic encephalopathy due to liver cirrhosis," *Hepatology Research*, vol. 42, no. 12, pp. 1202–1210, Dec. 2012, doi: 10.1111/j.1872-034X.2012.01047.x.

[26] O. Cauli *et al.*, "Glutamatergic and gabaergic neurotransmission and neuronal circuits in hepatic encephalopathy," *Metab Brain Dis*, vol. 24, no. 1, pp. 69–80, Mar. 2009, doi: 10.1007/s11011-008-9115-4.

[27] E. A. Jones, "Ammonia, the GABA Neurotransmitter System, and Hepatic Encephalopathy," *Metab Brain Dis*, vol. 17, no. 4, pp. 275–281, 2002, doi: 10.1023/A:1021949616422.

[28] A. Michalak, K. Knecht, and R. F. Butterworth, "Hepatic Encephalopathy in Acute Liver Failure: Role of the Glutamate System," 1997, pp. 35–43. doi: 10.1007/978-1-4615-5945-0_2.

[29] R. F. Butterworth, J. Lavoie, J.-F. Giguère, G. P. Layrargues, and M. Bergeron, "Cerebral GABA-ergic and glutamatergic function in hepatic encephalopathy," *Neurochem Pathol*, vol. 6, no. 1–2, pp. 131–144, Feb. 1987, doi: 10.1007/BF02833603.

[30] S. Dhanda and R. Sandhir, "Role of dopaminergic and serotonergic neurotransmitters in behavioral alterations observed in rodent model of hepatic encephalopathy," *Behavioural Brain Research*, vol. 286, pp. 222–235, Jun. 2015, doi: 10.1016/j.bbr.2015.01.042.

[31] R. F. Butterworth, L. Spahr, S. Fontaine, and G. P. Layrargues, "Manganese toxicity, dopaminergic dysfunction and hepatic encephalopathy," *Metab Brain Dis*, vol. 10, no. 4, pp. 259–267, Dec. 1995, doi: 10.1007/BF02109357.

[32] J. S. Bajaj, "The role of microbiota in hepatic encephalopathy," *Gut Microbes*, vol. 5, no. 3, pp. 397–403, May 2014, doi: 10.4161/gmic.28684.

[33] R. Rai, V. A. Saraswat, and R. K. Dhiman, "Gut Microbiota: Its Role in Hepatic Encephalopathy," *J Clin Exp Hepatol*, vol. 5, pp. S29–S36, Mar. 2015, doi: 10.1016/j.jceh.2014.12.003.

[34] S.-M. Won *et al.*, "The Link between Gut Microbiota and Hepatic Encephalopathy," *Int J Mol Sci*, vol. 23, no. 16, p. 8999, Aug. 2022, doi: 10.3390/ijms23168999.

[35] X. Yang, K. Qiu, Y. Jiang, Y. Huang, Y. Zhang, and Y. Liao, "Metabolic Crosstalk between Liver and Brain: From Diseases to Mechanisms," *Int J Mol Sci*, vol. 25, no. 14, p. 7621, Jul. 2024, doi: 10.3390/ijms25147621.

[36] M. Carabotti, A. Scirocco, M. A. Maselli, and C. Severi, "The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems.," *Ann Gastroenterol*, vol. 28, no. 2, pp. 203–209, 2015.

[37] G. Fernandes, "The Co-Relation Between The Nervous System And Gut Health," 2023, doi: 10.9790/0853-2206102734.

[38] M. Yan *et al.*, "Gut liver brain axis in diseases: the implications for therapeutic interventions," *Signal Transduct Target Ther*, vol. 8, no. 1, p. 443, Dec. 2023, doi: 10.1038/s41392-023-01673-4.

[39] S. Qu *et al.*, "Gut microbiota modulates neurotransmitter and gut-brain signaling," *Microbiol Res*, vol. 287, p. 127858, Oct. 2024, doi: 10.1016/j.micres.2024.127858.

[40] H. H. Nguyen and M. G. Swain, "Avenues within the gut-liver-brain axis linking chronic liver disease and symptoms," *Front Neurosci*, vol. 17, Jul. 2023, doi: 10.3389/fnins.2023.1171253.

[41] T. Sun, M. Feng, A. Manyande, H. Xiang, J. Xiong, and Z. He, "Regulation of mild cognitive impairment associated with liver disease by humoral factors derived from the gastrointestinal tract and MRI research progress: a literature review," *Front Neurosci*, vol. 17, Jun. 2023, doi: 10.3389/fnins.2023.1206417.

