

Gut microbiota in patients receiving dialysis: Mechanisms, complications and the road to personalized microbiome-based care (Review)

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Abstract. Gut dysbiosis is increasingly recognized as a potential contributor to poor outcomes in patients receiving dialysis, yet its mechanistic complexity and therapeutic implications remain incompletely understood in clinical practice. The uremic environment, dietary restrictions, polypharmacy and dialysis modality-specific factors collectively reshape the gut microbial ecology, promoting the overproduction of deleterious metabolites such as indoxyl sulfate, p-cresyl sulfate and trimethylamine N-oxide while depleting protective short-chain fatty acids. These alterations compromise intestinal barrier integrity, fuel systemic inflammation through endotoxemia and NOD-like receptor family pyrin domain containing 3 inflammasome activation and have been associated with cardiovascular disease, immune dysfunction, peritonitis, protein-energy wasting and cognitive impairment. Although probiotic, prebiotic, synbiotic and dietary interventions show promise, heterogeneous responses across trials underscore the inadequacy of one-size-fits-all strategies. Multi-omics

profiling has revealed substantial interindividual variability in microbial composition and metabolic capacity, providing a rationale for personalized approaches. The present review synthesizes current evidence on the mechanisms underlying dysbiosis and complications in patients receiving dialysis and proposes a roadmap toward personalized microbiome-based care to improve clinical outcomes.

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Abbreviations: 16S rRNA, 16S ribosomal RNA; CKD, chronic kidney disease; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; FMT, fecal microbiota transplantation; HD, hemodialysis; IS, indoxyl sulfate; LPS, lipopolysaccharide; NLRP3, NOD-like receptor family pyrin domain containing 3; PCS, p-cresyl sulfate; PD, peritoneal dialysis; PEW, protein-energy wasting; RAS, renin-angiotensin system; RS, resistant starch; SCFAs, short-chain fatty acids; TMAO, trimethylamine-N-oxide; AI, artificial intelligence; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCT, randomized controlled trial

Key words: gut microbiota, dysbiosis, dialysis, uremic toxins, inflammation, cardiovascular disease, multi-omics, personalized microbiome-based care

1. Introduction

End-stage kidney disease (ESKD) represents the final stage of chronic kidney disease (CKD), which affects millions of individuals worldwide and is associated with substantial morbidity and mortality despite advances in renal replacement therapy (1). Patients receiving dialysis constitute a particularly vulnerable population, experiencing cardiovascular event rates that exceed those of the general population and 5-year survival rates below those of numerous malignancies (2). Accumulating evidence has shifted the paradigm from viewing the kidney as an isolated filter organ toward recognizing the gut-kidney axis both as a critical determinant of systemic health in ESKD and as a bidirectional communication network wherein intestinal microbial communities and host physiology constantly interact (3,4). This bidirectional communication network

involves complex interactions between intestinal microbial communities and host physiology, wherein kidney dysfunction alters gut microbial ecology, and reciprocally, microbial metabolites influence systemic inflammation and cardiovascular risk. The conceptual foundation of the gut-kidney axis was established by a series of original studies over the past two decades. Evenepoel *et al* (5) provided a comprehensive overview establishing that protein-bound solutes such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS) originate from colonic microbial fermentation of aromatic amino acids. This colonic origin was definitively confirmed by Aronov *et al* (6), who demonstrated that these solutes were nearly absent in anephric patients without a colon, supporting their gut microbial provenance. Concurrently, Vaziri *et al* (7) performed the first systematic characterization of gut microbiota in chronic kidney disease, revealing notable compositional alterations and overgrowth of pathogenic bacteria. The clinical relevance of these metabolites was underscored by Barreto *et al* (8), who showed that serum IS levels independently predicted vascular disease and mortality, while Meijers *et al* (9) established that PCS levels were associated with cardiovascular risk. Mechanistically, Lekawanvijit *et al* (10) demonstrated that IS exerted direct toxic effects on cardiac fibroblasts and myocytes, providing a biological basis for the observed clinical associations. These foundational observations were formally synthesized into the 'gut-kidney axis' paradigm by Meijers and Evenepoel (11), which now serves as the conceptual framework for understanding microbiome-driven complications in patients receiving dialysis. This work forms the basis for the current understanding of microbiome-driven complications in dialysis patients.

