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RIFAXIMIN THERAPY FOR TREATMENT OF HEPATIC ENCEPHALOPATHY IN LIVER CIRRHOSIS: A SYSTEMATIC REVIEW

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ABSTRACT

Rifaximin is an oral nonsystemic antibiotic with minimal gastrointestinal absorption and broad-spectrum antibacterial activity covering both gram-positive and gram-negative organisms. Rifaximin is currently used worldwide in patients with cirrhosis for preventing recurrent HE because its efficacy and safety have been proven by large randomized clinical trials. In the last decade, experimental and clinical evidence suggest that rifaximin could have other beneficial effects on the course of cirrhosis by modulating the gut microbiome and affecting the gut-liver axis, which in turn can interfere with major events of the pathophysiological cascade underlying decompensated cirrhosis, such as systemic inflammatory syndrome, portal hypertension, and bacterial infections. However, the use of rifaximin for prevention or treatment of other complications, including spontaneous bacterial peritonitis or other bacterial infections, is not accepted because evidence by clinical trials is still very weak. The present review deals in the first part with the potential impact of rifaximin on pathogenic mechanisms in liver diseases, whereas in the second part, its clinical effects are critically discussed.In this review we focused on the effectivness of rifaximin for hepatic encephalopathy with consideration of different randomised control trials.

KEYWORDS: Hepatic encephalopathy, Rifaximin, Hyperammonia.

INTRODUCTION

Hepatic encephalopathy (HE) represents a diverse spectrum of complex neuropsychiatric disturbance resulting from liver disease and its concomitant metabolic and immunological derangements.[1] Hepatic encephalopathy (HE) presents in 30-60% of patients with cirrhosis of the liver. It is a clinical expression of a spectrum of potentially reversible neuropsychiatric abnormalities secondary to the accumulation of neurotoxic substances in brain tissue that is proportional to the synthetic function and functional reserve of the liver.[2] It is characterized by deficits in cognitive, psychiatric, and motor function and can range in severity from minimal (or covert) hepatic encephalopathy (MHE) to overt hepatic encephalopathy (OHE), coma, and death. Patients with MHE demonstrate neuropsychological alterations including disrupted sleep–wake cycle, personality changes, impairment of attention, cognitive and memory dysfunction, and changes in motor coordination. These can progress through to higher grades of OHE, including lethargy, stupor, coma, and death; these are more pronounced in patients with acute liver failure.[1] The most well understood pathophysiological mechanism of HE is the neurotoxicity of ammonia in the brain, either due to increased production or impaired excretion. The majority of ammonia production occurs in two primary areas: the intestines (both small and large, contributing about 50%) and the kidneys (around 40%). Within the gastrointestinal system, ammonia is formed through the breakdown of dietary proteins by urease-producing bacteria, as well as through the metabolism of glutamine by enterocyte glutaminase. In the kidneys, proximal tubular cells generate ammonia from glutamine while producing bicarbonate as a by-product. Various factors can influence the production of ammonia in these areas, including gastrointestinal bleeding, conditions of low blood volume, excessive diuresis, low potassium levels, acidosis, and high protein intake.[3]

The liver plays a crucial role in ammonia detoxification through the urea cycle (also known as the Krebs-cycle), which transforms ammonia into urea, a water-soluble compound. This urea is then excreted through the intestines and urine. When liver function is compromised due to cellular damage or shunting, its ability to detoxify ammonia decreases, leading to elevated ammonia levels in the bloodstream. Additionally, the kidneys may further hinder ammonia excretion due to imbalances in acid-base levels and potassium, increased protein consumption, and dysregulation of glucocorticoid hormones. Skeletal muscle also aids in ammonia detoxification via the enzyme glutamine synthase, which converts ammonia into glutamine. Thus, sarcopenia—a frequent complication of cirrhosis—can exacerbate issues related to hepatic encephalopathy. Changes in gut flora are a key factor in the development of hepatic encephalopathy (HE). It is believed that a reduction in bile acid

production enables urease-producing bacteria to thrive, replacing beneficial bacteria like *lachnospiraceae*. Research has consistently highlighted the microbiota's crucial role in HE progression. In addition to ammonia, other substances—especially altered neurotransmitters—could also contribute to the onset of HE. These substances may include glutamine, histamine, serotonin, γ-aminobutyric acid, and manganese. More research is needed to uncover other aspects of HE pathophysiology to facilitate quicker diagnosis and treatment.[3]

