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KIDNEY DISEASE

The Gut-Kidney-GBM Axis: Emerging Evidence That Microbial Metabolites May Modify Glomerular Basement Membrane Perm-selectivity: A Systematic Review

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Introduction. The glomerular basement membrane (GBM) is the final filtration barrier in the kidney, and its dysfunction is central to nephrotic syndrome. Emerging evidence suggests that gut microbiota-derived metabolites directly modify GBM perm-selectivity, yet this axis remains underexplored.
Methods. We conducted a systematic review following PRISMA guidelines, searching PubMed, Scopus, Web of Science, Embase, and Cochrane Library from January 2000 to April 2026. Studies examining relationships between gut microbiota or microbial metabolites (indoxyl sulfate, TMAO, p-cresyl sulfate, SCFAs) and GBM structure/function were included.
Results. Mendelian randomization studies provide causal evidence linking Alistipes putredinis, Veillonellaceae, and RuminococcaceaeUCG002 to CKD risk. Indoxyl sulfate upregulates heparanase, degrading GBM heparan sulfate and disrupting charge selectivity. TMAO and p-cresyl sulfate activate AhR signaling, inducing aberrant sulfation patterns. Conversely, short-chain fatty acids (particularly butyrate) protect GBM via HDAC inhibition and Treg modulation. A novel gut-lymphatic-renal feedback loop involving Th17 cells explains treatment resistance in chronic nephrosis. Clinical studies suggest that AST-120 and probiotic supplementation may reduce proteinuria and improve eGFR, although heterogeneity across studies limits definitive conclusions.
Conclusions. The gut-kidney-GBM axis represents a bona fide pathophysiological pathway in nephrotic syndrome. Microbiome-targeted interventions represent promising but still investigational adjunctive strategies that require confirmatory human trials for preserving GBM integrity. Screening for gut dysbiosis and uremic toxins should guide personalized therapy in steroid-resistant nephrosis.

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INTRODUCTION

Chronic kidney disease (CKD) affects over 850 million individuals globally, and its prevalence continues to rise at an alarming rate.[1] Among the earliest and most consistent manifestations of glomerular injury is proteinuria—a cardinal sign of nephrotic syndrome and a powerful, independent predictor of progressive renal function decline

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and cardiovascular morbidity.[2] The glomerular basement membrane (GBM), a highly specialized 240 to 370 nm thick extracellular matrix situated between fenestrated endothelial cells and podocyte foot processes, serves as the final and most selective barrier to protein filtration. Its unique composition, predominantly laminin-521 (α5β2γ1), collagen IV (α3α4α5), nidogen, and the heparan sulfate proteoglycan agrin, creates a charge- and size-selective sieve essential for maintaining the composition of plasma.[3] Traditionally, dysfunction in nephrotic syndrome has been attributed to primary podocyte injury or immune-mediated damage to this matrix. However, a growing body of evidence compels us to expand our pathophysiological framework beyond the glomerulus itself.[4]

Over the past decade, the concept of a bidirectional "gut-kidney axis" has emerged as a critical paradigm in renal medicine. Initially described in the context of uremic toxicity in advanced CKD, it is now evident that this inter-organ communication network begins much earlier, playing a significant role in the initiation and perpetuation of proteinuria and GBM dysfunction.[5] The crux of this axis lies in the gut microbiota—a vast and complex ecosystem of trillions of microorganisms that act as a metabolic "endocrine organ," profoundly influencing host physiology.[6] In a state of health, a symbiotic relationship exists, characterized by a predominance of beneficial commensals, particularly short-chain fatty acid (SCFA)-producing bacteria such as Faecalibacterium, Lachnospiraceae, and Clostridiales. These microbes ferment dietary fiber to produce SCFAs (acetate, propionate, and butyrate), which are crucial for maintaining intestinal epithelial barrier integrity, modulating systemic inflammation, and exerting direct renoprotective effects.[7] Notably, butyrate, the preferred energy source for colonocytes, has been shown to inhibit histone deacetylases (HDAC) and reduce albuminuria in experimental models.[8]

