

The enteric microbiota-kidney axis: a novel paradigm in the management of Hepatorenal syndrome

Abstract

Background: Hepatorenal syndrome (HRS) in cirrhosis carries high mortality, yet vasoconstrictor-based therapy remains incompletely effective. Evidence from clinical and preclinical studies indicates that gut-derived uremic toxins may directly contribute to renal injury, potentially through mechanisms beyond hemodynamic changes.

Aim: This review examines the “Enteric Microbiota-Kidney Axis” as a conceptual framework for understanding renal dysfunction in cirrhosis and evaluates the evidence supporting this paradigm.

Methods: A narrative synthesis of literature from PubMed, Scopus, and Web of Science (2015–2025) was performed, focusing on gut microbiota alterations, uremic toxin production, renal injury mechanisms, and therapeutic interventions in cirrhosis.

Results: Cirrhotic dysbiosis is characterized by depletion of butyrate-producing genera (Roseburia, Faecalibacterium, Coprococcus) and enrichment of urease-positive Proteobacteria (Escherichia-Shigella, Klebsiella). These compositional shifts may drive overproduction of indoxyl sulfate (IS) and p-cresyl sulfate (PCS). The mechanisms by which IS induces oxidative stress involve binding to the aryl hydrocarbon receptor (AhR) in proximal tubular epithelial cells, leading to downregulation of nuclear factor erythroid 2-related factor 2 (Nrf2), increased NADPH oxidase 4 (NOX4)-induced reactive oxygen species production, and activation of inflammatory transcription factors. Clinical cohort studies have suggested that elevated serum IS may predict HRS development, though these findings require validation. Randomized controlled trials in chronic kidney disease patients have demonstrated that synbiotic administration may stabilize renal function and that AST-120 reduces serum indoxyl sulfate levels, but these findings have not been confirmed in cirrhotic populations. Preclinical studies of phage therapy have shown efficacy against carbapenem-resistant Klebsiella pneumoniae in infection models, though direct relevance to HRS remains uncertain.

Conclusion: The enteric microbiota-kidney axis represents a testable conceptual framework for understanding hepatorenal syndrome, but current evidence is largely hypothesis-generating. High-quality randomized controlled trials in cirrhotic populations are needed before microbiome-directed therapies can be recommended for HRS management.

Keywords: Gut-kidney axis; hepatorenal syndrome; dysbiosis; indoxyl sulfate; p-cresyl sulfate; synbiotics; cirrhosis

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Abbreviations: AhR, Aryl hydrocarbon receptor; CKD, Chronic kidney disease; CLD, Chronic liver disease; CREB, cAMP response element binding protein; eGFR, Estimated glomerular filtration rate; eNOS, Endothelial nitric oxide synthase; FMT, Fecal microbiota transplantation; GPR43, G protein-coupled receptor 43; HRS, Hepatorenal syndrome; IPA, Indole-3-propionic acid; IS, Indoxyl sulfate; KPC, Klebsiella pneumoniae carbapenemase; LPS, Lipopolysaccharide; ELD-Na, Model for End-Stage Liver Disease – Sodium; NF-κB, Nuclear factor kappa B; NOX4, NADPH oxidase 4; Nrf2, Nuclear factor erythroid 2-related factor 2; OAT1/3, Organic anion transporter 1 and 3; PCS, p-Cresyl sulfate; RAAS, Renin-angiotensin-aldosterone system; RCT, Randomized controlled trial; ROS, Reactive oxygen species; SBP, Spontaneous bacterial peritonitis; SCFA, Short-chain fatty acid; SOCS2, Suppressor of cytokine signaling 2

Introduction

Chronic liver disease (CLD) affects approximately 1.5 billion people globally, with cirrhosis accounting for more than 1 million deaths annually.¹ Among the most devastating complications of

cirrhosis is hepatorenal syndrome (HRS), a form of progressive kidney failure that occurs in up to 40% of patients with ascites.² Without liver transplantation, three-month mortality exceeds 80%.³ The prevailing pathophysiological paradigm attributes HRS to splanchnic arterial vasodilation, effective hypovolemia, and subsequent renal vasoconstriction driven by the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system.⁴ Standard therapy accordingly combines vasoconstrictors (terlipressin or norepinephrine) with albumin infusion.⁵ However, renal recovery remains incomplete in 30–50% of treated patients, and relapse is common.⁶ This therapeutic ceiling suggests that additional, non-hemodynamic mechanisms may contribute to renal dysfunction in cirrhosis.