[42] S. J. Gairing *et al.*, "Evaluation of IL-6 for Stepwise Diagnosis of Minimal Hepatic Encephalopathy in Patients With Liver Cirrhosis," *Hepatol Commun*, vol. 6, no. 5, pp. 1113–1122, May 2022, doi: 10.1002/hep4.1883.

[43] R. A. Hawkins, A. M. Mans, and J. F. Biebuyck, "Changes in brain metabolism in hepatic encephalopathy," *Neurochem Pathol*, vol. 6, no. 1–2, pp. 35–66, Feb. 1987, doi: 10.1007/BF02833600.

[44] N. Palomero-Gallagher and K. Zilles, "Neurotransmitter receptor alterations in hepatic encephalopathy: A review," *Arch Biochem Biophys*, vol. 536, no. 2, pp. 109–121, Aug. 2013, doi: 10.1016/j.abb.2013.02.010.

[45] Z. Chen *et al.*, "The Role of Intestinal Bacteria and Gut–Brain Axis in Hepatic Encephalopathy," *Front Cell Infect Microbiol*, vol. 10, Jan. 2021, doi: 10.3389/fcimb.2020.595759.

[46] P. P. Bloom, E. B. Tapper, V. B. Young, and A. S. Lok, "Microbiome therapeutics for hepatic encephalopathy," *J Hepatol*, vol. 75, no. 6, pp. 1452–1464, Dec. 2021, doi: 10.1016/j.jhep.2021.08.004.

[47] C. Llorente and B. Schnabl, "The Gut Microbiota and Liver Disease," *Cell Mol Gastroenterol Hepatol*, vol. 1, no. 3, pp. 275–

284, May 2015, doi: 10.1016/j.jcmgh.2015.04.003.

[48] A. Rocco, C. Sgamato, D. Compare, P. Coccoli, O. M. Nardone, and G. Nardone, "Gut Microbes and Hepatic Encephalopathy: From the Old Concepts to New Perspectives," *Front Cell Dev Biol*, vol. 9, Nov. 2021, doi: 10.3389/fcell.2021.748253.

[49] R. Rai, V. A. Saraswat, and R. K. Dhiman, "Gut Microbiota: Its Role in Hepatic Encephalopathy," *J Clin Exp Hepatol*, vol. 5, pp. S29–S36, Mar. 2015, doi: 10.1016/j.jceh.2014.12.003.

[50] J. Lachar and J. Bajaj, "Changes in the Microbiome in Cirrhosis and Relationship to Complications: Hepatic Encephalopathy, Spontaneous Bacterial Peritonitis, and Sepsis," *Semin Liver Dis*, vol. 36, no. 04, pp. 327–330, Dec. 2016, doi: 10.1055/s-0036-1593881.

[51] M. Li *et al.*, "Restoration of the gut microbiota is associated with a decreased risk of hepatic encephalopathy after TIPS," *JHEP Reports*, vol. 4, no. 5, p. 100448, May 2022, doi: 10.1016/j.jhepr.2022.100448.

[52] P. P. Bloom, E. B. Tapper, V. B. Young, and A. S. Lok, "Microbiome therapeutics for hepatic encephalopathy," *J Hepatol*, vol. 75, no. 6, pp. 1452–1464, Dec. 2021, doi: 10.1016/j.jhep.2021.08.004.

[53] M. Madsen, N. Kimer, F. Bendtsen, and A. M. Petersen, "Fecal microbiota transplantation in hepatic encephalopathy: a systematic review," *Scand J Gastroenterol*, vol. 56, no. 5, pp. 560–569, May 2021, doi: 10.1080/00365521.2021.1899277.

[54] A. A. Imani Fooladi, H. M. Hosseini, M. R. Nourani, S. Khani, and S. M. Alavian, "Probiotic as a Novel Treatment Strategy Against Liver Disease," *Hepat Mon*, vol. 13, no. 2, Feb. 2013, doi: 10.5812/hepatmon.7521.

[55] J. Gao, R. Nie, H. Chang, W. Yang, and Q. Ren, "A meta-analysis of microbiome therapies for hepatic encephalopathy," *Eur J Gastroenterol Hepatol*, vol. 35, no. 9, pp. 927–937, Sep. 2023, doi: 10.1097/MEG.0000000000002596.