Among the factors associated with poor outcomes in patients receiving dialysis, gut dysbiosis has emerged as a potential contributor. Lin *et al* (12) demonstrated in a prospective cohort of patients receiving hemodialysis (HD) that gut dysbiosis independently predicted all-cause mortality, with specific taxonomic shifts associating with inflammatory markers and adverse clinical events. This observation suggested that microbial alterations may influence prognosis. Furthermore, circulating microbial signatures have been linked to cardiovascular death in ESKD populations. Sumida *et al* (13) reported that elevated levels of gut-derived circulating lipopolysaccharide (LPS)-binding protein were associated with increased cardiovascular mortality, supporting an association between bacterial product translocation and vascular pathology in patients receiving dialysis.

A critical methodological consideration in interpreting the gut microbiome literature is the distinction between correlation and causation. Most studies in dialysis populations are cross-sectional or prospective observational in design, which can establish associations but cannot establish causality (12,14). The evidence hierarchy for microbiome-disease relationships typically progresses from descriptive taxonomic associations to mechanistic *in vitro* and animal model studies, followed by human intervention trials that test whether modulating the microbiome alters clinical outcomes (14). In the present review, the strength of evidence for each proposed mechanism is critically appraised, explicitly distinguishing findings supported by experimental validation (such as animal models or human intervention studies) from those that remain associative

(cross-sectional or observational). This evidence-based approach allows identification of knowledge gaps where causal inference is uncertain and highlights priority areas for future research. Cross-sectional studies, which constitute the majority of the human data reviewed, can identify associations but cannot establish temporal or causal relationships. Therefore, causal claims in the present review are limited to findings supported by experimental models (*in vitro* or animal studies) or human intervention trials; all cross-sectional and observational associations are presented as correlational and require prospective longitudinal validation.

The uremic environment fundamentally disrupts intestinal homeostasis through multiple converging mechanisms. Popkov *et al* (3) comprehensively reviewed how accumulating uremic toxins reshape gut microbial composition, favoring the expansion of bacteria harboring urease, uricase and indole-producing enzymes while suppressing beneficial commensals. Shi *et al* (15) subsequently performed metagenomic analysis in patients receiving HD, revealing marked enrichment of LPS biosynthesis pathways and bacterial secretion systems that may potentiate systemic inflammation. Conventional dialysis modalities inadequately address protein-bound uremic toxins derived from gut microbial metabolism, as these solutes bind to albumin and escape efficient diffusive removal (3,16). This fundamental limitation of current renal replacement strategies fails to interrupt the self-perpetuating cycle of dysbiosis-driven toxin accumulation.

Dialysis modality exerts independent and distinct effects on gut microbial ecology. Luo *et al* (17) directly compared patients receiving HD with those receiving peritoneal dialysis (PD), demonstrating that PD was associated with greater preservation of beneficial commensals, although both modalities exhibited marked dysbiosis relative to healthy controls. However, the mechanistic basis for these differences remains incompletely understood, and whether modality selection could be guided by baseline microbial profiles to optimize outcomes represents an unanswered question. Beyond uremia itself, the dialysis population faces unique dysbiosis drivers including dietary restrictions, polypharmacy and procedure-related factors. Martín-del-Campo *et al* (18) reviewed how protein-energy wasting (PEW), which affects a substantial proportion of patients receiving dialysis, interacts bidirectionally with gut microbial disturbances, creating a vicious cycle of nutritional decline and microbial dysfunction.

The clinical consequences of dysbiosis extend across multiple organ systems. Bao *et al* (19) established a relationship between gut microbiota composition and vascular calcification severity in patients receiving HD, identifying specific bacterial taxa associated with calcification risk. He *et al* (20) further demonstrated that higher serum trimethylamine-N-oxide levels were independently associated with increased abdominal aortic calcification, extending these findings to clinically relevant outcomes. The protein-bound uremic toxin PCS has been mechanistically implicated in cardiovascular injury. Chaves *et al* (21) showed that unconjugated p-cresol activates macrophage macropinocytosis leading to increased low-density lipoprotein uptake, providing cellular evidence for how gut-derived metabolites promote atherosclerotic pathology. Collectively, these findings suggest that dysbiosis-driven metabolite imbalance may contribute to

the accelerated cardiovascular disease observed in dialysis populations.

