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How the gut-liver axis shapes hepatic encephalopathy: mechanistic and therapeutic perspectives

Arnulfo E. Morales-Galicia[1], Mariana N. Rincón-Sánchez[1], Mariana M. Ramírez-Mejía[1,2], Nahum Méndez-Sánchez[1,3]*

[1]Liver Research Unit, Medica Sur Clinic and Foundation, Mexico City 14050, Mexico
[2]Plan of Combined Studies in Medicine (PECEM-MD/PhD), Faculty of Medicine, National Autonomous University of Mexico, Mexico City 04360, Mexico
[3]Faculty of Medicine, National Autonomous University of Mexico, Mexico City 04360, Mexico

***Correspondence:** Nahum Méndez-Sánchez, Liver Research Unit, Medica Sur Clinic and Foundation, Puente de Piedra 150, Col. Toriello Guerra, Mexico City 14050, Mexico. nmendez@medicasur.org.mx
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Abstract

Hepatic encephalopathy (HE) is a debilitating neuropsychiatric complication of liver dysfunction that spans a continuum from subtle cognitive impairment to deep coma. While historically attributed to hyperammonemia, current insights reveal a multifactorial pathogenesis involving systemic inflammation, astrocyte dysfunction, blood-brain barrier (BBB) disruption, and altered neurotransmission. Central to this complex network is the gut-liver axis—a bidirectional system that links the gut microbiota, intestinal barrier integrity, bile acid metabolism, and hepatic immune responses. In cirrhosis, dysbiosis and increased intestinal permeability facilitate the translocation of microbial products—such as endotoxins and ammonia—that trigger hepatic and systemic immune activation, amplifying neurotoxicity through the gut-liver-brain axis. Experimental and clinical evidence has shown that ammonia and bilirubin synergistically promote neuroinflammation, mitochondrial dysfunction, and glial activation. Multiomics data further support the role of the microbiota as an active modulator of liver-brain homeostasis. Microbiota-targeted therapies—including rifaximin, probiotics, synbiotics, and fecal microbiota transplantation (FMT)—demonstrate efficacy in reducing HE recurrence, improving cognition, and restoring microbial balance. Novel receptor-based strategies targeting the farnesoid X receptor (FXR), Takeda G-protein-coupled receptor 5 (TGR5), and aryl hydrocarbon receptor (AhR) show promise for modulating bile acid pathways and mitigating neuroinflammation. Emerging approaches also focus on dietary interventions, the reinforcement of epithelial barrier function, and artificial intelligence (AI)-driven tools for personalized monitoring. Despite these advances, challenges persist regarding FMT standardization, long-term safety, and the integration of digital diagnostics into routine care.

Keywords

hepatic encephalopathy, microbiome, dysbiosis, gut-liver axis, chronic liver disease

Introduction

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that arises as a consequence of acute or chronic liver dysfunction. It is characterized by a broad spectrum of clinical manifestations, ranging from subtle cognitive impairments to deep coma [1]. Its presence signifies advanced hepatic impairment and represents one of the most serious complications in patients with cirrhosis; it is associated with a marked decline in quality of life, increased risk of hospitalization, and high mortality [2, 3]. Clinically, HE has traditionally been classified into minimal HE (MHE) and overt forms, with increasing recognition of the impact of recurrent episodes and progression to chronicity. In recent years, the pathophysiological understanding of HE has expanded beyond hyperammonemia to include mechanisms such as neuroinflammation, blood-brain barrier (BBB) dysfunction, and altered neurotransmission—an interplay reflecting the dynamic communication between the central nervous system (CNS), hepatic metabolism, and the intestinal environment [1, 4]. This dynamic interaction is strongly influenced by intestinal factors such as the gut microbiota composition, the production of short-chain fatty acids (SCFAs), the modulation of bile acid metabolism, and the maintenance of intestinal barrier integrity, which together determine the levels of microbial metabolites, endotoxins, and ammonia that reach the liver and systemic circulation, ultimately affecting neural homeostasis and inflammatory pathways.

Within this framework, the gut-liver axis has gained prominence as a bidirectional communication network that links the gastrointestinal tract, intestinal microbiota, and liver via immunological, humoral, and neural pathways [5]. Under physiological conditions, this axis maintains immunometabolic homeostasis through tight junction (TJ) integrity, balanced microbial diversity, and regulated mucosal immunity; however, in the context of chronic liver disease (CLD), gut dysbiosis, increased intestinal permeability and bacterial translocation lead to the systemic release of microbiota-derived products such as endotoxins, ammonia, and nitrogenous metabolites, further exacerbating hepatic inflammation and neurological dysfunction [6, 7]. Factors such as small intestinal bacterial overgrowth (SIBO), alterations in the production of urea-splitting bacterial enzymes, and changes in intestinal pH also contribute to enhanced ammonia generation and absorption, aggravating hyperammonemia and the neuropsychiatric burden of HE. Notably, SIBO—specifically hydrogen production—has been significantly associated with HE, as it promotes excessive intestinal ammonia production and is correlated with impaired liver function, thereby playing a direct and independent role in the development and severity of this condition [8].

Multiple studies have demonstrated that gut microbiota-targeted interventions, such as probiotics, prebiotics, nonabsorbable antibiotics, and dietary modifications, have shown clinically meaningful benefits, including reductions in the frequency of HE episodes and improvements in cognitive function [8, 9]. This has paved the way for targeted and personalized therapeutic strategies that may transform the clinical management of this severe hepatic complication [10].

Hepatic encephalopathy: a general overview

The most widely accepted classification differentiates between MHE and overt HE, which are further subdivided on the basis of severity (grades I to IV) and clinical pattern (episodic, recurrent, or persistent) [11–13]. MHE lacks evident clinical signs and is diagnosed through neuropsychological testing, such as the Psychometric Hepatic Encephalopathy Score and critical flicker frequency [14, 15]. In contrast, overt HE presents with alterations in consciousness, behavior, and neuromotor function, typically graded using tools such as the West Haven criteria (Table 1) [12, 16].

Epidemiological data reveal that MHE affects approximately 30–40% of patients with cirrhosis, while recurrent or persistent forms develop in up to 25% of cases, significantly increasing mortality and health care utilization [18–20]. Hospitalizations related to HE have risen by nearly 50% over the past decade, with

Table 1. West Haven criteria for the clinical grading of HE [17].