Over the past decade, the gut-liver axis has emerged as a critical modulator of hepatic inflammation and fibrosis. Bacterial translocation, endotoxemia, and dysbiosis are well-described phenomena in cirrhosis. However, the kidney receives 25% of cardiac output and is directly exposed to gut-derived metabolites, yet this organ has received less attention in the gut-liver framework. A recent comprehensive review established the gut-liver-kidney axis as a central regulatory network

orchestrating metabolic, immune, and inflammatory homeostasis across organ systems.⁷ According to this framework, the intestinal mucosal barrier maintains compartmentalization, while gut-derived metabolites including short-chain fatty acids (SCFAs), bile acids, and tryptophan derivatives influence hepatic and renal physiology. The liver regulates intestinal homeostasis through bile secretion and immune mediators, while the kidneys maintain metabolic equilibrium by clearing gut- and liver-derived uremic toxins.⁷ When gut dysbiosis or barrier dysfunction occurs, a self-perpetuating pathological cascade may ensue. For clarity, the term “uremic toxins” in this review refers to protein-bound solutes derived from gut microbial metabolism that accumulate when renal clearance is impaired. Two prototypical examples are indoxyl sulfate (IS, from dietary tryptophan via bacterial tryptophanase) and p-cresyl sulfate (PCS, from dietary tyrosine/phenylalanine via bacterial tyrosine phenol-lyase). Both are substrates for renal organic anion transporters (OAT1/3) and induce oxidative stress through aryl hydrocarbon receptor (AhR) activation and downregulation of nuclear factor erythroid 2-related factor 2 (Nrf2).

This review defines the **Enteric Microbiota-Kidney Axis** as the bidirectional communication between intestinal microbiota and renal function, mediated by microbial metabolites that enter the systemic circulation. In cirrhosis, this axis may become pathologically amplified, potentially contributing to renal dysfunction. It is important to clarify that this review does not propose a new clinical entity distinct from HRS; rather, it examines whether gut-derived uremic toxins represent an additional pathogenic mechanism operating alongside—not instead of—the well-established hemodynamic abnormalities. This synthesis evaluates the evidence for compositional and functional gut dysbiosis in cirrhosis, the mechanisms by which microbial metabolites may injure the kidney, clinical studies linking dysbiosis to HRS, emerging therapeutic strategies targeting the axis, and an integrated model for future research.

Methods

A systematic literature search of PubMed, Scopus, and Web of Science was conducted for articles published between January 2015 and March 2025. The search strategy combined MeSH terms and keywords, including “gut microbiota,” “intestinal microbiome,” “dysbiosis,” “hepatorenal syndrome,” “cirrhosis,” “indoxyl sulfate,” “p-cresyl sulfate,” “uremic toxins,” “probiotics,” “synbiotics,” and “rifaximin.” Original research articles, human cohort studies, randomized controlled trials (RCTs), animal models, and systematic reviews were included. Non-English publications, case reports (except for rare interventions), studies exclusively in dialysis-dependent patients without liver disease, and conference abstracts without full text were excluded. Two authors independently extracted data on study design, sample size, population characteristics (Child-Pugh score, MELD-Na), microbiota profiling method, measured metabolites, renal outcomes, and intervention details. Given heterogeneity in outcomes and study designs, a narrative synthesis was conducted rather than a meta-analysis.

Compositional alterations in cirrhotic dysbiosis

The healthy gut microbiota is dominated by Firmicutes (primarily Lachnospiraceae and Ruminococcaceae) and Bacteroidetes, with high diversity. These bacterial phyla work in concert to ferment dietary fibers, produce short-chain fatty acids, synthesize essential vitamins, and maintain intestinal barrier integrity through interactions with the host immune system.⁸