Despite observational evidence, translating these insights into clinical practice has proven challenging. Voroneanu *et al* (14) systematically reviewed gut microbiota modulation strategies in CKD, concluding that while probiotic, prebiotic and synbiotic interventions show promise, response heterogeneity across trials precludes definitive recommendations. Koshida *et al* (22) comprehensively characterized microbiome and metabolome profiles in patients with ESKD, emphasizing that interindividual variability in microbial composition and metabolic capacity likely underlies differential treatment responses. This heterogeneity supports the need for personalized microbiome-based care. Emerging evidence further implicates the gut-brain axis in dialysis-related cognitive dysfunction. Yu *et al* (23) recently reviewed research progress on the kidney-gut-brain axis in patients receiving maintenance HD, proposing that microbial metabolites including IS cross the blood-brain barrier and promote neuroinflammation, adding another layer of complexity to the clinical implications of dysbiosis.

Given these accumulating insights, the present review synthesizes current evidence on gut dysbiosis in patients receiving dialysis, critically evaluates mechanistic pathways linking microbial alterations to systemic complications and proposes a roadmap toward personalized microbiome-based care. Unlike previous narrative summaries, the present review specifically focuses on the unique context of dialysis, distinct from non-dialysis CKD, and integrates multi-omics discoveries with emerging therapeutic strategies. By identifying knowledge gaps and highlighting opportunities for precision interventions, the present review aimed to accelerate translation of microbiome research into improved outcomes for the dialysis population.

2. Drivers and landscape of gut dysbiosis in dialysis

Patients receiving dialysis are exposed to a unique constellation of dysbiosis drivers that extend beyond the uremic state and collectively reshape gut microbial ecology. These factors include uremic toxin accumulation, dietary restrictions, polypharmacy, dialysis modality-specific effects and procedure-related exposures. Understanding this multifactorial landscape is essential for identifying modifiable targets and interpreting the heterogeneous microbial alterations reported across studies. Fig. 1 provides an overview of the key drivers and their differential impacts on gut microbiota composition in HD vs. PD populations.

Uremic environment and intestinal barrier disruption. The uremic milieu fundamentally alters host-microbe interactions by promoting the overgrowth of toxin-producing bacteria while suppressing commensal populations. Davenport (24) demonstrated that more frequent HD does not effectively clear protein-bound azotemic solutes derived from gut microbial metabolism, indicating that conventional dialysis inadequately addresses the circulating toxin burden originating from the intestinal compartment. The accumulation of urea and other nitrogenous compounds in the intestinal lumen favors the expansion of urease-containing bacteria, which convert urea

into ammonia, raising luminal pH and further disrupting microbial homeostasis. Shi *et al* (15) identified notable alterations in gut microbial pathways and virulence factors in patients receiving HD, with enrichment of endotoxin biosynthesis and bacterial secretion systems that may potentiate systemic inflammation. The integrity of the intestinal epithelial barrier is progressively compromised in the uremic state, allowing luminal bacterial products such as LPS to translocate into the systemic circulation (25). This bidirectional relationship, whereby uremia drives dysbiosis and dysbiosis exacerbates toxin accumulation, establishes a self-perpetuating cycle that remains largely uninterrupted by standard dialysis care.

HD vs. PD: Distinct microbial signatures. Despite similar overall microbial diversity indices, evidence indicates that dialysis modality exerts independent and distinct effects on gut microbiota composition. In a comparative study, Stadlbauer *et al* (26) performed structural and functional analyses of gut microbiomes of patients receiving HD and those receiving PD and identified that PD was associated with greater alterations in both microbial diversity and compositional architecture compared with HD. Conversely, Chen *et al* (27) reported that patients receiving HD exhibited enrichment of Proteobacteria and Firmicutes, whereas patients receiving PD showed distinct taxonomic shifts that associated with dialysis vintage. Teixeira *et al* (28) compared patients receiving PD with their household contacts to control for environmental and dietary confounders, suggesting that PD-specific factors, rather than shared lifestyle elements, may contribute to unique microbial signatures. More recently, Voroneanu *et al* (29) characterized distinct gut microbiome signatures between HD and kidney transplant populations, emphasizing that the dialysis environment creates microbial alterations that are not simply reversed by transplantation. The superior removal of middle molecules in PD compared with HD may differentially impact circulating mediators that modulate gut microbial ecology, although the precise mechanisms remain incompletely elucidated (30).