Grade	Clinical findings
Grade 1	Unawareness, euphoria or anxiety, shortened attention span, and impairment of calculation ability.
Grade 2	Lethargy or apathy, minimal disorientation for time or place, subtle personality change, and inappropriate behavior.
Grade 3	Somnolence to stupor, responsiveness to stimuli, confusion, gross disorientation, and bizarre behavior.
Grade 4	Coma.

a higher incidence observed in older adults and men, likely because of the higher prevalences of cirrhosis and alcohol-associated liver disease in these groups [21]. Even a single HE episode results in a 15–20% one-year mortality risk, which increases with recurrence and is closely associated with progressive neurocognitive decline [19]. These trends underscore the necessity for comprehensive and targeted therapeutic strategies. Beyond recurrence reduction, rifaximin therapy has been associated with significant improvements in health-related quality of life (HRQL), as evidenced by enhanced scores across all domains of the CLD Questionnaire (CLDQ), including fatigue, emotional function, and general well-being [22, 23]. Although MHE is often underrecognized because of the absence of overt clinical signs, it still compromises daily functioning, such as attention, driving, and work performance, especially in younger individuals and women, where underdiagnosis is common [16]. These findings underscore the importance of early detection and classification, not only for clinical prognostication but also for the implementation of strategies that prevent disease progression.

In clinical practice, the diagnosis of HE requires the exclusion of structural, metabolic, toxic, or infectious neurological causes [12]. Laboratory workup includes liver function tests, bilirubin levels, INR, renal function, electrolytes, and ammonia, although the latter does not always correlate with severity [24, 25]. Neuroimaging and electroencephalography are used when clinical suspicion suggests alternative diagnoses [26, 27].

Classic pathophysiology of hepatic encephalopathy

The classic model of HE focuses on ammonia accumulation, which interacts with systemic inflammation, astrocytic dysfunction, BBB impairment, and glial-mediated neuroinflammation [28, 29]. Ammonia is a byproduct of the effects of gut bacterial urease activity on urea [28]. Under normal conditions, the liver detoxifies ammonia via the urea cycle, but in liver failure or portosystemic shunting, this pathway is impaired [30], allowing ammonia to cross the BBB as NH_3 or NH_4^+ via specific transporters [31]. In the brain, astrocytes convert ammonia to glutamine via the activity of glutamine synthetase. Excess glutamine causes astrocytic swelling, cytotoxic edema, and dysfunction [32]. These astrocytes exhibit Alzheimer type II morphology, with nuclear enlargement and cytoplasmic vacuolization [28, 33]. Mitochondrial glutamine overload exacerbates oxidative stress and impairs energy production [30]. Ammonia enhances GABAergic tone through neurosteroids that modulate GABA-A receptors, causing CNS depression [2]. It also suppresses glutamatergic signaling by interfering with glutamate uptake and energy metabolism [30]. Immunologically, ammonia activates microglia, which release tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), IL-6, and reactive oxygen species (ROS), further damaging the BBB and promoting neuroinflammation [34].

Recent research has highlighted bilirubin as a potential contributor to HE beyond its role as a marker of liver dysfunction [35]. Unconjugated bilirubin crosses the BBB, disrupts neuronal and mitochondrial membranes, and induces oxidative stress by impairing antioxidant defenses [29, 31, 36]. It inhibits mitochondrial complexes I and IV, leading to energy failure that worsens ammonia-induced glial toxicity, both toxins activate microglia and cytokine release, amplifying inflammation and neuronal injury (Figure 1) [31, 34]. Moreover, bilirubin inhibits ornithine transcarbamylase, impairing ammonia detoxification [28], whereas ammonia exacerbates cholestasis and alters transporter expression, establishing a vicious cycle [27]. While these findings provide a useful framework for understanding the multifactorial pathogenesis of HE, the proposed mechanisms of bilirubin still need to be confirmed by well-designed translational and clinical studies.