Cirrhosis induces a reproducible dysbiotic signature that becomes more pronounced as liver disease progresses. A study employing 16S rDNA high-throughput sequencing technology characterized the intestinal microbiota of 60 patients with chronic liver disease (including 16 with chronic hepatitis B, 37 with cirrhosis, and 7 with hepatocellular carcinoma) compared to 37 healthy volunteers.⁹ The investigators found that all chronic liver disease groups exhibited significantly reduced intestinal flora richness and diversity compared to healthy controls, with a progressive decline across the disease continuum from chronic hepatitis B to cirrhosis to hepatocellular carcinoma.⁹ In terms of species abundance, the study identified that with disease progression, the abundance of *Escherichia-Shigella*—a genus of Proteobacteria that includes potentially pathogenic strains—increased progressively. At the genus level, the study found that eight beneficial genera showed reduced relative abundance in chronic liver disease patients compared to healthy controls, including *Faecalibacterium* (a major butyrate-producing genus with anti-inflammatory properties), *Agathobacter*, *Roseburia*, *Coprococcus*, and other butyrate producers.⁹ The consistent depletion of butyrate-producing genera across multiple studies represents a reproducible finding in cirrhotic dysbiosis.^{10,11}

Concurrently, increased abundance of potentially pathogenic Proteobacteria, specifically Enterobacteriaceae (such as *Escherichia coli* and *Klebsiella pneumoniae*), Streptococcaceae, and Veillonellaceae, has been consistently reported.^{12,13} A meta-analysis quantified the relationship between gut microbiota composition and liver disease severity, finding that the MELD-Na score inversely correlates with *Faecalibacterium prausnitzii* abundance.¹⁴

Functional metagenomic changes in cirrhosis

Compositional shifts in the gut microbiota translate into functional alterations at the metagenomic level that have direct implications for host metabolism. Metagenomic sequencing of cirrhotic fecal samples reveals enrichment of gene pathways involved in the production of potentially harmful metabolites. Specifically, researchers have identified increased abundance of genes encoding urease (the ureABC operon, which converts urea to ammonia), tryptophanase (*tnaA*, which converts tryptophan to indole), and enzymes involved in tyrosine and p-cresol production.¹⁵ These metabolic pathways have direct relevance to the production of uremic toxins. Tryptophanase converts dietary tryptophan to indole, which is absorbed from the intestine, transported to the liver where it undergoes sulfation to form indoxyl sulfate (IS), and then excreted by the kidneys under normal conditions. Similarly, tyrosine phenol-lyase converts dietary tyrosine and phenylalanine to p-cresol, which is then sulfated to form p-cresyl sulfate (PCS). One study reported that these toxin-producing gene pathways account for only a minimal proportion of total microbial gene content in healthy individuals, but constitute 5–12% of total microbial gene content in patients with Child-Pugh class C cirrhosis, the most advanced stage of liver disease.¹⁵ The physiological basis for these functional alterations relates to the metabolic environment in cirrhosis. As liver function declines, serum ammonia and urea levels rise. Urea that diffuses from the systemic circulation into the intestinal lumen serves as a nitrogen source for urease-positive bacteria, promoting their growth and further increasing ammonia production.¹⁶ This creates a vicious cycle in which liver dysfunction promotes gut dysbiosis, which in turn produces metabolites that can potentially affect both the liver and kidneys.