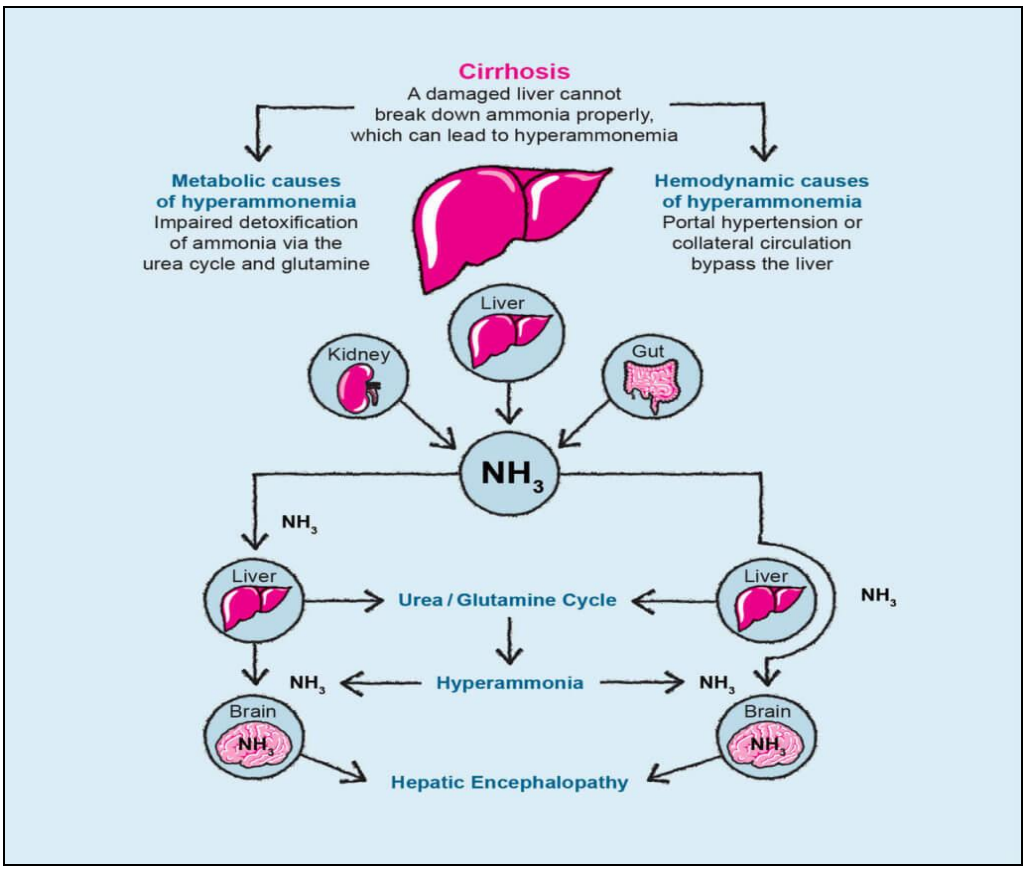


Fig. 1: Pathophysiology of Hepatic encephalopathy.