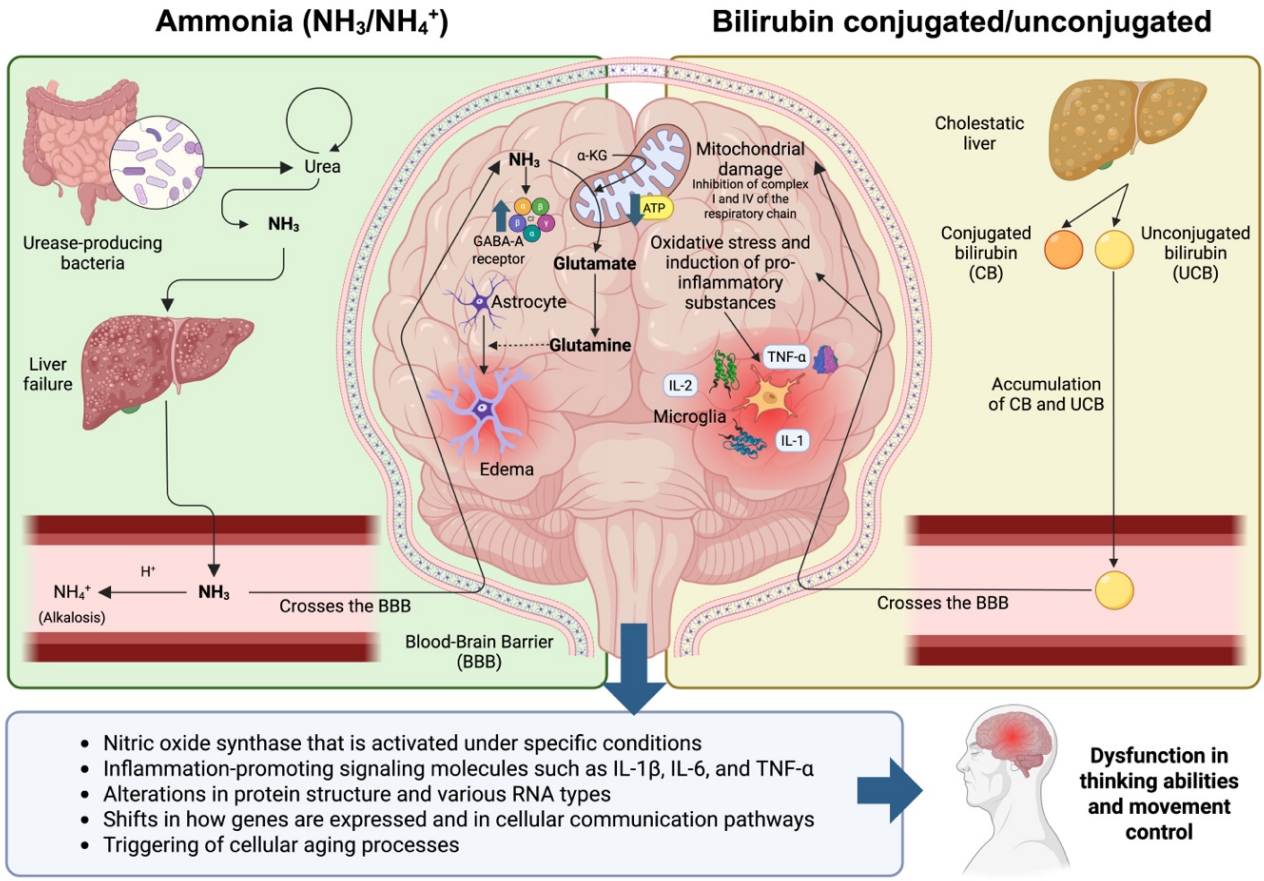

Figure 1. Canonical neurotoxic mechanisms of ammonia (NH_3/NH_4^+) and bilirubin (conjugated and unconjugated) in hepatic encephalopathy (HE). Overview of the principal pathophysiological mechanisms by which hyperammonemia and hyperbilirubinemia contribute to neurotoxicity in hepatic failure, leading to HE. On the left, the ammonia generated in the gastrointestinal tract by urease-producing bacteria escapes hepatic detoxification because of liver failure, leading to elevated systemic concentrations. In its nonionized form (NH_3), ammonia readily traverses the blood-brain barrier (BBB), a process facilitated by systemic alkalosis. Once in the central nervous system (CNS), NH_3 is predominantly taken up by astrocytes, where it is enzymatically converted to glutamine. This accumulation of intracellular glutamine induces osmotic dysregulation and astrocytic swelling, resulting in cytotoxic cerebral edema. Concurrently, ammonia impairs mitochondrial oxidative phosphorylation by inhibiting complexes I and IV of the electron transport chain, thereby promoting mitochondrial dysfunction, oxidative stress, and the generation of reactive oxygen species (ROS). Simultaneously, the right panel illustrates the impact of cholestatic injury and hepatic insufficiency on systemic bilirubin levels. Both conjugated bilirubin (CB) and unconjugated bilirubin (UCB) accumulate in the circulation and can permeate the BBB, particularly when its integrity is compromised. Once within the CNS parenchyma, bilirubin induces neurotoxicity through several mechanisms: it disrupts mitochondrial bioenergetics, generates oxidative stress, and activates microglia. This microglial activation leads to the release of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, which further amplify neuroinflammatory cascades. These molecular events trigger alterations in gene expression, posttranscriptional RNA modifications, and protein structure, collectively promoting neuronal dysfunction and cellular senescence. Overall, the synergistic effects of astrocytic edema, mitochondrial impairment, redox imbalance, and neuroinflammation culminate in the disruption of neurotransmission and neuronal connectivity. These processes underlie the cognitive impairment and motor dysfunction that characterize the clinical spectrum of HE, connecting systemic liver failure with progressive neurological decline. Created in BioRender. Ramírez, M. (2025) https://BioRender.com/d4312nk.

The gut-liver-brain axis

Structure and function

The gut-liver axis comprises a complex bidirectional communication network between the gastrointestinal tract, its microbiota, and the liver. This interaction is primarily mediated by the portal vein, bile acids, immune signaling, and microbial metabolites [5, 6]. At the intestinal interface, the epithelial barrier and gut microbiota jointly regulate the entry of luminal contents into the circulation. The barrier consists of mucus, a monolayer of epithelial cells bound by TJs, and mucosal immune cells, which together limit the translocation of microbial products [37]. The gut microbiota complements this defense by producing metabolites, such as SCFAs, that shape the host's metabolism and immune responses while maintaining epithelial integrity [38–40]. Beyond bacteria, emerging evidence highlights the importance of the virome and mycobiome in shaping the gut-liver axis. The intestinal virome is mainly composed of bacteriophages, with a smaller fraction of eukaryotic viruses, including pathogenic and non-pathogenic species. Phages

regulate bacterial dynamics, influence gene expression, and shape metabolic functions, thereby indirectly affecting the gut-liver axis [41]. Beyond bacteria and viruses, the gut mycobiome represents another important, yet less explored, component of the gut ecosystem. Although fungi constitute less than 1% of the gut microbiota, they play a disproportionate role in shaping host immunity and maintaining microbial balance [42]. Commensal species, such as *Saccharomyces* and *Candida*, interact with bacteria and immune cells through competition for nutrients, production of metabolites, and modulation of immune and epithelial responses [43]. These interactions contribute to the stability of the intestinal barrier and influence systemic immune regulation. Although the mycobiome is more variable and less stable than the bacterial microbiota, it remains an integral partner in maintaining intestinal homeostasis, and its alteration has been linked to several chronic inflammatory diseases [42].

A key element of the gut-liver axis is the portal vein, which supplies approximately 70% of the liver's blood flow and transports nutrients and metabolites from the intestine. Under normal conditions, the intestinal barrier prevents significant translocation of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). In contrast, the liver continuously monitors low-level microbial and host-derived signals, reflecting its role as an organ of immune surveillance that preserves systemic homeostasis [37, 44]. This sensing is mediated by dendritic cells, lymphocytes, and pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and Nod-like receptors (NLRs), expressed in Kupffer cells and liver sinusoidal endothelial cells (LSECs), enabling rapid but balanced responses that maintain immune tolerance [6, 44].

Bile acids represent another key signaling mechanism within the axis. Produced in the liver and secreted into the intestine, they act on receptors such as farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5) to regulate lipid metabolism, intestinal motility, and immune function [5, 45]. The gut microbiota further modifies bile acids, shaping enterohepatic circulation and reinforcing the dynamic reciprocity of the system [46].

Alterations of the gut-liver axis in liver disease

The main alteration of the gut-liver axis in CLD is dysbiosis, defined as an imbalance in the intestinal microbial ecosystem, characterized by a decrease in beneficial bacteria, an increase in potentially harmful microbes, and a loss of overall microbial diversity [39, 47]. Distinct dysbiotic patterns have been described in alcohol-related liver disease (ALD), metabolic dysfunction-associated steatotic liver disease (MASLD), cirrhosis, and viral hepatitis [48, 49]. In cirrhosis, for example, harmful bacterial families such as Proteobacteria (Alcaligeneceae and Pasteurellaceae) and Enterobacteriaceae expand, while beneficial taxa such as Firmicutes (Ruminococcaceae and Lachnospiraceae), *Lactobacillus*, and *Bifidobacterium* decrease.