Mechanisms of renal injury by gut-derived metabolites

Indoxyl sulfate: from gut to kidney injury

Indoxyl sulfate (IS) is derived from dietary tryptophan through a multistep pathway involving both microbial and host metabolism. Dietary tryptophan is converted by gut bacterial tryptophanase to indole. Indole is absorbed across the intestinal epithelium, transported via the portal circulation to the liver, where it undergoes sulfation to form indoxyl sulfate. Under normal physiological conditions, IS is efficiently excreted by the kidneys via organic anion transporters, particularly OAT1 and OAT3 located on the basolateral membrane of proximal tubular epithelial cells.¹⁷ In cirrhosis, two factors may converge to elevate serum IS levels. First, the enrichment of tryptophanase-positive bacteria such as *Klebsiella* species and *Escherichia coli* may increase the production of indole from dietary tryptophan. Second, reduced renal clearance due to declining kidney function allows IS to accumulate. A systematic review comprehensively documented the uremic toxicity of IS and PCS, concluding that these compounds are consistently associated with vascular and renal disease progression across multiple studies.¹⁸ The molecular mechanisms by which IS induces renal injury have been elucidated in considerable detail. After cellular uptake of IS by organic anion transporters OAT1 and OAT3 in renal proximal tubular cells, IS binds to the aryl hydrocarbon receptor (AhR) in the cytoplasm. The aryl hydrocarbon receptor is a ligand-activated transcription factor that, upon binding to its ligand, translocates to the nucleus and regulates target gene expression. Following IS binding to AhR, there is downregulation of nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator of antioxidant responses.¹⁹ The reduced Nrf2 activity leads to increased expression of NADPH oxidase 4 (NOX4), an enzyme that generates reactive oxygen species (ROS). The increased ROS production causes mitochondrial dysfunction, lipid peroxidation, DNA damage, and activation of stress signaling pathways. Simultaneously, the oxidative stress induces activation of cAMP response element binding protein (CREB) and nuclear factor- κ B (NF- κ B), two transcription factors that promote inflammatory responses.¹⁹ One study provided quantitative evidence for IS-mediated renal injury in human proximal tubular epithelial cell cultures.²⁰ Their work demonstrated that exposure to IS reduces cell viability and upregulates collagen IV expression, a marker of interstitial fibrosis. Further mechanistic insights come from research showing that IS suppresses the expression of klotho, an anti-aging protein that plays a protective role against chronic kidney disease progression.²¹ Beyond direct tubular toxicity, IS has been shown to induce pro-inflammatory cytokine production through crosstalk between AhR, NF- κ B, and suppressor of cytokine signaling 2 (SOCS2) in human macrophages.²²

p-Cresyl sulfate: mechanisms of renal and vascular injury

p-Cresyl sulfate (PCS) originates from the microbial metabolism of dietary tyrosine and phenylalanine. Gut bacteria express tyrosine phenol-lyase, which converts tyrosine to p-cresol, which is then sulfated in the liver to form PCS. Like IS, PCS is normally cleared by the kidneys but accumulates when renal function declines. PCS has been shown to cause renal tubular cell damage through mechanisms involving oxidative stress. Research in animal models demonstrated that PCS induces podocyte injury characterized by foot process effacement and albuminuria, indicating loss of glomerular barrier function.²³ Another study reported that PCS also causes endothelial dysfunction by reducing nitric oxide bioavailability.²⁴ Nitric oxide

is a key vasodilator produced by endothelial nitric oxide synthase (eNOS) that maintains vascular tone. Endothelial dysfunction in the renal microvasculature may contribute to impaired perfusion and accelerate decline in glomerular filtration rate. In addition to its direct cellular effects, PCS competes with other organic anions at organic anion transporters OAT1 and OAT3.²⁵ This competitive inhibition may reduce the secretion of other uremic solutes and impair the renal elimination of drugs that are substrates for these transporters. One cohort study of cirrhotic patients found that serum PCS exceeding 15 μ M was independently associated with increased risk of HRS after adjustment for potential confounders.²⁶

Synergistic effects of uremic toxins

A growing body of evidence indicates that IS and PCS may synergize to amplify renal injury. Investigators conducted experiments in which human proximal tubular epithelial cells were co-incubated with both IS and PCS, finding that co-incubation increased reactive oxygen species production to a greater extent than exposure to either compound alone.²⁷ This synergistic effect exceeded the additive effect expected from simply summing the individual responses, indicating true biological synergy. The mechanistic basis for this synergy may involve convergent effects on common pathways, including oxidative stress activation, organic anion transporter inhibition, and inflammatory cytokine production.

The Gut-kidney axis in renal homeostasis

Under physiological conditions, the gut-kidney axis maintains a state of balanced communication that supports both intestinal and renal health. Short-chain fatty acids (SCFAs) produced by the gut microbiota, particularly butyrate, propionate, and acetate, have been shown to confer renal protection through multiple mechanisms.²⁸ Butyrate enhances epithelial barrier integrity by activating G protein-coupled receptor 43 (GPR43), which upregulates the expression of tight junction proteins in renal tubular epithelial cells.²⁸ Additionally, certain indole derivatives produced by the gut microbiota may have protective effects. Indole-3-propionic acid (IPA), for example, has been shown to suppress IS-induced expression of fibrotic and inflammatory genes in proximal tubular cells.²⁹ This finding suggests that the balance between protective and harmful microbial metabolites is a critical determinant of renal health.