Hyperammonemia is a metabolic condition characterized by the raised levels of ammonia, a nitrogen-containing compound. Normal levels of ammonia in the body vary according to age. Hyperammonemia can result from various congenital and acquired conditions in which it may be the principal toxin. Hyperammonemia may also occur as a part of other disorders that involve various other metabolic abnormalities. Normally, ammonia is produced in the colon and small intestine from where it is transported to the liver to be converted to urea via the urea cycle. Urea, a water-soluble compound, can then be excreted via the kidneys. Ammonia levels rise if the liver is unable to metabolize this toxic compound as a result of an enzymatic defect or hepatocellular damage. The levels may also rise if portal blood is diverted to the systemic circulation, bypassing the liver, or there is increased production of ammonia due to an infection with certain microorganisms.[4]

Classification

According to national guidelines, HE is classified using four main axes. The first criterion is based on the underlying cause of HE. Type A is HE seen in acute liver failure, Type B in the portal-systemic bypass setting with no intrinsic hepatocellular disease, and Type C is in the setting of cirrhosis with portal hypertension or systemic shunting.[4]

Type of H.E	Description
Type A	Encephalopathy from acute liver failure
Type B	Encephalopathy caused by portosystemic shunting without intrinsic liver disease
Type C	Encephalopathy associated with portosystemic shunting episodic

Table 1: Types and grade of H.E.

Grade 0: Minimal HE	No clinical manifestations, but some abnormalities on psychometric testing
Grade 1: Mild HE	Alterations in behavior, mild confusion, slurred speech, disordered sleep
Grade 2: Moderate HE	Lethargy, moderate confusion
Grade 3: Severe HE	Stupor, incoherent speech, sleeping
Grade 4: Coma	Coma, unresponsiveness

Diagnosis

There is no standardised serologic testing or imaging modality to accurately diagnose HE and assess its severity. Ammonia is classically associated with HE; however, increased blood ammonia level alone does not help with the diagnosis or prognosis of HE. Elevation of ammonia in combination with the clinical picture of HE can be more useful, as isolated increased ammonia level can be seen in other medical conditions.[5]

Treatment

The first-line pharmacologic therapy for HE is laxative. The initial goal of therapy is to prevent ammonia absorption through non-absorbable disaccharides (i.e., lactulose).[6] They are potent laxatives and additionally help alter the intestinal microbiome to non-urease-producing bacteria that reduce ammonia production.[7] Lactulose also lowers the pH of the colon, causing conversion of ammonia to the ammonium ion, which is not readily absorbable in the colon. Disaccharide enemas and polyethylene glycol have also been proven to be useful for removing excess ammonia from the colon.

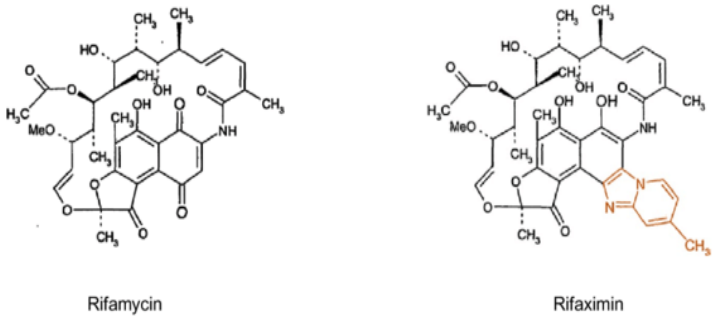
Table 2: Different therapy used for H.E.

Therapy	Mechanism	Benefits	Comments
Lactulose	Osmotic laxative Acidification of the colon ↓ urease-producing bacteria ↓ ammonia production/ absorption	Improved cognitive function Most extensively studied ↓ progression to overt HE	Cost effective Mainstay of HE treatment Result in dehydration if severe diarrhoea
Rifaximin	↓ urease-producing bacteria ↓ ammonia production	Improved cognitive function ↓ HE-related hospitalisations	Modulates gut flora Expensive
BCAA	Promotes synthesis of glutamine from ammonia in the skeletal muscle	Improves recurrent HE	No effect on overall mortality
LOLA	Ammonia scavenging ↑ production of urea in hepatocytes, activating glutamine synthase in hepatocytes and skeletal muscle	↓ progression to overt HE	Further studies required to prove efficacy
Glycerol phenylbutyrate	↑ excretion of glutamine	↑ time to HE recurrence	No benefit for patients on rifaximin
Zinc	If deficient, reduced urea cycle utilisation of ammonia	Improvement in cognitive tests	No evidence on other outcomes
FMT	Manipulate gut microbiome	Improvement in HE recurrence	Currently under investigation Used for recurrent HE

From all that therapy, we decided to focus on the treatment of the antibiotics that is Rifaximin.