A key consequence of dysbiosis is the disruption of intestinal barrier integrity, commonly referred to as 'leaky gut'. Under normal conditions, the mucosal barrier restricts the passage of luminal antigens into circulation. In CLD, dysbiosis reduces the expression of TJ proteins (occludin, claudins) and adherens junction proteins (E-cadherin), while also diminishing mucin production [50, 51]. This weakens the paracellular seal of the intestinal epithelium, enabling microbial products such as endotoxins, ammonia, and even whole microorganisms to translocate into the portal circulation [52, 53]. Furthermore, reduced IgA secretion and impaired mucosal immunity exacerbate this dysfunction [37, 46]. In immunosuppressed individuals—such as those with human immunodeficiency virus (HIV) infection—fungal and viral elements also contribute to this intestinal barrier disruption and systemic immune imbalance [44, 54].

Beyond the epithelium, the gut-vascular barrier (GVB) provides an additional line of defense. Composed of specialized endothelial cells with tight and adherens junctions, it normally limits the passage of bacteria and immunogenic molecules. In cirrhosis, however, inflammatory signals and dysbiosis disrupt vascular endothelial-cadherin and junctional adhesion molecules, mirroring epithelial breakdown and facilitating bacterial translocation [55, 56]. Portal hypertension further aggravates this condition by inducing intestinal congestion and mucosal ischemia, which impair regeneration and weaken local defenses [57].

Metabolic consequences of dysbiosis amplify these effects. Reduced SCFAs production compromises mucosal immunity [47, 58], while urease-positive bacteria increase ammonia generation, a key driver of HE [59]. Altered bile acid profiles in CLD reshape the microbiota, reinforcing dysbiosis [37, 60], and microbial metabolites such as trimethylamine (TMA), indoxyl sulfate, and phenylacetic acid exert direct hepatotoxic effects through oxidative stress, aggravating liver injury [45, 61].

Disease-specific contexts highlight these alterations. In hepatitis C virus (HCV) infection, dysbiosis often persists even after antiviral therapy, sustaining proinflammatory signaling [39, 40, 48, 49]. In MASLD, microbial shifts exacerbate insulin resistance and promote hepatic steatosis [38, 45]. Dysbiosis also impairs hepatic regeneration by disrupting signals that regulate hepatocyte proliferation, endothelial function, and macrophage polarization, identifying potential therapeutic targets for fibrosis and inflammation [37, 38, 44, 51].

From the gut-liver-brain axis to hepatic encephalopathy

HE arises from dysregulated communication within the gut-liver-brain axis [62, 63]. Recent clinical data have reinforced the central role of this axis in HE pathophysiology. In particular, reduced gut microbial diversity and specific taxonomic alterations, such as increased *Veillonella parvula* and decreased *Bacteroidetes*, have been associated with HE severity, recurrence, and mortality. These microbial signatures may serve as prognostic biomarkers, further validating the axis as a therapeutic and diagnostic target [5, 64, 65].

In cirrhosis, autochthonous microbes such as Lachnospiraceae and Ruminococcaceae decrease, and the abundance of urease-positive and neurotoxin-producing bacteria increases [9, 66]. These microbial shifts lead to increased production of ammonia and other neuroactive compounds, including indoles and SCFAs [67, 68]. In support of these findings, Mendelian randomization analyses have revealed that microbial taxa such as *Bifidobacterium* are genetically protective against HE, suggesting potential prophylactic avenues for microbiome-based interventions. Similarly, enrichment of *Prevotella* is associated with favorable hepatic outcomes in patients with cirrhosis [69].

Besides bacterial dysbiosis, alterations in the gut virome have also been linked to HE and its complications. Recent evidence highlights its clinical relevance, with specific changes in bacteriophages observed in cognitive dysfunction and MHE. In a cross-sectional and longitudinal study, Jinato et al. [70] demonstrated that phages related to *Streptococcus*, *Faecalibacterium*, and *Lactobacillus* were enriched in patients with cognitive impairment and cirrhosis, and that these alterations persisted with changes in MHE status over time. Similarly, Bajaj et al. [71] reported that the interaction networks between phages and bacteria were significantly altered in cirrhosis compared to healthy controls, with a collapse of the network around urease-producing *Streptococcus* species in patients with HE. Notably, rifaximin treatment did not significantly alter phage diversity, but it did modify these links between phages and bacteria, reducing associations with ammonia-producing taxa.

In addition to bacterial and viral components, it is increasingly recognized that the gut microbiome contributes to HE. In a recent multi-omic study, Li et al. [72] characterized the gut microbiota, microbiota, and metabolites in decompensated cirrhosis and found that pathogenic fungi, such as *Saccharomyces*, were positively correlated with disease severity scores and markers of liver dysfunction, while genera such as *Aspergillus*, *Wallemia*, and *Cladosporium* showed negative correlations with these clinical indicators. These data suggest that fungal imbalance parallels bacterial dysbiosis in cirrhosis and may exacerbate the metabolic and inflammatory alterations that contribute to HE.

As microbial and viral translocation increases, PAMPs reach the liver and activate Kupffer and hepatic stellate cells, maintaining a cycle of inflammation [73, 74]. This systemic inflammation increases BBB permeability, allowing cytokines and endotoxins to infiltrate the CNS and activate microglia and astrocytes, thereby disrupting neurotransmission [75, 76]. Chronic neuroinflammation alters synaptic signaling, leading to excitotoxicity and edema of the brain [77–79]. Additionally, gut-derived metabolites such as tryptophan catabolites and histamine modulate microglial responses, reinforcing the role of the microbiota in immune and neuroimmune regulation (Figure 2) [9, 66].