Clinical evidence linking gut microbiota to hepatorenal syndrome

Cohort studies of uremic toxins and hrs risk

Several cohort studies have examined the association between gut-derived metabolites and the risk of developing HRS in patients with cirrhosis. A prospective cohort study enrolled 210 cirrhotic patients without baseline renal dysfunction and measured fecal microbial composition and serum IS levels at enrollment, then followed patients for 12 months to monitor for the development of HRS.³⁰ The results demonstrated that higher IS levels and specific microbial signatures were associated with increased HRS risk. A multicenter European study enrolled 305 cirrhotic patients and examined the relationship between serum IS levels and HRS risk, finding that each 10 μ M increase in serum IS was associated with a 22% increase in HRS risk after adjusting for potential confounders including age, sex, liver disease severity, and baseline renal function.³¹ However, it is important to note that these observational studies cannot definitively establish causation, as unmeasured confounding factors may contribute to both elevated toxin levels and HRS risk. Furthermore, a study by Wang and

colleagues found that serum IS levels correlate with MELD score but not with HRS development after adjusting for baseline renal function, highlighting the need for caution in interpreting these associations.³²

Antibiotic intervention studies

Rifaximin is a minimally absorbed antibiotic widely used for the treatment and prevention of hepatic encephalopathy. A randomized, double-blinded, placebo-controlled trial investigated whether rifaximin could reduce serum levels of IS and PCS in patients with stage 3-5 chronic kidney disease.³³ The results showed that a 10-day course of rifaximin failed to reduce serum concentrations of either IS, PCS, or inflammatory cytokines compared to placebo. The study did observe differences in colonic bacterial communities between the rifaximin and placebo groups, but these microbial changes did not translate into reductions in circulating toxin levels. Several explanations for this negative finding warrant consideration, including insufficient treatment duration and the possibility that rifaximin primarily targets aerobic bacteria while many uremic toxin-producing bacteria may be less susceptible.

Negative and contradictory evidence

It is essential to acknowledge that not all studies support a pathogenic role for gut microbiota in HRS. A randomized trial by Jiang and colleagues found that probiotic therapy in cirrhotic patients did not reduce serum creatinine or prevent HRS development.³⁴ A meta-analysis by Chaplin and colleagues concluded that current evidence does not support microbiome-directed therapy for HRS prevention, citing limited sample sizes, heterogeneous interventions, and lack of standardized outcomes across studies.³⁵ These negative findings underscore the hypothesis-generating nature of the current evidence base and highlight the need for definitive randomized controlled trials in cirrhotic populations specifically.

Therapeutic strategies targeting the enteric microbiota-kidney axis

Synbiotics: rationale and clinical evidence

Synbiotics combine probiotic bacteria with prebiotic fibers designed to support the growth and activity of the probiotic strains. The rationale for synbiotic therapy is to restore a healthier gut microbial community that produces fewer uremic toxins and more protective metabolites

such as short-chain fatty acids. A randomized, placebo-controlled trial evaluated the effects of synbiotic supplementation on chronic kidney disease progression in 60 patients with stage IIIa to V chronic kidney disease who were not on dialysis.³⁶ The synbiotic formulation contained *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Bifidobacterium longum* combined with fructooligosaccharides and Psyllium Husk as prebiotic components. Over 24 weeks, patients receiving the synbiotic supplement showed no significant changes in serum urea, creatinine, eGFR, or albumin-to-creatinine ratio, while patients receiving placebo showed significant deterioration in kidney function. No adverse events were reported in the synbiotic group.³⁶

A separate multicenter randomized controlled trial investigated the effects of AST-120 (an oral carbon adsorbent that binds uremic toxins in the gut) and synbiotics on the gut microbiome in patients with chronic kidney disease.³⁷ After six months, levels of indoxyl sulfate were significantly lower in the AST-120 and AST-120 plus synbiotics groups compared to placebo. Gut microbiome analysis revealed that the combination of AST-120 and synbiotics enhanced the abundance of short-chain fatty acid-producing bacteria including *Agathobacter*, *Coprococcus comes*, and *Lachnoclostridium*.³⁷

Critically important caveat: Both of these trials were conducted in patients with chronic kidney disease, not cirrhosis or HRS. Extrapolation of these findings to cirrhotic populations requires substantial caution due to fundamental differences in pathophysiology, as summarized in Table 1. No randomized controlled trial has yet evaluated synbiotics or AST-120 specifically in cirrhotic patients with or at risk for HRS.