Pharmacological characteristics of Rifaximin: Rifaximin is a semisynthetic, water-insoluble, rifamycin-based nonsystemic antibiotic with very low gastrointestinal absorption and good antibacterial

activity.[8] intestinal absorption and good antibacterial activity.[8] Compared with rifampicin, it contains an extra pyrido-imidazole ring to reduce systemic absorption that is less than 1% after oral administration.[8,9] (Fig. 2). Nevertheless, it is important to note that rifaximin plasma concentrations are not negligible in patients with cirrhosis, particularly in those with moderate-to-severe liver function impairment (Child B or C patients).[10] There are some published reports on potential muscle toxicity in cirrhosis in patients receiving rifaximin in combination with simvastatin 40 mg/day.[11] However, the possibility of these systemic muscle effects of rifaximin seems remote because in studies with large numbers of patients with cirrhosis, no muscle or other systemic adverse events have been reported. The slight increase in systemic exposure to rifaximin in subjects with cirrhosis should be interpreted in the context of its low systemic availability as well as the rifaximin safety data in cirrhosis. Therefore, no dosage adjustment in patients with advanced cirrhosis is recommended. Both experimental and clinical data show that rifaximin has a broad-spectrum antibacterial action covering gram-positive and gram-negative aerobic and anaerobic bacteria.[8] Rifaximin elicits its antimicrobial properties by binding the betaDNA-dependent RNA polymerase and thus inhibting subunit of the bacterial RNA synthesis. It has the advantage of low microbial resistance and few systemic adverse events and is safe in all patient populations.[8] Being virtually nonabsorbed, bioavailability of rifaximin within the gastrointestinal tract is high with intraluminal and fecal drug concentrations largely exceeding the minimal inhibitory concentration values observed *in vitro* against a wide range of pathogenic organisms. The gastrointestinal tract represents, therefore, the primary therapeutic target of rifaximin.[8,9] Rifaximin has been shown to modify the gut microbiome. However, changes in overall gut microbiome composition have shown to be relatively sparse, and the effects on microbiome have been described to be mediated also by rifaximin-induced changes in bile acid composition and modulation of microbiome function.



Rifamycin Rifaximin

Fig. 2: Structure of Rifaximin and Rifamycin.

Table 3: Summary of Studies Reporting the Use of Rifaximin for Treatment or Prevention of HE in Cirrhosis.

Type of Study	Number of Trials (Sample Size)	Results
Short-term therapy studies (5–30 days)		
Rifaximin vs. placebo	1 (93)	Asterixis improved only with rifaximin. PSE index, mental status, and intellectual func- tion improved similarly in both groups.
Rifaximin 200 mg vs. 400 mg vs. 800 mg per day	1 (54)	PSE index improved only in 400-mg and 800-mg groups.
Rifaximin vs. other antibiotics similarly in both (6	7 (227)	Ammonia improved more with rifaximin than neomycin (1 RCT) or RCTs). PSE index improved similarly in both groups (1 RCT). Intellectual function or mental status improved similarly in both groups (5 RCTs). Asterixis improved faster with rifaximin than with neomycin (1 RCT).
Rifaximin vs. Nonabsorbable disaccharides	6 (448)	Higher ammonia improvement with rifaximin (3 RCTs) or similarly in both groups (3 RCTs)

Long-term studies (3-6 months cyclical)		
Rifaximin vs. nonabsorbable disaccharides compared	2 (80)	Ammonia and mental status improved with both trials with all strategies with baseline. Higher improvement in PSE index, EEG, and mental status with rifaximin. In the second study, rifaximin ± lactitol did better than lactitol alone with mental status.
Rifaximin vs. neomycin	1 (60)	Improvement in psychometric/neurophysiologic tests, mental status, and ammonia were similar across both groups.
Inpatient use		
Rifaximin + lactulose vs. lactulose alone lactulose compared	1 (120)	Higher HE reversal and lower death in group given rifaximin and with lactulose alone
Prevention of recurrence		
Rifaximin vs. placebo	1 (299)	Reduction in recurrent HE episodes and hospitalization in the rifaximin group with significantly higher improvement in neurophysiological, quality of life, and ammo- nia in the rifaximin group. In both groups, 91% of patients were on lactulose.