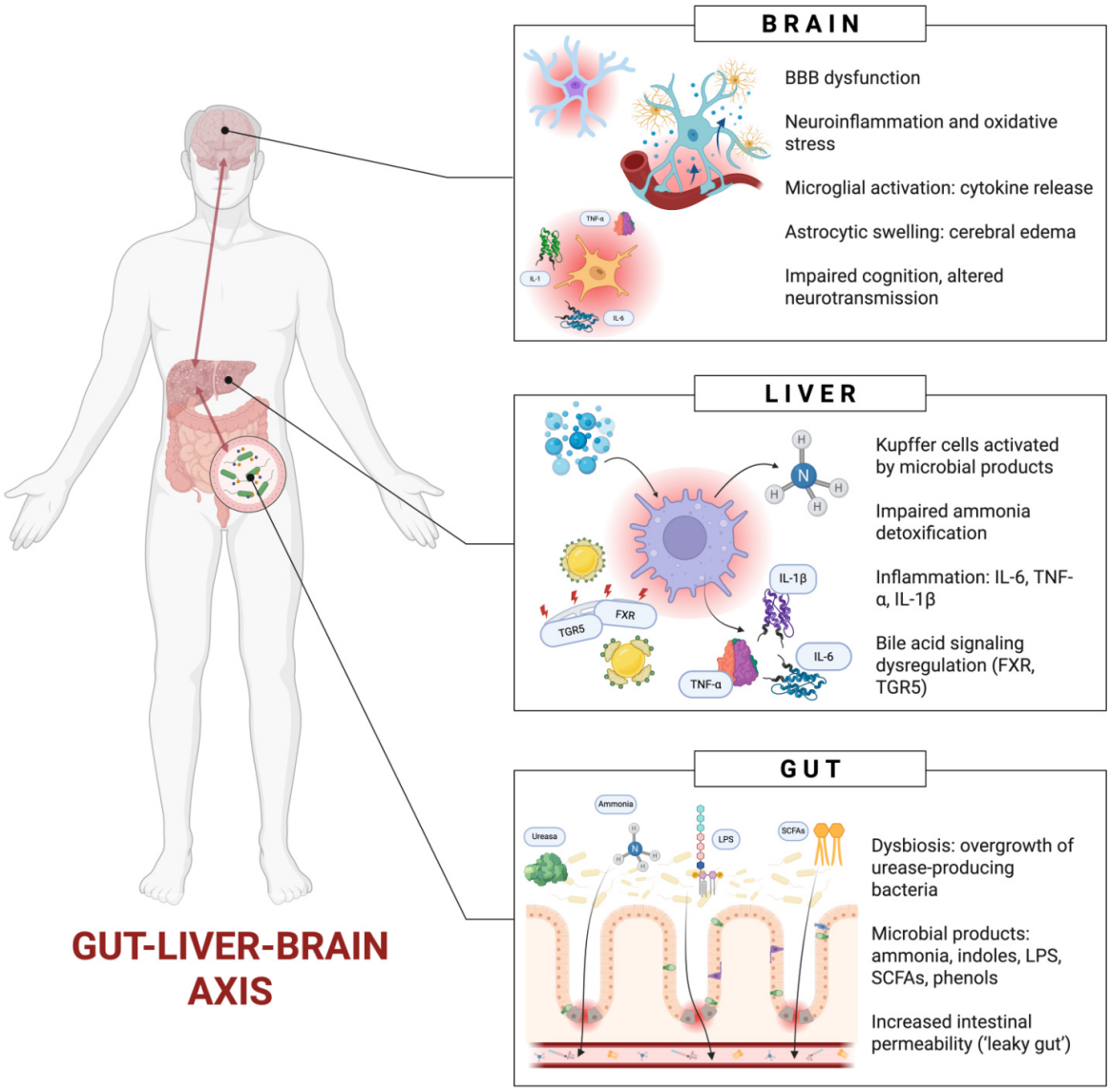

Figure 2. Pathophysiological cascade from intestinal dysbiosis to neuroinflammation through the gut-liver-brain axis in hepatic encephalopathy (HE). In cirrhotic patients, profound gut dysbiosis is characterized by an overgrowth of urease-producing bacteria and a shift in microbial composition, leading to excessive production of neurotoxic metabolites, including ammonia, lipopolysaccharide (LPS), short-chain fatty acids (SCFAs), indoles, and phenolic compounds. This dysbiotic environment compromises intestinal epithelial integrity by disrupting tight junction proteins, thereby increasing intestinal permeability—a phenomenon commonly referred to as 'leaky gut'. The translocation of microbe-derived products into the portal circulation elicits hepatic immune responses, notably via the activation of Kupffer cells and hepatic stellate cells, resulting in the release of proinflammatory cytokines such as IL-6, TNF-α, and IL-1β. Concurrently, the impaired hepatic clearance of ammonia, secondary to hepatocellular dysfunction and portosystemic shunting, exacerbates systemic hyperammonemia. Dysregulation of bile acid homeostasis through altered farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5) signaling further contributes to hepatic and systemic inflammation. Circulating neurotoxins and inflammatory mediators permeate the blood-brain barrier (BBB), whose integrity is compromised in advanced liver disease. Within the central nervous system (CNS), this milieu promotes microglial activation, oxidative stress, and astrocytic swelling, leading to cerebral edema and disturbances in neurotransmitter synthesis and synaptic transmission. These neurotoxic mechanisms culminate in the cognitive, motor, and behavioral manifestations characteristic of HE. Created in BioRender. Ramírez, M. (2025) https://BioRender.com/eatk8bi.

A central mechanism is ammonia-induced astrocytic glutamine accumulation, which increases intracellular osmotic pressure, causing astrocyte swelling and cytotoxic brain edema. This edema compromises cerebral perfusion, elevates intracranial pressure, and exacerbates neurological deterioration [10]. Furthermore, bile acid signaling through FXR and TGR5 is disrupted [66, 73], contributing to immune dysregulation and sustaining a proinflammatory CNS environment in which activated glial cells release neurotoxic cytokines and ROS. Dysregulated metabolism of tryptophan, altered SCFA profiles, and reduced serotonin availability further impair cognition and mood [9, 76]; low serotonin levels disturb neural circuits associated with arousal and emotional regulation, intensifying cognitive and affective HE symptoms. Intestinal microbes significantly influence tryptophan catabolism. *Escherichia coli* converts tryptophan into

indole, which can subsequently be oxidized to oxindole, a metabolite linked to neurological deterioration in liver diseases [80]. *Bifidobacterium* and *Lactobacillus* produce indole-3-propionate and indole-3-lactate, while *Clostridium* and *Bacteroides spp*. produce skatole and indole-3-aldehyde [81]. In parallel, systemic inflammation activates the indoleamine-2,3-dioxygenase (IDO)/kynurenine pathway, increasing metabolites such as quinolinic acid and 3-hydroxykynurenine while depleting serotonin. In experimental models, inhibition of IDO reversed memory decline and anxiety-like behaviors, highlighting its pathogenic role and therapeutic potential in HE [82]. Importantly, clinical studies have confirmed that this pathway is already upregulated in patients with covert HE, where increased IDO activity and elevated quinolinic acid levels correlate with systemic inflammation [83].

These processes are compounded by mitochondrial dysfunction, oxidative stress, and energy failure in neurons resulting from gut-liver-brain metabolic alterations [74, 84, 85], ultimately impairing ion transport, neurotransmitter vesicle cycling, and synaptic integrity. Finally, multiomics studies have shown that microbial profiles correlate with host gene expression patterns related to inflammation, synaptic function, and tissue repair (Table 2) [73, 75, 86], underscoring the central role of the microbiota in the pathogenesis of HE [66]. Taken together, these interconnected mechanisms, including dysbiosis, microbial and viral translocation, systemic inflammation, BBB dysfunction, ammonia accumulation, astrocytic swelling, glial activation, neurotransmitter imbalance, oxidative stress, and mitochondrial dysfunction, converge to drive the progressive cerebral dysfunction and edema that characterize HE.