Phage therapy: preclinical evidence

Bacteriophages are viruses that infect and lyse specific bacterial strains, offering a targeted approach to reducing the abundance of pathogenic or toxin-producing bacteria. An investigation examined the effectiveness of three novel bacteriophages in a neutropenic murine model of carbapenemase-producing *Klebsiella pneumoniae* (KPC) gastrointestinal colonization, translocation, and disseminated infection.³⁸ Treatment with the phage cocktail administered via intraperitoneal injection significantly reduced renal KPC colony-forming units. The combination of bacteriophage therapy with the antibiotic ceftazidime-avibactam produced a synergistic effect, resulting in greater bacterial reduction than either agent alone.³⁸

Table 1 Key differences between CKD trial populations and cirrhosis with HRS

Parameter	CKD (trial populations)	Cirrhosis with HRS
Primary pathophysiology	Glomerular/tubular disease of various etiologies	Functional vasoconstriction + potential toxin injury
Baseline IS/PCS levels	Elevated due to reduced clearance	Variable; production increased but clearance often preserved until late
Liver function	Normal	Severely impaired
Coagulopathy	Absent	Universal (INR elevated)
Risk of SBP/encephalopathy	None	Substantial
Gastrointestinal transit	Normal	Often altered

Important limitations: This study modeled KPC infection with direct renal seeding—a fundamentally different pathophysiology from HRS, which is not primarily an infectious process. The mice were neutropenic, which does not accurately model the complex immune dysfunction of cirrhosis. The outcome measured was renal bacterial burden, not IS/PCS levels or creatinine-based renal function.

Furthermore, the phage cocktail was administered intraperitoneally, which has no direct relevance to reducing gut colonization or preventing uremic toxin absorption. Therefore, while this study demonstrates proof-of-concept for phage therapy in treating KPC infection, its direct relevance to the gut-kidney axis in HRS remains uncertain.

AST-120: adsorbent therapy

AST-120 (Kremezin) is an oral spherical carbon adsorbent that binds uremic toxin precursors in the intestinal lumen, preventing their absorption and subsequent conversion to sulfated toxins. The randomized controlled trial discussed above provides evidence that AST-120 monotherapy significantly reduces serum IS levels in patients with CKD.³⁷ However, AST-120 has not been specifically studied in cirrhotic patients with or at risk for HRS, and its effects on clinical outcomes including HRS prevention remain unknown.

Other interventions and emerging approaches

Dietary interventions represent another approach to modulating the gut-kidney axis. The “diet-microbiota-drug” triad suggests that dietary modifications can influence the composition and function of the gut microbiota.⁷ Low-protein diets reduce substrate available for uremic toxin production but may increase the risk of sarcopenia in patients with cirrhosis. Plant-based, low-tryptophan diets have been studied in small trials and shown to reduce IS levels without worsening nitrogen balance, but larger studies are needed. Fecal microbiota transplantation (FMT) involves the transfer of stool from a healthy donor to a recipient. FMT carries risks in patients with cirrhosis, including the potential for introducing pathogenic organisms and procedural complications. Encapsulated, donor-screened FMT is being tested in clinical trials.³⁹ Until results from these trials are available, defined synbiotics with characterized bacterial strains may represent a safer approach for investigation in cirrhotic populations.

Addressing the hemodynamic versus microbial paradox

A critical question arises from the proposed framework: if gut-derived uremic toxins are major contributors to HRS, why does liver transplantation rapidly reverse HRS before significant changes in gut microbiota occur? Similarly, why does terlipressin—which does not reduce IS or PCS levels—achieve renal recovery in 50-70% of HRS patients?

These observations do not invalidate a role for microbial toxins but rather suggest a hierarchical relationship between hemodynamic and microbial mechanisms. Liver transplantation corrects portal hypertension and the hyperdynamic circulation within days, restoring renal perfusion pressure. This rapid hemodynamic improvement may be sufficient to reverse functional renal impairment even if toxin-induced tubular injury remains. However, in patients with more advanced or prolonged HRS, toxin-mediated tubular damage may become irreversible, explaining why some patients fail to respond to vasoconstrictors.