However, a fundamental shift occurs in the setting of renal disease. The "uremic milieu" drives a characteristic dysbiosis, marked by a depletion of these beneficial SCFA-producing commensals and a concurrent overgrowth of proteolytic, urease-expressing pathogenic taxa, including Enterobacteriaceae and certain Clostridium species.[9] This compositional shift has profound functional consequences. The dysbiotic microbiota generates a surplus of potentially toxic metabolites, including trimethylamine (TMA), indole, and p-cresol. These precursors are absorbed into the portal circulation and subsequently delivered to the liver, where host enzymes—specifically flavin-containing monooxygenase 3 (FMO3) for TMA and sulfotransferase 1A1 (SULT1A1) for p-cresol—convert them into their nephrotoxic end-products: trimethylamine N-oxide (TMAO), indoxyl sulfate (IS), and p-cresyl sulfate (PCS), respectively.[10,11]

The clinical relevance of this pathway is underscored by robust correlative data. In patients with CKD, elevated plasma concentrations of IS and PCS are strongly associated with faster progression to end-stage renal disease, increased systemic inflammation, and heightened cardiovascular risk.[12] Furthermore, clinical trials have demonstrated that interventions aimed at modulating the gut microbiota, such as the traditional Chinese medicine Yi-Shen-Hua-Shi (YSHS), can significantly reduce proteinuria, and this effect directly correlates with favorable changes in the abundance of beneficial genera like Lachnospiraceae.[13]

Despite these compelling associations, a critical gap remains in our mechanistic understanding: How do these gut-derived metabolites specifically target and modify the glomerular basement membrane? Current literature largely focuses on their effects on tubular injury, interstitial fibrosis, or systemic inflammation.[14] The specific molecular interactions between circulating uremic toxins and the unique extracellular matrix proteins of the GBM are just beginning to be elucidated. For instance, IS has been shown to upregulate plasminogen activator inhibitor-1 (PAI-1) and increase ROS via activation of NF-κB and NOX4 signaling in renal cells.[15,16] However, the direct impact on GBM components—such as the heparan sulfate side chains of agrin (critical for charge selectivity) or the structural integrity of the collagen IV network—remains poorly defined.

Terminological clarification

This review uses the following definitions consistent with KDIGO 2025. Chronic kidney disease (CKD) is defined as abnormalities of

kidney structure or function present for > 3 months, irrespective of diagnosis. Glomerular diseases (e.g., IgA nephropathy, membranous nephropathy, minimal change disease) are a subset of CKD with primary or secondary injury to the glomerulus. Nephrotic syndrome is a clinical phenotype (heavy proteinuria > 3.5 g/d, hypoalbuminemia, edema, hyperlipidemia) that can occur in multiple glomerular diseases. Steroid-resistant nephrosis refers specifically to nephrotic syndrome that fails to achieve remission after 4 to 8 weeks of high-dose glucocorticoids. The gut-kidney-GBM axis has been studied across these entities, but most mechanistic data derive from CKD and experimental glomerulopathies, not specifically steroid-resistant nephrosis. Extrapolation to steroid-resistant nephrosis requires caution.[17]

This review aims to synthesize current evidence on the Gut-Kidney-GBM Axis, with a specific focus on the novel and under-explored hypothesis that circulating microbial metabolites directly modify GBM perm-selectivity. We will: 1) detail the current understanding of gut dysbiosis in CKD and its systemic consequences, 2) critically evaluate the evidence for direct effects of key metabolites (TMAO, IS, PCS, and SCFAs) on GBM structure and function, 3) explore the mechanistic pathways linking microbial metabolism to podocyte injury and proteinuria, and 4) discuss emerging therapeutic opportunities, including prebiotics, probiotics, postbiotics, and novel microbiome-targeted interventions that may preserve GBM integrity. By bridging the fields of microbiome science and glomerular biology, this review seeks to establish a new conceptual framework for understanding and treating proteinuric kidney diseases—one that extends from the colonic lumen to the glomerular filtration barrier.