Dietary restrictions, nutritional status and PEW. Dietary management in patients receiving dialysis involves stringent restrictions on phosphorus, potassium and fluid intake, often coupled with reduced protein consumption, all of which influence gut microbial substrate availability. Lin and Hung (31) conducted a case-control study examining the association between subjective global assessment of nutritional status and gut microbiota in patients receiving HD, demonstrating that malnourished individuals harbored reduced abundances of beneficial butyrate-producing genera. PEW, which affects a substantial proportion of the dialysis population, has been mechanistically linked to gut microbial alterations. Hu *et al* (32) identified a notable association between intestinal flora disruption and PEW in patients with ESKD, with depletion of short-chain fatty acid (SCFA) producers representing a consistent finding. In a longitudinal observational study, Bi *et al* (33) tracked gut microbiota changes in patients receiving HD with PEW over time and reported that microbial instability predicted worsening nutritional parameters, suggesting that dysbiosis may both result from and contribute to PEW pathogenesis. The relationship between nutritional

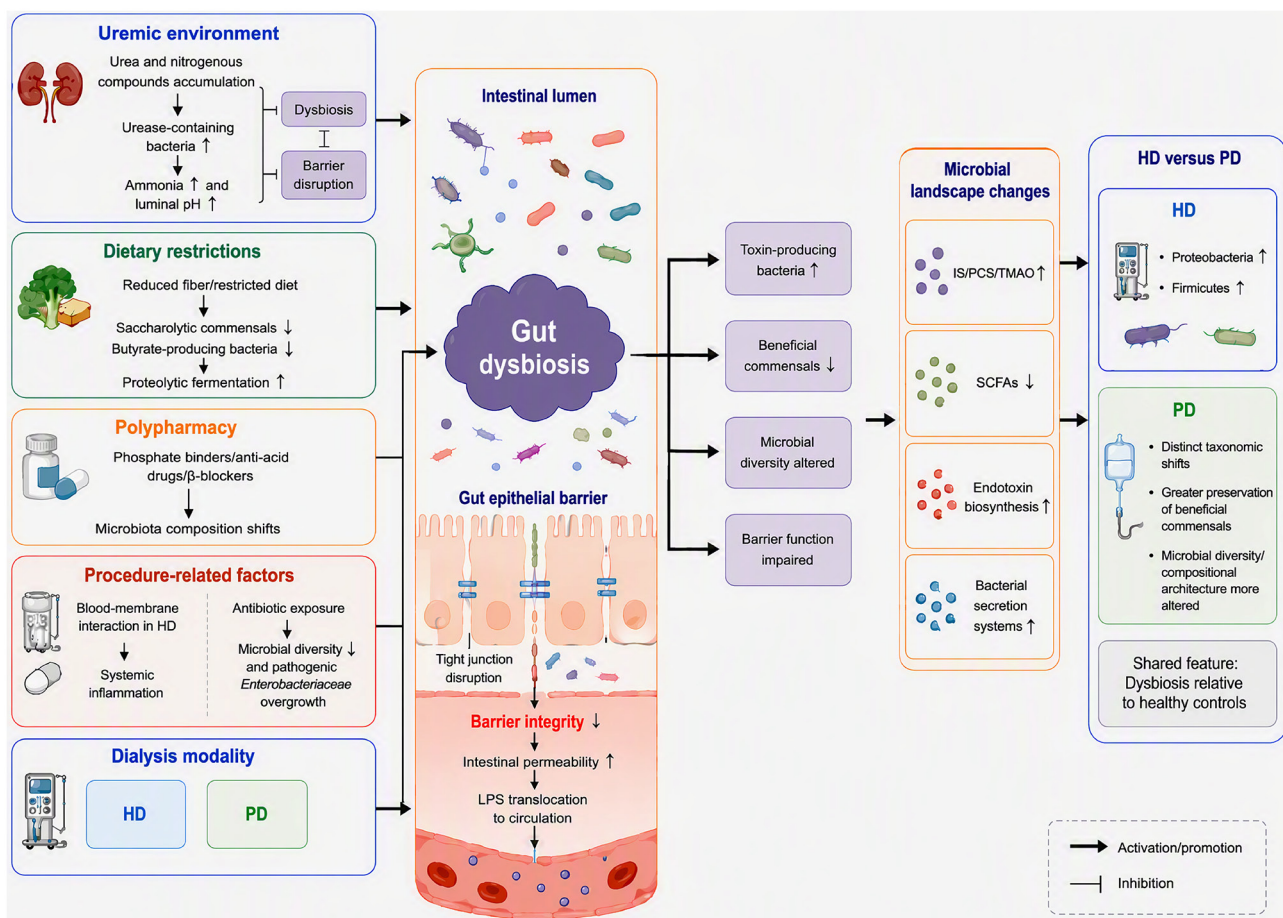


Figure 1. Key drivers of gut microbiota dysbiosis in patients receiving dialysis, and differential compositional effects of HD and PD in a cohort of 25 patients receiving HD and 25 patients receiving PD (17). All comparisons were between HD and PD groups (no healthy control group was included). Patients receiving HD had 2.6-fold higher Proteobacteria relative abundance compared with patients receiving PD (18.7% vs. 7.2%; $P=0.013$) and elevated Firmicutes levels (42.1% vs. 30.5%; $P=0.021$). Patients receiving PD showed a 61.3% reduction in butyrate-producing *Roseburia/Faecalibacterium* relative abundance compared with patients receiving HD (2.3% in PD vs. 5.9% in HD; $P=0.007$), alongside depleted *Bifidobacterium* and *Lactobacillus*. Pathogenic *Enterobacteriaceae* were 3.1-fold more abundant in patients receiving HD compared with patients receiving PD (11.4% vs. 3.7%; $P<0.01$). Statistical significance was indicated by $P<0.05$ for HD vs. PD comparisons. HD, hemodialysis; PD, peritoneal dialysis; LPS, lipopolysaccharide; IS, indoxyl sulfate; PCS, p-cresyl sulfate; TMAO, trimethylamine-N-oxide; SCFAs, short-chain fatty acids.

status and the microbiome is further complicated by reduced dietary fiber intake, which reduces substrate availability for saccharolytic commensals and shifts microbial metabolism toward proteolytic fermentation pathways that generate nephrotoxic metabolites (18).