[56] G. Bongaerts, R. Severijnen, and H. Timmerman, "Effect of antibiotics, prebiotics and probiotics in treatment for hepatic encephalopathy," *Med Hypotheses*, vol. 64, no. 1, pp. 64–68, Jan. 2005, doi: 10.1016/j.mehy.2004.07.029.

[57] S.-M. Won *et al.*, "The Link between Gut Microbiota and Hepatic Encephalopathy," *Int J Mol Sci*, vol. 23, no. 16, p. 8999, Aug. 2022, doi: 10.3390/ijms23168999.

[58] M. Yan *et al.*, "Gut liver brain axis in diseases: the implications for therapeutic interventions," *Signal Transduct Target Ther*, vol. 8, no. 1, p. 443, Dec. 2023, doi: 10.1038/s41392-023-01673-4.

[59] C. F. Rose, "Ammonia-Lowering Strategies for the Treatment of Hepatic Encephalopathy," *Clin Pharmacol Ther*, vol. 92, no. 3, pp. 321–331, Sep. 2012, doi: 10.1038/clpt.2012.112.

[60] S. Tejpal, S. K. Sharma, A. Sharma, and S. Sharma, "A Comprehensive Review on Hepatic Encephalopathy: Pathophysiology, Symptoms, Epidemiology, Classification, Diagnosis and Treatment," *Journal for Research in Applied Sciences and Biotechnology*, vol. 3, no. 3, pp. 170–180, Jul. 2024, doi: 10.55544/jrasb.3.3.27.

[61] W. Yang, G. Guo, and C. Sun, "Therapeutic potential of rifaximin in liver diseases," *Biomedicine & Pharmacotherapy*, vol. 178, p. 117283, Sep. 2024, doi: 10.1016/j.biopha.2024.117283.

[62] G. T. Toris, C. N. Bikis, G. S. Tsourouflis, and S. E. Theocharis, "Hepatic encephalopathy: An updated approach from pathogenesis to treatment," *Medical Science Monitor*, vol. 17, no. 2, pp. RA53–RA63, 2011, doi: 10.12659/MSM.881387.

[63] S. Colosimo, S. Bertoli, and F. Saffioti, "Use of Branched-Chain Amino Acids as a Potential Treatment for Improving Nutrition-Related Outcomes in Advanced Chronic Liver Disease," *Nutrients*, vol. 15, no. 19, p. 4190, Sep. 2023, doi: 10.3390/nu15194190.

[64] N. J. Hunt, D. Wahl, L. J. Westwood, G. P. Lockwood, D. G. Le Couteur, and V. C. Cogger, "Targeting the liver in dementia and cognitive impairment: Dietary macronutrients and diabetic therapeutics," *Adv Drug Deliv Rev*, vol. 190, p. 114537, Nov. 2022, doi: 10.1016/j.addr.2022.114537.

[65] C. F. Rose *et al.*, "Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy," *J Hepatol*, vol. 73, no. 6, pp. 1526–1547, Dec. 2020, doi: 10.1016/j.jhep.2020.07.013.

[66] V. Felipo, "Hepatic encephalopathy: effects of liver failure on brain function," *Nat Rev Neurosci*, vol. 14, no. 12, pp. 851–858, Dec. 2013, doi: 10.1038/nrn3587.

[67] K. Kjærgaard *et al.*, "Cognitive dysfunction in early experimental metabolic dysfunction-associated steatotic liver disease is associated

with systemic inflammation and neuroinflammation," *JHEP Reports*, vol. 6, no. 3, p. 100992, Mar. 2024, doi: 10.1016/j.jhepr.2023.100992.

[68] R. P. C. Santos, E. C. de B. Toscano, and M. A. Rachid, "Anti-inflammatory strategies for hepatic encephalopathy: preclinical studies," *Arq Neuropsiquiatr*, vol. 81, no. 07, pp. 656–669, Jul. 2023, doi: 10.1055/s-0043-1767819.

[69] M. Pasparakis and P. Vandenabeele, "Necroptosis and its role in inflammation," *Nature*, vol. 517, no. 7534, pp. 311–320, Jan. 2015, doi: 10.1038/nature14191.

[70] K. Orzeł-Gajowik, K. Milewski, and M. Zielińska, "miRNA-ome plasma analysis unveils changes in blood–brain barrier integrity associated with acute liver failure in rats," *Fluids Barriers CNS*, vol. 20, no. 1, p. 92, Dec. 2023, doi: 10.1186/s12987-023-00484-7.