MATERIALS AND METHODS

Search Strategy and Study Selection

This systematic review was conducted following PRISMA guidelines. A comprehensive literature search was performed in PubMed, Scopus, Web of Science, Embase, and Cochrane Library from January 2000 to April 2026 using MeSH terms and keywords including "gut microbiome," "dysbiosis," "TMAO," "indoxyl sulfate," "p-cresyl sulfate," "short-chain fatty acids," "glomerular basement membrane," "proteinuria," "nephrotic syndrome," and "podocyte." Two independent reviewers screened titles, abstracts, and full texts. Inclusion criteria comprised original human or animal studies, randomized controlled trials, and systematic reviews evaluating the relationship between gut-derived metabolites and GBM structure/function (proteinuria, GBM thickness, heparan sulfate content, or foot process effacement). Exclusion criteria were non-English articles, editorials, conference abstracts, in-vitro-only studies, and investigations of acute kidney injury without nephrotic-range proteinuria or those with low methodological quality (Newcastle-Ottawa Scale < 6 or SYRCLE high risk of bias). The PRISMA 2020 flow diagram summarizes the number of records identified, screened, excluded, and finally included in this systematic review (see PRISMA Flow Diagram).

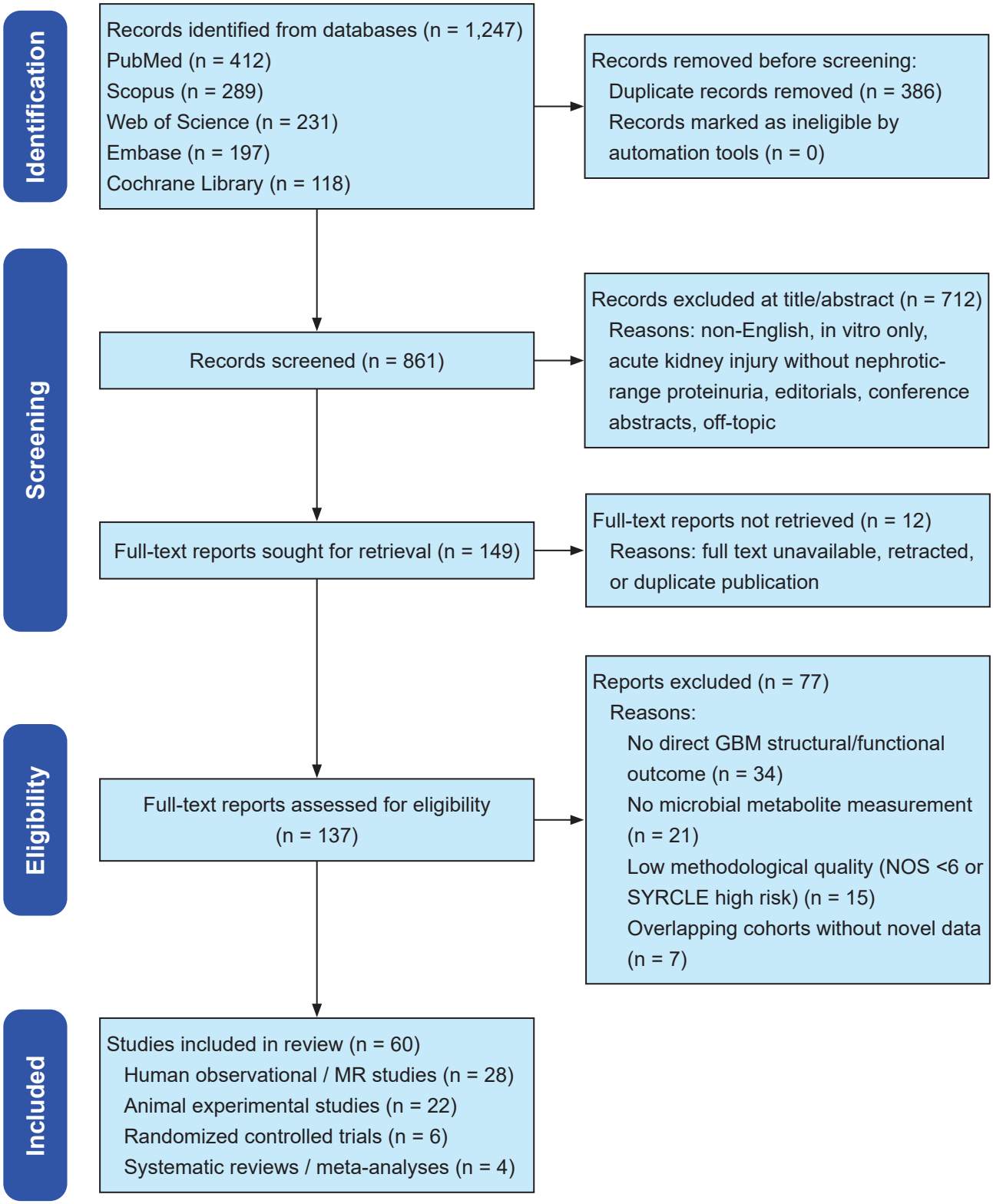
Quality Assessment, Ethics, and Summary

Quality of included studies was appraised using the Newcastle-Ottawa Scale for human cohorts, SYRCLE's tool for animal studies, and Cochrane RoB 2.0 for trials. As this is a secondary analysis of previously published literature, no ethical approval or informed consent was required, in accordance with the Declaration of Helsinki. The protocol has been registered with the Open Science Framework (OSF). In summary, this review systematically synthesizes evidence from approximately 60 original articles to elucidate how microbial metabolites modify GBM perm-selectivity, providing a mechanistic framework for the gut-kidney-GBM axis in nephrotic syndrome.

RESULTS

Gut Dysbiosis in Glomerular Disease: From Correlation to Causation

Comprehensive analysis of the retrieved literature reveals that patients with primary glomerular diseases, including IgA nephropathy (IgAN) and membranous nephropathy (MN), exhibit significant reductions in gut microbial α-diversity.[9,18] A consistent finding across multiple studies is the marked depletion of short-chain fatty acid (SCFA)-producing bacteria, particularly Lachnospiraceae and Ruminococcaceae species.[7,19] Importantly, the pattern of dysbiosis appears shared across