A more nuanced interpretation is that uremic toxins reduce **renal functional reserve**—the capacity of the kidneys to maintain filtration despite reduced perfusion. This reduction makes the kidneys more vulnerable to hemodynamic challenges, such that a modest decrease in renal perfusion that would normally be well-tolerated may precipitate HRS. Vasoconstrictors address the hemodynamic trigger, but if toxin-induced damage has sufficiently reduced functional reserve, even restored perfusion may be insufficient for full recovery. This model is hypothesis-generating and requires direct testing in appropriately designed studies.

An integrated pathophysiological model: dual-hit hypothesis

A dual-hit model for HRS that integrates hemodynamic and microbial mechanisms has been proposed within the gut-liver-kidney

axis framework.⁷ Similar “two-hit” models have been described for acute kidney injury in cirrhosis, and this framework builds upon that foundation.⁴

The **first hit (hemodynamic)** consists of splanchnic arterial vasodilation driven by portal hypertension and the release of vasodilatory mediators including nitric oxide and tumor necrosis factor- α . This vasodilation reduces effective arterial blood volume, activating the renin-angiotensin-aldosterone system and the sympathetic nervous system, which causes renal vasoconstriction and mild renal hypoperfusion. The first hit alone rarely causes overt HRS unless severe, because the kidneys have substantial functional reserve.

The **second hit (microbial)** consists of gut dysbiosis leading to elevated levels of IS, PCS, and other microbial metabolites. These metabolites cause direct tubular injury through oxidative stress mechanisms, organic anion transporter inhibition, promotion of fibrosis, and induction of inflammatory responses. The cumulative effect is a reduction in renal functional reserve. When the second hit amplifies the first hit, the reduced renal functional reserve means that the kidneys are less able to compensate for hemodynamic challenges. A relatively modest reduction in renal perfusion that would normally be well-tolerated may then precipitate a decline in glomerular filtration rate, manifesting clinically as HRS. Importantly, vasoconstrictors address the first hit but do not remove uremic toxins or repair toxin-induced tubular injury. Microbiome-directed therapies potentially address the second hit. The optimal strategy, if this model is validated, may be combination therapy that simultaneously addresses both hits. However, this model remains hypothetical and requires prospective validation in clinical trials.

Future directions and unanswered questions

Mechanistic uncertainties

Current evidence does not clearly establish whether uremic toxins directly damage glomeruli in addition to their well-documented effects on proximal tubular epithelial cells. A single-nucleus RNA sequencing study of human kidney biopsies from cirrhotic patients with and without HRS would help map cell-type-specific toxin responses and identify the earliest sites of injury.

Safety considerations for emerging therapies

Fecal microbiota transplantation carries risks of infection in patients with cirrhosis, who often have impaired immune function and increased intestinal permeability. Regarding phage therapy, a safety study showed mild hepatic and renal congestion following intravenous administration, suggesting that the route of administration requires careful consideration.⁴⁰ The observation that intranasal administration was associated with fewer adverse effects than intravenous administration indicates that topical or localized administration may be preferred.

Clinical trial priorities

A definitive multicenter randomized controlled trial comparing terlipressin plus albumin plus synbiotic versus terlipressin plus albumin alone in HRS type 1 is needed. However, prior to such a trial, pilot studies in cirrhotic patients without HRS are necessary to establish the safety, tolerability, and basic efficacy of synbiotic therapy in this population. Such pilot studies should include measurement of IS and PCS levels as secondary outcomes and collect fecal samples for metagenomic analysis to identify microbial determinants of treatment response. Other priority investigations include studies of AST-120 in cirrhotic patients with elevated IS levels and studies of dietary interventions in patients at high risk for HRS development.

Proposed clinical trial design for future research

For investigators considering definitive trials, the following elements should be considered:

- a) **Population:** Cirrhotic patients with HRS type 1 (rapidly progressive renal failure)
- b) **Intervention:** Synbiotic or AST-120 added to standard terlipressin plus albumin
- c) **Control:** Standard therapy plus matching placebo
- d) **Primary outcome:** Reversal of HRS (defined as serum creatinine <1.5 mg/dL)
- e) **Secondary outcomes:** 30-day mortality, need for renal replacement therapy, changes in IS/PCS levels, changes in gut microbial composition
- f) **Sample size:** Approximately 200 patients per group to detect a 20% absolute improvement in HRS reversal (power 80%, alpha 0.05)
- g) **Exclusion criteria:** Active infection, prior liver transplantation, dialysis dependence

Limitations

This review has several important limitations that must be acknowledged.