Medications as unrecognized microbiome modulators. The pharmacologic burden in patients receiving dialysis is substantial, and accumulating evidence indicates that commonly prescribed medications exert previously unrecognized effects on gut microbial communities. Phosphate binders, used to control hyperphosphatemia, have emerged as modulators. Wu *et al* (34) compared gut microbiome differences between ferric citrate and calcium carbonate phosphate binders in patients with ESKD, demonstrating that iron-based binders produced distinct compositional shifts, including increased abundances of commensal Lactobacillaceae. Abdelbary *et al* (35) further characterized the impact of sucroferic oxyhydroxide on both oral and intestinal microbiomes in patients receiving HD, observing that binder-induced changes in gut microbiota associated with reductions in

serum phosphorus and inflammatory markers. Conversely, the non-calcium-based binder sevelamer has been associated with unfavorable effects on gut-derived uremic toxins. Dai *et al* (36) reported that sevelamer use in patients with ESKD was paradoxically associated with higher levels of gut-derived uremic toxins, raising the possibility of drug-microbiome interactions that warrant further investigation. Beyond phosphate binders, anti-acid medications and β -blockers also modulate gut microbial composition. Lin *et al* (37) demonstrated that anti-acid drug treatment induces notable changes in the gut microbiome of patients receiving HD, while the same group (38) identified distinct microbial differences between patients receiving HD who were treated with or without β -blockers, highlighting the influence of polypharmacy.

Procedure-related factors: Blood-membrane interactions and antibiotic exposures. The dialysis procedure itself introduces unique stressors that may influence gut microbial ecology. In HD, contact between blood and dialysis membranes triggers systemic inflammatory responses that can indirectly affect the intestinal microenvironment (39).

He and Xie (40) compared the effects of different hemodialysis methods on gut microbiota in patients with uremia, finding that high-flux and hemofiltration modalities differentially modulated microbial composition compared with conventional HD. In PD, the introduction of dialysate into the peritoneal cavity alters intra-abdominal pressure and may influence intestinal transit and permeability (30). Frequent antibiotic exposures (for vascular access infections in HD or peritonitis in PD) represent a major iatrogenic driver of dysbiosis. Zhou *et al* (41,42) explored the association between intestinal flora and PD-related peritonitis, identifying an association between prior antibiotic courses and dysbiosis characterized by reduced microbial diversity and overgrowth of pathogenic Enterobacteriaceae. More recently, Zhang *et al* (43) performed risk factor assessment and microbiome analysis in PD-related peritonitis, reporting that cumulative antibiotic exposure was independently associated with loss of commensal *Bifidobacterium* species. The repeated disruption and incomplete recovery of gut microbial communities following antibiotic courses likely contribute to the progressive dysbiosis observed with longer dialysis vintage (2). Collectively, these diverse drivers operate in combination rather than isolation, necessitating integrated approaches to characterize and ultimately modify the gut microbiome in patients receiving dialysis.