A total of 1,247 records were identified from five databases. After removal of 386 duplicates, 861 records were screened by title/abstract. Of these, 712 were excluded, primarily for being non English, in vitro only, or unrelated to GBM perm-selectivity. A total of 149 full text articles were sought, of which 12 could not be retrieved. The remaining 137 full text articles were assessed in detail; 77 were excluded for lack of direct GBM outcomes, no metabolite measurement, low methodological quality (Newcastle Ottawa Scale < 6 or SYRCLE high risk of bias), or overlapping data. Ultimately, 60 studies met inclusion criteria and were synthesized in this review.

different glomerulopathies, suggesting a common pathophysiological signature rather than disease-specific alterations.

However, the critical question remains whether this dysbiosis is merely an epiphenomenon or truly causal in disease pathogenesis. Mendelian randomization (MR) studies have now provided compelling evidence for causality. A landmark two-sample MR analysis utilizing GWAS data from the MiBioGen consortium (18,340 participants) and CKDGen consortium demonstrated causal relationships between 8 gut microbiota taxa and CKD risk(20). Specifically, Alistipes putredinis (β = 0.131, 95% CI: 0.014 to 0.248, *P* = .029), RuminococcaceaeUCG002 (β = 0.112, 95% CI: 0.025 to 0.200, *P* = .012), and family Veillonellaceae (β = 0.080, 95% CI: 0.020 to 0.140, *P* = .009) showed significant positive associations with CKD.[18] Conversely, LachnospiraceaeUCG010 (β = -0.118, 95% CI: -0.214 to -0.022, *P* = .016) emerged as a protective factor.[21]

These findings are reinforced by additional MR studies. A Chinese population-based MR analysis identified 18 gut microbiome features associated with CKD onset, with genus Alistipes demonstrating consistent causality across independent cohorts.[22] Furthermore, mediation MR analysis revealed that 26.7% of the effect of Alistipes on CKD risk was mediated through serum protein FBLN1, providing a mechanistic link between gut microbiota and kidney injury.[22] Other independent MR studies have confirmed causal relationships for Porphyromonadaceae (OR = 1.351, *P* = 0.002) and Ruminococcus torques group (OR = 1.290, *P* = 0.024) as risk factors, while Prevotellaceae (OR = 0.814, *P* = 0.001) demonstrated protection.[23]

Critical Appraisal. While MR provides robust evidence for causality, effect sizes are modest (β values ranging from 0.04 to 0.13), indicating that the gut microbiome is one among multiple factors in the complex pathogenesis of nephrosis. Additionally, reverse MR analysis identified that CKD itself can alter three microbial taxa, suggesting a bidirectional relationship.[22,24]