Table 2. Key pathophysiological mechanisms linking gut-liver axis alterations to HE.

Component	Mechanism	Impact on HE pathogenesis
Dysbiotic microbiota	Overgrowth of urease-producing and endotoxin-generating bacteria; decreased SCFA-producing commensals	Increases ammonia and endotoxin production; impairs gut homeostasis and neurochemical balance
Increased gut permeability	Disruption of TJ proteins and mucosal immune dysfunction	Enables translocation of LPS and PAMPs into portal circulation, activating hepatic immune responses
Portal hypertension	Splanchnic vasodilation, mucosal hypoxia, and epithelial injury	Aggravates intestinal barrier breakdown and promotes systemic inflammation
Kupffer cell activation	Recognition of PAMPs via TLRs/NLRs triggers cytokine release	Promotes hepatic inflammation and systemic immune activation
Ammonia accumulation	Impaired hepatic detoxification; increased intestinal production and reduced renal clearance	Causes astrocytic swelling, glutamine accumulation, and cerebral edema
Microglial and astrocytic activation	Central nervous system entry of cytokines and microbial products activates neuroinflammatory cascades and oxidative stress	Contributes to synaptic dysfunction, neurotransmitter imbalance, and brain edema
Tryptophan catabolism alterations	Microbiota-driven modulation of kynurenine and serotonin pathways	Affects cognition, mood regulation, and microglial phenotype
Mitochondrial dysfunction	Disruption of oxidative phosphorylation and reactive oxygen species generation by ammonia, bilirubin, and microbial metabolites	Reduces neuronal energy availability and enhances neuronal vulnerability

HE: hepatic encephalopathy; LPS: lipopolysaccharide; NLRs: Nod-like receptors; PAMPs: pathogen-associated molecular patterns; SCFA: short-chain fatty acid; TJ: tight junction; TLRs: Toll-like receptors.

In this context, probiotic interventions have shown promising results. A double-blind randomized trial demonstrated that multistrain probiotics improved cognitive function, increased the serum glutamine/glutamate ratio, and reduced the fall risk in cirrhotic patients. These effects were supported by the results of metabolomic analyses indicating enhanced ammonia clearance and reduced systemic inflammation [87, 88].

Finally, metabolic comorbidities, such as diabetes, aggravate the pathophysiology of HE by acting at multiple levels of the gut-liver-brain axis. Autonomic dysfunction and delayed intestinal transit promote bacterial overgrowth in the small intestine and increased ammonia production, while insulin resistance accelerates muscle protein breakdown and increases the systemic ammonia load. At the brain level,

impaired insulin signaling disrupts synaptic plasticity and neurotransmitter regulation, exacerbating neurocognitive decline. Diabetes also represents a proinflammatory state, with cytokines such as IL-6 and TNF-α amplifying systemic inflammation and BBB dysfunction [89].

Emerging therapeutic strategies

Emerging strategies increasingly focus on leveraging the gut-liver axis to restore microbial balance, reinforce the epithelial barrier, and modulate host signaling. Among these, microbiota-based therapies are pivotal. Fecal microbiota transplantation (FMT) has shown promise in the THEMATIC trial, where cirrhotic patients receiving donor microbiota had improved psychometric scores, reduced ammonia levels, and exhibited durable shifts toward eubiotic communities enriched in *Bifidobacterium* and Lachnospiraceae [90]. These clinical findings are supported by mechanistic evidence indicating that FMT enhances secondary bile acid production and restores bile acid-microbiota homeostasis, thereby modulating FXR and TGR5 signaling, which are critical for maintaining intestinal and neurological function in patients with cirrhosis [91, 92]. However, variability in donor selection, risk of pathogen transmission, and uncertain long-term engraftment remain significant limitations [93, 94]. Importantly, despite encouraging evidence, FMT is not yet considered a standard therapeutic option in current guidelines, such as those from EASL 2022 [12].

Beyond FMT, probiotic, prebiotic, and synbiotic strategies modulate microbiota composition and function. For example, targeted strains such as *Escherichia coli Nissle 1917* have improved colonization resistance, reduced ammonia levels, and enhanced cognition in MHE without adverse events [95]. This strain exerts its effects by outcompeting urease-producing pathogens, increasing epithelial nitrate respiration, and promoting local anti-inflammatory cytokine expression, and its safety profile has been validated in multiple controlled settings [93, 94]. In a recent comparative study, Wang et al. [96] demonstrated that probiotics, rifaximin, and lactulose were safe and effective for MHE, with recovery rates of 58.8%, 45.5%, and 57.1%, respectively, and that all treatments partially restored gut microbial composition by enriching taxa associated with anti-inflammatory and cognitive benefits. Here, it is important to clarify that TJ proteins maintain epithelial barrier integrity; when their expression is reduced by dysbiosis, paracellular permeability increases, facilitating the translocation of harmful metabolites—a key target of these therapies. Rifaximin suppressed pathogenic overgrowth and indirectly modulated bile acid metabolism and FXR/TGR5 activation by altering the intestinal microbiota composition, whereas lactulose enhanced ammonia excretion through luminal acidification and nitrogen trapping [97, 98]. Mechanistically, *Bifidobacterium* species metabolize lactulose into acetate and lactate, feeding butyrate-producing bacteria and strengthening the mucosa [99]. These fermentation products increase regulatory T-cell activity, inhibit NF-κB-mediated inflammation, and promote epithelial restitution, as supported by decompensated cirrhosis models and meta-analyses demonstrating reduced hospitalization and mortality [93, 100, 101]. Despite promising advances with microbiota-based interventions such as probiotics and FMT, their clinical application remains limited by variability in patient response, lack of standardized protocols, and uncertainty about their long-term stability. Further large-scale, long-term, comparative, and cost-effectiveness studies are needed before they can be fully integrated into clinical practice.

Dietary interventions complement microbiota-based approaches. Protein-adjusted, vegetarian-based regimens supplemented with prebiotics and branched-chain amino acids increase SCFA production, upregulate the expression of barrier markers such as TJ proteins, and lower the risk of HE recurrence [102]. SCFAs, particularly butyrate, stimulate mucosal immunity, regulate TJ assembly via histone deacetylase inhibition, and serve as energy sources for colonocytes, collectively improving barrier function and reducing systemic endotoxemia [93, 101].