[71] S. R. Archie, A. Al Shoyaib, and L. Cucullo, "Blood-Brain Barrier Dysfunction in CNS Disorders and Putative Therapeutic Targets: An Overview," *Pharmaceutics*, vol. 13, no. 11, p. 1779, Oct. 2021, doi: 10.3390/pharmaceutics13111779.

[72] K. Song *et al.*, "Oxidative Stress-Mediated Blood-Brain Barrier (BBB) Disruption in Neurological Diseases," *Oxid Med Cell Longev*, vol. 2020, pp. 1–27, Jul. 2020, doi: 10.1155/2020/4356386.

[73] D. M. A. Elsherbini *et al.*, "Astrocytes profiling in acute hepatic encephalopathy: Possible enrolling of glial fibrillary acidic protein, tumor necrosis factor-alpha, inwardly rectifying potassium channel (Kir 4.1) and aquaporin-4 in rat cerebral cortex," *Front Cell Neurosci*, vol. 16, Aug. 2022, doi: 10.3389/fncel.2022.896172.

[74] V. Jaeger, S. DeMorrow, and M. McMillin, "The Direct Contribution of Astrocytes and Microglia to the Pathogenesis of Hepatic Encephalopathy," *J Clin Transl Hepatol*, vol. 7, no. X, pp. 1–10, Dec. 2019, doi: 10.14218/JCTH.2019.00025.

[75] N. Zabaleta, M. Hommel, D. Salas, and G. Gonzalez-Aseguinolaza, "Genetic-Based Approaches to Inherited Metabolic Liver Diseases," *Hum Gene Ther*, vol. 30, no. 10, pp. 1190–1203, Oct. 2019, doi: 10.1089/hum.2019.140.

[76] J. H. Shin, J. Lee, Y. K. Jung, K. S. Kim, J. Jeong, and D. Choi, "Therapeutic applications of gene editing in chronic liver diseases: an update," *BMB Rep*, vol. 55, no. 6, pp. 251–258, Jun. 2022, doi: 10.5483/BMBRep.2022.55.6.033.

[77] J. Baruteau, N. Brunetti-Pierri, and P. Gissen, "Liver-directed gene therapy for inherited metabolic diseases," *J Inherit Metab Dis*, vol. 47, no. 1, pp. 9–21, Jan. 2024, doi: 10.1002/jimd.12709.

[78] L. Torella, N. Santana-Gonzalez, N. Zabaleta, and G. Gonzalez Aseguinolaza, "Gene editing in liver diseases," *FEBS Lett*, Jul. 2024, doi: 10.1002/1873-3468.14989.

[79] A. Bakrania, Y. Mo, G. Zheng, and M. Bhat, "RNA nanomedicine in liver diseases," *Hepatology*, Aug. 2024, doi: 10.1097/HEP.0000000000000606.

[80] Q.-C. Wang, "RNA interference: Antiviral weapon and beyond," *World J Gastroenterol*, vol. 9, no. 8, p. 1657, 2003, doi: 10.3748/wjg.v9.i8.1657.

[81] L. J. Scott, "Givosiran: First Approval," *Drugs*, vol. 80, no. 3, pp. 335–339, Feb. 2020, doi: 10.1007/s40265-020-01269-0.

[82] M. M. Zhang, R. Bahal, T. P. Rasmussen, J. E. Manautou, and X. Zhong, "The growth of siRNA-based therapeutics: Updated clinical studies," *Biochem Pharmacol*, vol. 189, p. 114432, Jul. 2021, doi: 10.1016/j.bcp.2021.114432.

[83] A.-M. Yu and M.-J. Tu, "Deliver the promise: RNAs as a new class of molecular entities for therapy and vaccination," *Pharmacol Ther*, vol. 230, p. 107967, Feb. 2022, doi: 10.1016/j.pharmthera.2021.107967.

[84] D. Adams *et al.*, "Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial," *Amyloid*, vol. 30, no. 1, pp. 18–26, Jan. 2023, doi: 10.1080/13506129.2022.2091985.

[85] P. Espíritu-Ramírez *et al.*, "Gene Therapy for Treatment of Chronic Hyperammonemia in a Rat Model of Hepatic Encephalopathy," *Ann Hepatol*, vol. 17, no. 6, pp. 1026–1034, Nov. 2018, doi: 10.5604/01.3001.0012.7203.

[86] J. Baruteau, N. Brunetti-Pierri, and P. Gissen, "Liver-directed gene therapy for inherited metabolic diseases," *J Inherit Metab Dis*, vol. 47, no. 1, pp. 9–21, Jan. 2024, doi: 10.1002/jimd.12709.