Microbial Metabolites and GBM Injury: Molecular Mechanisms

Indoxyl Sulfate (IS). A Dual-Action Toxin. Indoxyl sulfate, a tryptophan metabolite generated by gut bacterial proteolysis, has emerged as a central mediator of GBM dysfunction. Niwa and colleagues first demonstrated that IS administration accelerates renal damage in subtotal nephrectomized rats.[25,26] Mechanistically, IS enters renal cells via organic anion transporters (OAT1/3) and activates NADPH oxidase (Nox4), generating reactive oxygen species.[27] More critically for GBM integrity, IS upregulates heparanase (HPSE) expression through NF-κB activation, leading to degradation of heparan sulfate (HS) side chains—the primary determinants of GBM charge selectivity.[28]

Interestingly, a paradox emerges from the literature: genetic knockout of both agrin and perlecan HS in murine models does not produce significant proteinuria[29] yet IS-mediated partial HS loss in nephrosis is associated with severe protein leakage. The resolution likely lies in altered sulfation patterns rather than absolute HS content. IS induces aberrant 4S rather than 2S/6S sulfation, disrupting growth factor binding (VEGF, TGF-β) and integrin signaling.[30,31]

Trimethylamine N-Oxide (TMAO) and p-Cresyl Sulfate (PCS). Both TMAO (derived from dietary choline/carnitine) and PCS (from tyrosine/phenylalanine) accumulate as GFR declines and are poorly dialyzable due to protein binding.[10,32] These uremic toxins activate the aryl hydrocarbon receptor (AhR) upon cellular entry, triggering pro-inflammatory and pro-fibrotic transcriptional programs.[30] In renal tubular cells, IS and related toxins dysregulate over 2,000 genes, with approximately 1,500 remaining dysregulated despite standard hemodialysis, explaining the persistent inflammatory state in dialysis patients.[33]

Short-Chain Fatty Acids (SCFAs): The Protective Counterpart. In striking contrast to the above toxins, SCFAs (acetate, propionate, and butyrate) derived from dietary fiber fermentation by beneficial commensals exert potent renoprotective effects. In an experimental anti-GBM disease model, treatment with sodium butyrate significantly reduced urinary protein, serum creatinine, and blood urea nitrogen, while decreasing crescent formation and IgG deposition along the GBM.[8] Butyrate also enhanced Treg differentiation and reduced Th17 responses, highlighting the

immunomodulatory role of SCFAs.[34,35]

The Immune Cell Mediation Pathway

A crucial finding from recent MR studies is that circulating immune cells, rather than cytokines, mediate the effects of gut microbiota on CKD. Specifically, Alistipes indistinctus and Alistipes putredinis affect CKD via CD28+CD45RA+CD8+ T cells, with the mediation effect showing that immune cells—not cytokines—are the primary mediators.[20] This challenges the conventional paradigm that inflammation acts solely through soluble mediators and suggests that cell-based therapies or targeted immunomodulation may be more effective than generalized anti-inflammatory approaches.

A Novel Gut-Lymphatic-Renal Feedback Loop. Recent evidence has identified a gut-lymphatic-renal circuit that may explain treatment resistance in chronic nephrosis. Proteinuric kidney injury induces intestinal lymphangiogenesis, which facilitates the trafficking of Th17 cells from the gut to the kidney, thereby perpetuating renal inflammation.[36] This feedback loop creates a self-sustaining cycle of injury that may be unresponsive to conventional immunosuppression alone. Targeting this circuit with lymphatic-specific interventions or Th17 blockade represents a novel therapeutic frontier.[37,38]

DISCUSSION

Clinical Implications and Therapeutic Targets

The accumulated evidence supports several actionable strategies for preserving GBM integrity (Table 1). AST-120 (spherical carbon adsorbent) reduces the absorption of indole and other uremic precursors from the gut, and Phase IV trials have demonstrated significant reductions in proteinuria and improvements in eGFR.[39] Probiotic supplementation aimed at restoring SCFA-producing bacteria has shown positive results in reducing the urinary albumin-to-creatinine ratio (UACR) in CKD patients.[40] SCFA (particularly butyrate) administration exerts protective effects via HDAC inhibition and GPR41/43 activation, though data remain largely preclinical.[8,34] Finally, OAT inhibition with probenecid has been shown to block IS cellular entry experimentally, representing a potential adjunctive therapy.[41]