First, most intervention trials discussed in this review include fewer than 50 patients and were conducted in chronic kidney disease populations, not cirrhosis with HRS. Extrapolation from CKD to HRS is not scientifically justified without explicit caveats, which this review has provided in Section 6.1 and Table 1.

Second, no human renal biopsy data currently confirm microbial metabolite-induced injury specifically in cirrhosis. The mechanistic evidence for IS- and PCS-mediated injury comes primarily from cell culture studies, animal models, and studies in other patient populations such as CKD.

Third, diuretics such as spironolactone and furosemide, which are commonly used to manage ascites in cirrhosis, alter gut transit time and may directly affect the composition of the gut microbiota. Similarly, lactulose, used for encephalopathy prevention, alters gut microbial composition. No study cited has adequately controlled for these medications.

Fourth, endotoxemia from bacterial translocation is a well-established mechanism of renal injury in cirrhosis. Lipopolysaccharide (LPS) causes renal vasoconstriction, inflammation, and direct tubular injury. The effects attributed to IS and PCS could be partially or fully mediated by LPS, which was not measured in most cited studies.

Fifth, as a narrative review rather than a systematic review, we did not perform formal bias assessment using tools such as ROBINS-I for cohort studies or the Cochrane Risk of Bias tool for randomized controlled trials. A systematic review with PROSPERO registration would be needed to draw definitive conclusions about effect sizes.

Sixth, the field suffers from publication bias, as positive studies are more likely to be published than negative studies. The negative studies cited in Section 5.3 (Jiang et al., Chaplin et al., Wang et al.) are exceptions that may not represent the full scope of unpublished null findings.

Seventh, no study exceeds six months of follow-up, so the long-term safety of microbiome-directed therapies is unknown.

Conclusion

The Enteric Microbiota-Kidney Axis represents a testable conceptual framework that expands the classical understanding of hepatorenal syndrome. By identifying specific microbial metabolites—indoxyl sulfate and p-cresyl sulfate—as potential direct nephrotoxins, supported by mechanistic studies elucidating the role of AhR activation, Nrf2 downregulation, and NOX4-mediated oxidative stress, this framework opens new avenues for investigation.

The evidence for compositional changes in the gut microbiota of patients with cirrhosis is robust, with consistent findings across multiple studies of depletion of butyrate-producing genera and enrichment of potentially pathogenic Proteobacteria. The progressive decline in microbial diversity from chronic hepatitis to cirrhosis to hepatocellular carcinoma suggests that gut dysbiosis worsens with disease progression.

However, it is critical to emphasize that none of the therapeutic strategies discussed—synbiotics, AST-120, or phage therapy—have been tested specifically in cirrhotic patients with or at risk for HRS. The extrapolation from CKD and animal infection models to HRS is promising but unproven. Furthermore, negative studies and meta-analyses have not demonstrated benefit for microbiome-directed therapy in cirrhosis, and the association between uremic toxins and HRS may be explained by reverse causation or confounding by disease severity. The observation that liver transplantation and terlipressin effectively reverse HRS without directly targeting the gut microbiota suggests that hemodynamic mechanisms remain the dominant pathogenic pathway. Microbial toxins, if they play a role, likely act as a permissive or amplifying factor that reduces renal functional reserve rather than as a primary driver of HRS.

Until rigorous randomized controlled trials are completed in cirrhotic populations specifically, microbiome-directed therapies remain investigational and should not replace standard care. The optimal approach to managing HRS continues to be early diagnosis, treatment of the underlying liver disease where possible, vasoconstrictor therapy with terlipressin or norepinephrine combined with albumin infusion, and consideration of liver transplantation in eligible patients. The Enteric Microbiota-Kidney Axis framework provides a roadmap for future research that may ultimately expand the therapeutic armamentarium for this devastating condition.

Conflict of interest

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