In addition to microbiota modulation, barrier-targeted strategies directly aim to strengthen the epithelial barrier and limit microbial translocation. Nutraceuticals such as epigallocatechin-3-gallate (EGCG) upregulate mucin genes, restore TJ proteins, and reduce endotoxemia in HE models, with histological and behavioral improvements [103]. EGCG also activates the Nrf2 pathway to limit oxidative stress and neuroinflammation, although poor oral bioavailability remains a challenge [93, 98]. Additionally,

a combination of *Lactobacillus rhamnosus*, glutamine, and zinc has been shown to increase enterocyte turnover, restore innate immune defense, and reduce lipopolysaccharide (LPS) translocation and the expression of proinflammatory cytokines such as IL-6 and TNF-α [94, 100, 101]. Another group of agents with growing relevance in cirrhosis is alpha-glucosidase inhibitors (AGIs) used in patients with diabetic cirrhosis to protect barrier function by slowing carbohydrate fermentation, thus lowering luminal stress and permeability while improving postprandial glycemic control [104]. Experimental studies have shown that miglitol, an AGI, can alter the intestinal microbial composition and the production of SCFAs, leading to increased butyrate levels and upregulation of hepatic CYP7A1, the rate-limiting enzyme in bile acid synthesis [105]. Its translational potential is supported by clinical data. In a nationwide cohort study of patients with diabetes and compensated cirrhosis, prolonged use of AGI was associated with a significantly lower risk of decompensation, hepatocellular carcinoma, HE, and mortality compared to non-users [106].

Receptor-based interventions represent another frontier. FXR agonists modulate bile acid synthesis and inflammation while supporting barrier integrity by upregulating the expression of TJ proteins such as claudin-1 and promoting SHP-mediated suppression of CYP7A1 [107–109]. FXR activation also increases urea cycle enzyme expression, enhancing hepatic ammonia metabolism, although overactivation can cause pruritus and dyslipidemia [92]. Intestinal FXR signaling induces FGF19, which not only suppresses hepatic bile acid synthesis but also improves hepatic glucose and nitrogen metabolism, contributing to reduced hyperammonemia [97, 110, 111]. TGR5 agonists complement FXR modulation by attenuating neuroinflammation through caspase-8/NLRP3 inhibition in microglia and increasing intracellular cAMP levels, which suppresses NF-κB signaling [112–114]. However, their limited CNS penetration is being addressed by newer synthetic analogs [93, 98]. Similarly, aryl hydrocarbon receptor (AhR) activation by microbial tryptophan metabolites such as indole-3-aldehyde upregulates IL-22 levels, enhances mucosal tolerance, strengthens the barrier, and modulates astrocytic and microglial responses, although prolonged AhR stimulation may affect CYP1A1 expression and carry oncogenic risks [93, 115, 116]. In parallel, bacterial-derived benzodiazepine-like substances have emerged as additional neurotoxins implicated in HE. These compounds can cross the BBB, modulate GABA-A receptors, and induce astrocytic swelling, thereby amplifying CNS depression and neurotransmitter imbalance. Experimental evidence supports their contribution to the neurobehavioral phenotype of HE, particularly in synergy with ammonia [47].

Multimodal approaches are gaining traction as the results show synergy when combining these strategies. In post-transjugular intrahepatic portosystemic shunt (TIPS) patients, triple therapy with rifaximin, lactulose, and FXR agonists reduced the HE incidence and readmissions, highlighting the value of simultaneously targeting microbial composition, barrier integrity, and bile acid signaling [98, 117, 118]. Accordingly, current guidelines increasingly recommend tailored protocols integrating microbiota diagnostics, nutraceuticals, and receptor modulators [34]. Personalized strategies enable patient stratification by microbial signatures, bile acid profiles, and ammonia metabolism rates, optimizing treatment [94, 119]. The role of the TIPS has also been reevaluated. While effective for portal hypertension, it may increase the risk of HE because of the shunting of gut toxins. New TIPS technologies aim to balance hemodynamic benefits with microbiota preservation [118]. Observational studies report variations in HE post-TIPS based on pressure changes and biomarkers of endotoxemia [120].

From a clinical perspective, comparative efficacy and cost-effectiveness are important in guiding therapeutic adoption. A comprehensive network meta-analysis by Dhiman et al. [121], which included 25 randomized trials with over 1,500 participants, confirmed that rifaximin and lactulose are the most effective agents for reversing MHE, while lactulose and *L*-ornithine *L*-aspartate were superior for preventing overt HE. Probiotics showed benefits but scored lower in efficacy compared to these agents, although they remain attractive in many settings due to their lower cost and accessibility.

Finally, emerging perspectives include designer probiotics engineered to express glutaminase inhibitors or SCFA-producing enzymes, with the goal of reducing intestinal ammonia production and strengthening barrier function, although regulatory challenges related to genetic stability and biosafety persist [93]. Next-generation TGR5 agonists with improved brain penetration and selective AhR

modulators for neuroprotection are under development [52, 116, 122, 123]. The integration of host-microbial omics promises real-time therapeutic monitoring and more precise modulation of the gut-liver-brain axis [93, 98]. Another emerging line of research involves the use of bacteriophages to selectively target harmful gut microbes involved in liver disease [41]. Preclinical studies have shown that, in alcoholic hepatitis, certain strains of *Enterococcus faecalis* that produce the cytolysin exotoxin aggravate the severity of the disease and mortality. In experimental models, oral administration of phages specifically targeting these cytolytic strains was able to counteract liver damage, while phages against non-cytolytic strains had no effect [124]. Similarly, studies on diet-induced steatohepatitis demonstrated that the elimination of ethanol-producing *Klebsiella pneumoniae* with adapted phages prior to fecal transplantation prevented the development of diet-induced steatohepatitis [125]. However, to date, no studies have been conducted to evaluate phage therapy in the context of HE. To translate these findings into clinical practice, challenges related to safety, regulatory approval, and long-term microbial stability will need to be addressed. Nevertheless, phage-based strategies represent a promising complement to existing therapies targeting the microbiota and barrier within the gut-liver-brain axis.