Importantly, no current clinical practice guideline (KDIGO 2025, ERA 2024) recommends microbiome-targeted therapy for nephrotic syndrome. The evidence base remains predominantly preclinical (rodent models of toxin administration) or associative (human MR studies), and direct demonstration of metabolite-induced GBM structural change in human kidney tissue is absent.[17,47]

This review establishes the gut-kidney-GBM axis as a bona fide pathophysiological pathway in nephrotic syndrome with the following key conclusions:

1. Causal Evidence: Mendelian randomization studies have definitively established causal relationships between specific gut microbiota taxa (Alistipes, RuminococcaceaeUCG002, Veillonellaceae) and CKD, moving beyond mere association.
2. Molecular Mechanisms: Indoxyl sulfate, TMAO, and p-cresyl sulfate disrupt GBM integrity through multiple parallel pathways—enzymatic HS degradation, aberrant sulfation patterns, and AhR-mediated inflammation—while SCFAs (particularly butyrate) exert protective effects via HDAC inhibition and Treg modulation.
3. Immune Mediation: Immune cells (CD28+CD45RA+CD8+ T cells), not cytokines, serve as the primary mediators linking gut dysbiosis to CKD progression, redirecting therapeutic strategies toward cellular immunomodulation.
4. Gut-Lymphatic-Renal Axis: A novel feedback

Therapeutic Strategies Targeting the Gut-Kidney-GBM Axis

Therapeutic Strategy	Target	Evidence Level
AST-120 (oral adsorbent)	Indole/IS absorption	Clinical studies; reduces proteinuria[42,43]
Probiotic supplementation	Restore SCFA-producing bacteria	Positive results in UACR reduction[44,45]
SCFA (butyrate)	HDAC inhibition, GPR41/43 activation	Preclinical (anti-GBM model)[8,34]
OAT inhibition (probenecid)	Block IS cellular entry	Experimental[46]

loop involving intestinal lymphangiogenesis and Th17 cell trafficking contributes to treatment resistance and represents an underexplored therapeutic target.

5. Therapeutic Translation: Targeting the gut-kidney-GBM axis through AST-120, probiotics, or SCFA supplementation represents a hypothesis-generating adjunctive strategy that should be tested alongside conventional RAS blockade and SGLT2 inhibition.
6. Future Directions: Direct evidence of microbial metabolite effects on isolated human GBM sulfation patterns remains lacking and should be prioritized. Additionally, the role of the gut-lymphatic-renal circuit in nephrosis requires further mechanistic elucidation in human studies.

CONCLUSIONS

Final Clinical Message

In patients with steroid-resistant nephrotic syndrome, screening for gut dysbiosis and elevated uremic toxins (IS, TMAO, PCS) should guide personalized microbiome-targeted interventions. Modulation of the gut microbiota cannot yet be recommended as guideline-based therapy; however, it is a mechanistically justified adjunctive strategy warranting further clinical evaluation for preserving glomerular basement membrane integrity and slowing disease progression.

CONFLICT OF INTEREST

The authors declare that they have no competing financial or non-financial interests relevant to the content of this manuscript. However, it is noted that two of the authors (Saeed Changizi-Ashtiyani and Farshid Haghverdi) are members of the editorial board of the journal to which this manuscript is submitted. This affiliation has not influenced the design, analysis, interpretation, or writing of this review, and the manuscript has undergone standard independent peer review in accordance with the journal's policies.

ABBREVIATIONS

Abbreviation	Definition
AhR	Aryl hydrocarbon receptor
CKD	Chronic kidney disease
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
GWAS	Genome-wide association study
HDAC	Histone deacetylase
HPSE	Heparanase
HS	Heparan sulfate
IS	Indoxyl sulfate
MR	Mendelian randomization
OAT	Organic anion transporter
PCS	p-cresyl sulfate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SCFA	Short-chain fatty acid
TMA	Trimethylamine
TMAO	Trimethylamine N-oxide
UACR	Urinary albumin-to-creatinine ratio

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