Real-world and open-label rifaximin experience

Open-label extension and precomparison/postcomparison	2 (474)	Open-label extension and addition of new patients on rifaximin was associated with continued reduction in HE-related and all-cause hospitalization.
Evaluation of health care systems after rifaximin introduction	5 (760)	patients from placebo to rifaximin further reduced HE episodes. Reduction in mean hospitalizations, readmissions, and length of stay

Real-World" Use of Rifaximin

Open-label experiences and evaluation of a placeboassigned group that was subsequently given rifaximin showed continued reduction in HE-related episodes, even outside the clinical trial setting.

Effect of Rifaximin on bacterial translocation

Based on its pharmacological characteristics and the putative effects on pathogenetic mechanisms of cirrhosis, rifaximin is considered by many hepatologists to be the logical alternative to quinolones or other systemic antibiotics for the prophylaxis of spontaneous bacterial peritonitis (SBP) and potentially of non-SBP bacterial infections, with the belief that rifaximin is active on a broader range of intestinal gram-positive and gram-negative bacteria, is safer, and carries a low risk of inducing resistance to antibiotics.

Unfortunately, after more than a decade of clinical research, a conclusive indication on the use of rifaximin in prevention of bacterial infections cannot currently be given. Almost all the published data are related to primary or secondary prophylaxis for SBP. In general, retrospective studies have shown that the use of rifaximin is associated with lower incidence of SBP and other complications of the disease.

Conversely, prospective observational studies have yielded less consistent results. Only a few RCTs have been performed so far, in Egypt and South Arabia, comparing the efficacy of rifaximin versus norfloxacin; in these studies, an advantage was seen in favor of rifaximin given for primary or secondary SBP; in the former study, rifaximin was also given alternated to norfloxacin and compared with norfloxacin alone. However, the strength of these positive results is undermined by some methodological drawbacks. To overcome the limitations inherent to each single study, several systematic reviews and meta-analysis assessing both the observational cohort studies and the RCTs have been performed. Again, results suggest that only low-quality evidence supports the superiority of rifaximin over norfloxacin or other systemic antibiotics for either primary or secondary SBP prophylaxis.) In all these studies, the high heterogeneity in terms of patient inclusion criteria, type and modalities of administration of the comparative prophylactic therapies, primary and secondary endpoints, and the moderate-to-high risk of methodological biases related to randomization, blinding, attrition, and intention-to-treat analysis preclude the possibility to reach solid conclusions.[12]

Table 4: Different trial showing effectiveness of Rifaximin.