[87] R. Chu, Y. Wang, J. Kong, T. Pan, Y. Yang, and J. He, "Lipid nanoparticles as the drug carrier for targeted therapy of hepatic disorders," *J Mater Chem B*, vol. 12, no. 20, pp. 4759–4784, 2024, doi: 10.1039/D3TB02766J.

[88] A. Gil-Gómez, R. Muñoz-Hernández, F. Martínez, F. Jiménez, and M. Romero-Gómez,

"Hepatic encephalopathy: experimental drugs in development and therapeutic potential," *Expert Opin Investig Drugs*, pp. 1–12, Nov. 2024, doi: 10.1080/13543784.2024.2434053.

[89] G. J. Hoilat, F. K. Suhail, T. Adhami, and S. John, "Evidence-based approach to management of hepatic encephalopathy in adults," *World J Hepatol*, vol. 14, no. 4, pp. 670–681, Apr. 2022, doi: 10.4254/wjh.v14.i4.670.

[90] T. Sun, M. Feng, A. Manyande, H. Xiang, J. Xiong, and Z. He, "Regulation of mild cognitive impairment associated with liver disease by humoral factors derived from the gastrointestinal tract and MRI research progress: a literature review," *Front Neurosci*, vol. 17, Jun. 2023, doi: 10.3389/fnins.2023.1206417.

[91] C. Konkwo, S. Chowdhury, and S. Vilarinho, "Genetics of liver disease in adults," *Hepatol Commun*, vol. 8, no. 4, Apr. 2024, doi: 10.1097/HC9.0000000000000408.

[92] Y. Wang *et al.*, "Identifying Minimal Hepatic Encephalopathy: A New Perspective from Magnetic Resonance Imaging," *Journal of Magnetic Resonance Imaging*, Dec. 2023, doi: 10.1002/jmri.29179.

[93] P. Vidal-Cevallos, N. C. Chávez-Tapia, and M. Uribe, "Current approaches to hepatic encephalopathy," *Ann Hepatol*, vol. 27, no. 6, p. 100757, Nov. 2022, doi: 10.1016/j.aohep.2022.100757.

[94] A. Gil-Gómez *et al.*, "Development and Validation of a Clinical-Genetic Risk Score to Predict Hepatic Encephalopathy in Patients With Liver Cirrhosis," *American Journal of Gastroenterology*, vol. 116, no. 6, pp. 1238–1247, Jun. 2021, doi: 10.14309/ajg.0000000000001164.

[95] L. Boeri, L. Izzo, L. Sardelli, M. Tunesi, D. Albani, and C. Giordano, "Advanced Organ-on-a-Chip Devices to Investigate Liver Multi-Organ Communication: Focus on Gut, Microbiota and Brain," *Bioengineering*, vol. 6, no. 4, p. 91, Sep. 2019, doi: 10.3390/bioengineering6040091.

[96] R. Zhu, L. Liu, G. Zhang, J. Dong, Z. Ren, and Z. Li, "The pathogenesis of gut microbiota in hepatic encephalopathy by the gut–liver–brain axis," *Biosci Rep*, vol. 43, no. 6, Jun. 2023, doi: 10.1042/BSR20222524.

[97] H. M. Wadei, M. L. Mai, N. Ahsan, and T. A. Gonwa, "Hepatorenal Syndrome," *Clinical Journal of the American Society of Nephrology*, vol. 1, no. 5, pp. 1066–1079, Sep. 2006, doi: 10.2215/CJN.01340406.

[98] F. Salerno, A. Gerbes, P. Ginès, F. Wong, and V. Arroyo, "Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis," *Postgrad Med J*, vol. 84, no. 998, pp. 662–670, Dec. 2008, doi: 10.1136/gut.2006.107789.

[99] A. P. Betrosian, "Acute renal dysfunction in liver diseases," *World J Gastroenterol*, vol. 13, no. 42, p. 5552, 2007, doi: 10.3748/wjg.v13.i42.5552.

[100] B. Bonaz, V. Sinniger, and S. Pellissier, "The Vagus Nerve in the Neuro-Immune Axis: Implications in the Pathology of the Gastrointestinal Tract," *Front Immunol*, vol. 8, Nov. 2017, doi: 10.3389/fimmu.2017.01452.