Future perspectives and challenges

The future of HE management is shifting toward a personalized, technology-integrated model centered on the gut-liver-brain axis. While FMT has gained recognition as a therapeutic strategy for modulating dysbiosis and restoring microbial balance, its widespread application continues to face challenges such as no standardized protocols, donor variability, and incomplete data on long-term engraftment and safety outcomes [126]. In addition to conventional microbiota transfer, novel strategies involve exploring host-microbe interactions at the molecular level. For instance, Li et al. [127] proposed targeting cellular pathways, such as modulating autophagy via ST3GAL2-regulated sialylated glycosphingolipids, to influence gut-liver metabolic crosstalk and mitigate neuroinflammation. However, these molecular targets still require robust clinical validation before being adopted into routine care [127]. Understanding host metabolic pathways, including bilirubin metabolism, opens new therapeutic windows for modulating oxidative stress and inflammation in liver-brain axis disorders such as HE [128].

Concurrently, digital health tools and artificial intelligence (AI)-driven innovations are transforming HE monitoring and management. Mobile applications using machine learning algorithms for stool pattern recognition and consistency scoring have demonstrated potential in guiding dynamic lactulose titration—enhancing ammonia clearance, improving adherence, and reducing the recurrence of overt episodes [129, 130]. Moreover, AI applications in hepatology have expanded beyond diagnostics; they now integrate clinical, behavioral, and microbiome-derived data to generate predictive models that support early decision-making and risk assessment in HE [131]. These platforms empower patients through real-time self-monitoring and support clinician decision-making, reinforcing the paradigm of responsive, patient-centered care [132]. Recent validation studies confirm that such tools facilitate individualized therapeutic adjustments, reduce hospitalization risk, and improve longitudinal outcomes in cirrhotic patients [133]. For example, Qiu et al. [134] demonstrated the use of AI-based prognostic models to predict 28-day outcomes in patients with liver failure, underscoring their applicability in risk stratification for HE patients.

In parallel, diagnostic innovation is emerging as a cornerstone of next-generation HE strategies. Functional neuroimaging modalities, particularly functional magnetic resonance imaging (fMRI), allow for early detection of MHE, which often precedes overt HE but significantly impairs quality of life and cognitive function. fMRI enables the visualization of subtle changes in neural connectivity, improving risk stratification and supporting earlier therapeutic intervention in at-risk patients with cirrhosis [85]. Furthermore, the integration of host-microbial multiomics—including metagenomics, transcriptomics, metabolomics, and proteomics—has begun to reveal distinct molecular signatures associated with HE progression, offering a blueprint for individualized treatment selection and therapeutic monitoring [93, 98]. Bajaj et al. [135] reported that gut microbiome profiles could effectively exclude HE in ambiguous clinical cases, highlighting how omics data can enhance diagnostic specificity and reduce overtreatment. Similarly, Sah et al. [136] proposed a future in which AI and omics converge to redefine diagnostic frameworks for

cirrhosis-related syndromes, emphasizing their complementary potential in tailoring interventions. However, the implementation of diagnostics based on omics and AI technologies faces significant obstacles. Multi-omics platforms remain costly and technically demanding, with limited availability outside specialized research centers, restricting their routine clinical application. Standardization of sample processing, data integration, and interpretation also lags technological advances, posing challenges for reproducibility and clinical decision-making. In terms of AI, predictive models rely on representative, high-quality datasets, but current studies often include small or region-specific cohorts, limiting their generalizability. Furthermore, integrating AI tools into existing clinical workflows requires not only robust validation but also regulatory approval, digital infrastructure, and training for clinicians to ensure safe and effective use [137, 138].

Nonetheless, these technological advances must be accompanied by comprehensive public health strategies to address persistent care gaps. For instance, Miwa et al. [139] highlighted that MHE remains widely underrecognized by both health care professionals and patients, underscoring the need for standardized diagnostic pathways and educational initiatives to promote timely detection and intervention. This is particularly crucial in high-risk contexts, such as post-TIPS placement, where integrated strategies that combine early biomarkers, neurocognitive testing, and microbiota modulation may reduce the incidence of HE and improve patient outcomes [140]. The trajectory of HE management is evolving toward an integrated framework that combines molecularly targeted therapies, precision microbiota modulation, AI-enabled digital tools, and advanced neuroimaging. Realizing this vision will require ongoing clinical validation of emerging therapies, infrastructure for implementing omics-based diagnostics, and the upskilling of health care providers to interpret and apply novel technologies effectively [132]. Coordinated efforts across research, clinical practice, and policy will be essential to translate these innovations into measurable improvements in patient care, prognosis, and quality of life.

Conclusions

HE represents a multifactorial neuropsychiatric disorder intricately linked to the gut-liver-brain axis, in which gut dysbiosis, increased intestinal permeability, microbial metabolite production, and systemic inflammation converge to disrupt hepatic and neurological homeostasis. Advances in our understanding of this axis have redefined the pathophysiological framework of HE, shifting the focus from isolated hyperammonemia toward a dynamic, integrative model that includes microbial, immunological, and metabolic pathways. Clinical and experimental evidence supports microbiota-targeted therapies—such as rifaximin, probiotics, and FMT—as promising interventions that can modulate the underlying mechanisms of HE. Furthermore, emerging therapeutic strategies involving receptor agonists, barrier-enhancing nutraceuticals, and AI-driven monitoring tools illustrate a shift toward personalized and mechanistically guided management. Nonetheless, the translation of these innovations into widespread clinical practice requires rigorous validation, optimization of diagnostic tools, and equitable access to novel technologies. Ultimately, embracing a multidimensional, microbiome-centered paradigm will be essential for improving outcomes and quality of life in patients affected by this severe hepatic complication.

Abbreviations

AGIs: alpha-glucosidase inhibitors

AhR: aryl hydrocarbon receptor

AI: artificial intelligence

BBB: blood-brain barrier

CLD: chronic liver disease

CNS: central nervous system

EGCG: epigallocatechin-3-gallate

fMRI: functional magnetic resonance imaging

FMT: fecal microbiota transplantation

FXR: farnesoid X receptor

HE: hepatic encephalopathy

IDO: indoleamine-2,3-dioxygenase

IL: interleukin

MASLD: metabolic dysfunction-associated steatotic liver disease

MHE: minimal hepatic encephalopathy

NLRs: Nod-like receptors

PAMPs: pathogen-associated molecular patterns

ROS: reactive oxygen species

SCFAs: short-chain fatty acids

SIBO: small intestinal bacterial overgrowth

TGR5: Takeda G-protein-coupled receptor 5

TIPS: transjugular intrahepatic portosystemic shunt

TJ: tight junction

TNF-α: tumor necrosis factor alpha

Declarations

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Author contributions

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Conflicts of interest

Nahum Méndez-Sánchez, who is the Associate Editor and Guest Editor of Exploration of Digestive Diseases, was not involved in the decision-making or the review process of this manuscript. The other authors declare no conflicts of interest.

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