Reference	Study Design	Patient Population	Main Outcomes
Assem et al.2016[13]	Prospective randomized, open-label, comparative multicenter study	239 patients with cirrhosis with ascites randomized to 3 groups: rifaximin (550 mg bid), norfloxacin, or alternat- ing rifaximin/norfloxacin	Primary outcome: incidence of SBP Overall, 10 patients developed HRS (6 patients [7.6%] in the norfloxacin group, 2 [2.4%] in the rifaximin group and 2 [2.5%] in the combined group; P > 0.05). HRS was the main cause of mortality.
Sharma et al. 2013[14]	RCT	120 patients with overt HE randomizedinto 2 groups: lactulose + rifaximin (1,200 mg/ day) vs. lactulose + placebo	Primary outcome: reversal of HE Addition of rifaximin was associated with the following: Reduced mortality (24% vs. 49%, P < 0.05), with no differences in HRS- related and gastrointestinal bleeding–related deaths
Dong et al. 2016[15]	Retrospective study	88 patients on rifaximin (550 mg bid) for ≥90 days vs. 88 matched controls	Rifaximin reduced the following: - The incidence rate ratio of AKI (IRR, 0.71; 95% CI, 0.54-0.94) and HRS (IRR, 0.21; 95% CI, 0.06-0.70) - The requirement of RRT (5.7% vs. 15.9%; OR, 0.23; 95% CI, 0.07-0.74)
Vlachogiannakos et al. 2013[16]	Prospective, non-randomized case-control study	23 patients with known hemodynamic response (HVPG) to short-term rifaximin treated with long-term ri- faximin (1,200 mg/day) vs. 46 matched controls	Primary outcomes: survival, variceal bleeding, HE, SBP, HRS Rifaximin therapy was as follows: - An independent negative predictor of variceal bleeding (RH, 0.246; 95% CI, 0.069-0.870; P = 0.03) - The only factor associated with lower probability of HRS (RH, 0.110; 95% CI, 0.012-0.973; P = 0.047) - Predictor of 5-year survival (RH for mortality, 0.258; 95% CI, 0.075-0.891; P = 0.032)
Kimer et al. 2017[17]	Double-blind RCT	54 stable outpatients with cirrhosis and ascites with HVPG ≥ 10 mm Hg rand-omized to rifaximin 550 mg bid (n = 36) or placebo bid (n = 18) for 4 weeks	Primary outcomes: hepatic and systemic hemodynamics, renal function No effect of rifaximin on the following: - HVPG (P = 0.94) - PRA (P = 0.12) or other vasoactive hormones (P = NS) - GFR (P = 0.14)
Kalambokis et al. 2012[18]	Open-label, prospec- tive, single-center pilot study	13 patients with alcohol-associated cirrhosis and ascites treated with rifaximin (1,200 mg/day) for 4 weeks	Primary outcomes: systemic hemodynamics and renal function Rifaximin: - increased MAP (P = 0.05) in keeping with increased SVR (P = 0.01), decreased PRA (P = 0.02), and decreased CO (P = 0.02) - improved renal function, consistent with increase in GFR (P = 0.006) and urinary sodium excretion (P = 0.03) - decreased plasma endotoxin (P = 0.005), IL-6 (P = 0.01), and TNF-α (P = 0.02) levels
Vlachogiannakos et al. 2009[19]	Prospective study	30 patients with alcohol-associated cirrhosis and ascites treated with rifaximin (1,200 mg/day) for 28 days	Primary outcomes: hepatic hemodynamics Rifaximin: - decreased HVPG (P < 0.0001) - increased MAP (P < 0.05) - reduced plasma endotoxin levels both in systemic (P < 0.0001) and splanchnic circulation (P < 0.0001)
Lim et al. 2017[20]	Open-label RCT	73 patients with HVPG ≥ 12 mm Hg rand-omized to propranolol mono- therapy (n = 54) or rifaximin (1,200 mg/day) + propranolol (n = 19) for 3 months	Primary outcome: HVPG response rate The combination therapy achieved the following: - a significant decline of HVPG (P = 0.016) - higher HVPG response rate than propranolol alone (87% vs. 56%; P = 0.034). - higher rates of reduction of LPS (P = 0.009) and LPS binding protein (P = 0.002) compared with propranolol monotherapy
Salehi et al. 2019[21]	Retrospective cohort study	101 patients with HE: 66 treated with rifaximin vs. 35 naïve	Rifaximin therapy achieved the following: - reduced all-cause admissions (P = 0.037) - reduced admissions for complications of ascites, including HRS (P = 0.008) and variceal bleeding (P =

			0.026) increased time to hospital readmission (P = 0.040)
Kang et al. 2017[22]	Retrospective cohort study	1,042 patients with previous HE: 621 patients with HCC (173 receiving rifaximin 1,200 mg/ day + lactulose, 448 controls receiving lactulose alone) and 421 without HCC (145 rifaximin + lactulose, 276 lactulose alone)	Rifaximin was associated with lower risk of variceal bleeding in the following: Entire cohort (HR, 0.520; 95% CI, 0.349-0.773; P = 0.001) Non-HCC cohort (aHR, 0.425; 95% CI, 0.220-0.821; P = 0.011).Rifaximin was associated with a nonsignificant trend toward lower risk of HRS in the following:Non-HCC cohort (HR, 0.595; 95% CI, 0.334-1.060; P = 0.078).Rifaximin was associated with a lower risk of death in the following: - Entire cohort (HR, 0.702; 95% CI, 0.504-0.978; P = 0.036) - Non-HCC cohort (aHR, 0.697; 95% CI, 0.510-0.954; P = 0.024)