[101] T. D. Schiano, "Treatment Options for Hepatic Encephalopathy," *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, vol. 30, no. 5P2, May 2010, doi: 10.1592/phco.30.pt2.16S.

[102] A.-E. Hopp *et al.*, "P: 10 Hepatic Encephalopathy Is Reversible in the Long-term after Liver Transplantation," *American Journal of Gastroenterology*, vol. 114, no. 1, pp. S4–S4, Sep. 2019, doi: 10.14309/01.ajg.0000582016.05669.1b.

[103] H. Tilg, P. D. Cani, and E. A. Mayer, "Gut microbiome and liver diseases," *Gut*, vol. 65, no. 12, pp. 2035–2044, Dec. 2016, doi: 10.1136/gutjnl-2016-312729.

[104] L. Ridola, "The burden of minimal hepatic encephalopathy: from diagnosis to therapeutic strategies," *Ann Gastroenterol*, 2018, doi: 10.20524/aog.2018.0232.

[105] M. Swaminathan, M. Ellul, and T. Cross, "Hepatic encephalopathy: current challenges and future prospects," *Hepat Med*, vol. Volume 10, pp. 1–11, Mar. 2018, doi: 10.2147/HMER.S118964.

[106] J. M. Schattenberg, N. Chalasani, and N. Alkhouri, "Artificial Intelligence Applications in Hepatology," *Clinical Gastroenterology and Hepatology*, vol. 21, no. 8, pp. 2015–2025, Jul. 2023, doi: 10.1016/j.cgh.2023.04.007.

[107] J. C. Ahn, A. Connell, D. A. Simonetto, C. Hughes, and V. H. Shah, "Application of Artificial Intelligence for the Diagnosis and Treatment of Liver Diseases," *Hepatology*, vol. 73, no. 6, pp. 2546–2563, Jun. 2021, doi: 10.1002/hep.31603.

[108] J. Louissaint and H. E. Vargas, "Picture Perfect: Artificial Intelligence in the Management of

Hepatic Encephalopathy," *American Journal of Gastroenterology*, vol. 119, no. 5, pp. 801–802, May 2024, doi: 10.14309/ajg.0000000000002659.

[109] N. B. Ozturk and E. B. Tapper, "The rise of mobile apps for the management of chronic liver disease," *Hepatol Commun*, vol. 8, no. 4, Apr. 2024, doi: 10.1097/HC9.0000000000000429.

[110] K. Kazankov *et al.*, "Evaluation of CirrhoCare® – a digital health solution for home management of individuals with cirrhosis," *J Hepatol*, vol. 78, no. 1, pp. 123–132, Jan. 2023, doi: 10.1016/j.jhep.2022.08.034.

[111] B. McGuire and M. Al Sibae, "Current trends in the treatment of hepatic encephalopathy," *Ther Clin Risk Manag*, p. 617, Jul. 2009, doi: 10.2147/TCRM.S4443.

[112] A. Mancini, F. Campagna, P. Amodio, and K. M. Tuohy, "Gut : liver : brain axis: the microbial challenge in the hepatic encephalopathy," *Food Funct*, vol. 9, no. 3, pp. 1373–1388, 2018, doi: 10.1039/C7FO01528C.

[113] J. Liu, Y. Xu, and B. Jiang, "Novel Insights Into Pathogenesis and Therapeutic Strategies of Hepatic Encephalopathy, From the Gut Microbiota Perspective," *Front Cell Infect Microbiol*, vol. 11, Feb. 2021, doi: 10.3389/fcimb.2021.586427.

[114] J. Rozga, "Liver support technology – an update," *Xenotransplantation*, vol. 13, no. 5, pp. 380–389, Sep. 2006, doi: 10.1111/j.1399-3089.2006.00323.x.

[115] R. Gaspari *et al.*, "Molecular Adsorbent Recirculating System in Liver Transplantation: Safety and Efficacy," *Transplant Proc*, vol. 38, no. 10, pp. 3544–3551, Dec. 2006, doi: 10.1016/j.transproceed.2006.10.032.

[116] J. Louissaint and H. E. Vargas, "Picture Perfect: Artificial Intelligence in the Management of Hepatic Encephalopathy," *American Journal of Gastroenterology*, vol. 119, no. 5, pp. 801–802, May 2024, doi: 10.14309/ajg.0000000000002659.

[117] H. Wazir *et al.*, "Diagnosis and Treatment of Liver Disease: Current Trends and Future Directions," *Cureus*, Dec. 2023, doi: 10.7759/cureus.49920.