COCLUSION

HE remains one of the major challenges and morbidities facing patients with decompensated liver cirrhosis. Even in its subclinical presentation, it exerts a profound influence on patient quality of life and functional capability and confers a damning prognosis. Recurrent encephalopathy is in itself an extended criterion for consideration of liver transplantation. Increasing understanding of the interplay between the liver, the intestinal microbiome, and the innate immune system allows for the development of exciting new technologies and treatments to include in the clinician's armory for tackling this neurophysiological manifestation of decompensated liver disease (Fig. 3). A low threshold of suspicion and early specialist review, complex neuropsychological evaluation, and identification and treatment of precipitants are required in the approach to a patient with liver cirrhosis and altered mentation.

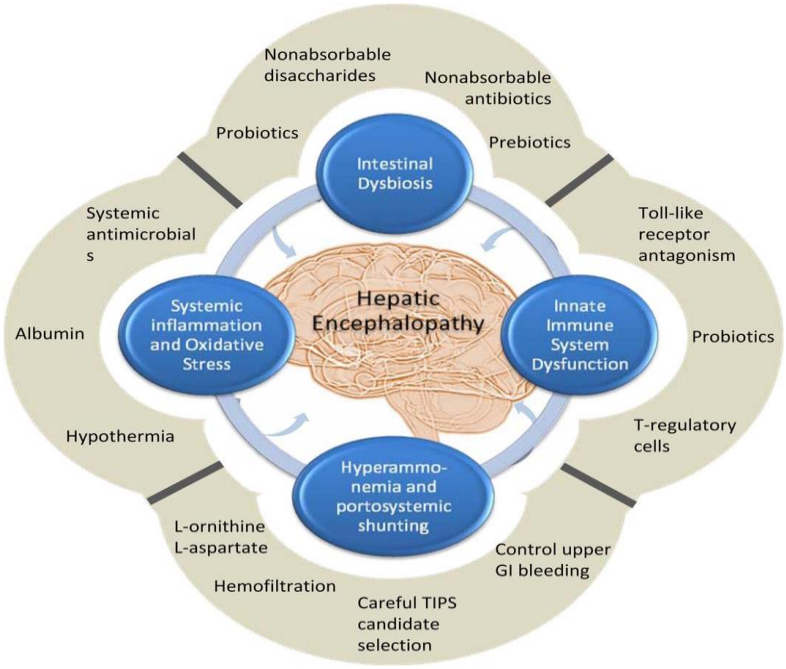


Fig. 3: Overlapping pathophysiological mechanisms underpinning the development of hepatic encephalopathy and revealing targets for therapeutic intervention. No single pathophysiological pathway explains in full the development of HE; and it is increasingly recognized that hyperammonemia, systemic inflammation, and intestinal dysbiosis act in a synergistic cascade that terminates in the development of HE. Equally, no single treatment is completely effective at ensuring resolution and preventing the recurrence of HE. Recognizing the multifaceted pathophysiological process driving the development of HE has allowed for innovative therapeutic targeting. The utilization of a multipronged treatment strategy is central to management of this condition.

Use of rifaximin is effective in treatment of hepatic encephalopahty in order to.

Reduction of Ammonia-Producing Bacteria: Rifaximin alters the gut microbiota by reducing the

population of urease-producing bacteria, which decreases ammonia production in the intestine.

Anti-inflammatory Effects: It modulates gut inflammation and permeability, potentially reducing systemic inflammation and endotoxemia.

Effects on Gut-Brain Axis: Rifaximin stabilizes gut microbiota and reduces bacterial translocation, which helps prevent neurotoxic effects on the brain.

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