3. Pathophysiological mechanisms linking gut dysbiosis to systemic complications

Gut dysbiosis in patients receiving dialysis is linked to systemic complications through interconnected mechanistic pathways centered on microbial metabolite imbalance, intestinal barrier disruption and host inflammatory signaling. The overproduction of microbiota-derived uremic toxins including IS, PCS and trimethylamine-N-oxide (TMAO) promotes vascular inflammation and fibrosis, whereas depletion of protective SCFAs compromises immune regulation. Concomitant gut barrier dysfunction facilitates bacterial product translocation, activating NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and systemic inflammatory cascades that link dysbiosis to cardiovascular disease, immune dysfunction and other systemic complications. Fig. 2 summarizes the central pathophysiological mechanisms connecting gut dysbiosis to systemic complications in patients receiving dialysis.

Microbiota-derived uremic toxins. Protein-bound uremic toxins originating from gut microbial metabolism accumulate in patients receiving dialysis due to inadequate clearance by conventional HD. Brito *et al* (44) demonstrated that dietary tryptophan intake associates with plasma IS levels in patients receiving HD. Stockler-Pinto *et al* (45) further showed that IS and PCS modulate NF- κ B/Nrf2 expression, providing mechanistic evidence for how gut-derived toxins propagate oxidative stress and inflammation. The cardiovascular impact of TMAO was elucidated by Zhang *et al* (46) demonstrated that this metabolite promotes vascular calcification through NLRP3 inflammasome and NF- κ B pathway activation. More recently, He *et al* (20) reported that higher serum TMAO levels are independently associated with increased abdominal aortic

calcification in patients receiving HD, extending these findings to clinical outcomes. Bao *et al* (19) further confirmed a relationship between gut microbiota composition and vascular calcification severity, identifying specific bacterial taxa associated with calcification risk.

Collectively, these studies suggest that gut-derived uremic toxins may contribute to the accelerated cardiovascular pathology observed in dialysis populations. However, it is important to distinguish between experimental and clinical evidence. The mechanistic pathways linking TMAO to vascular calcification via NLRP3 inflammasome and NF- κ B activation have been validated in animal models and cell-based systems (46), whereas the association between gut microbiota composition and calcification severity in humans remains observational and subject to confounding by dietary intake and medication use (19,20). The protein-bound toxins IS and PCS have demonstrated pro-inflammatory and pro-oxidative effects *in vitro*, but the extent to which these mechanisms operate in the complex uremic milieu of patients receiving dialysis requires further investigation through prospective intervention studies (45,47).

SCFA depletion and barrier integrity. The depletion of SCFA-producing commensals represents a consistent finding in patients receiving dialysis with consequences for intestinal barrier function and immune homeostasis. Lin and Hung (31) demonstrated that malnourished patients receiving HD exhibit reduced abundances of butyrate-producing genera, including *Faecalibacterium*, *Roseburia* and *Coprococcus*, linking nutritional status to SCFA availability. Hu *et al* (48) employed high-throughput sequencing to characterize intestinal flora changes in patients with ESKD, identifying marked reductions in SCFA producers compared with healthy controls. The functional implications of SCFA depletion were examined by Ficek *et al* (49), who demonstrated associations among plasma zonulin (a marker of intestinal permeability), bacterial LPS and inflammatory markers in patients receiving HD, suggesting that loss of SCFA-mediated barrier protection promotes endotoxin translocation. Engen *et al* (50) similarly reported that gut-derived inflammation associates with increased intestinal permeability in neurodegenerative disease models, a mechanism that may also be relevant to dialysis-related systemic inflammation. The study by de Andrade *et al* (51) found that dietary interventions in patients receiving PD modulated gut-derived uremic toxins but did not fully restore SCFA profiles, indicating persistent dysbiosis despite nutritional manipulation. These findings suggest that SCFA depletion may be both a consequence and a driver of gut barrier dysfunction.

Endotoxemia and systemic inflammation. The translocation of bacterial products across a compromised intestinal barrier generates persistent low-grade endotoxemia that fuels systemic inflammation in patients receiving dialysis. Ficek *et al* (49) established associations between circulating LPS levels and proinflammatory cytokines in patients receiving HD, indicating an association between gut barrier dysfunction and systemic inflammatory burden. Borges *et al* (52) demonstrated in a randomized trial that

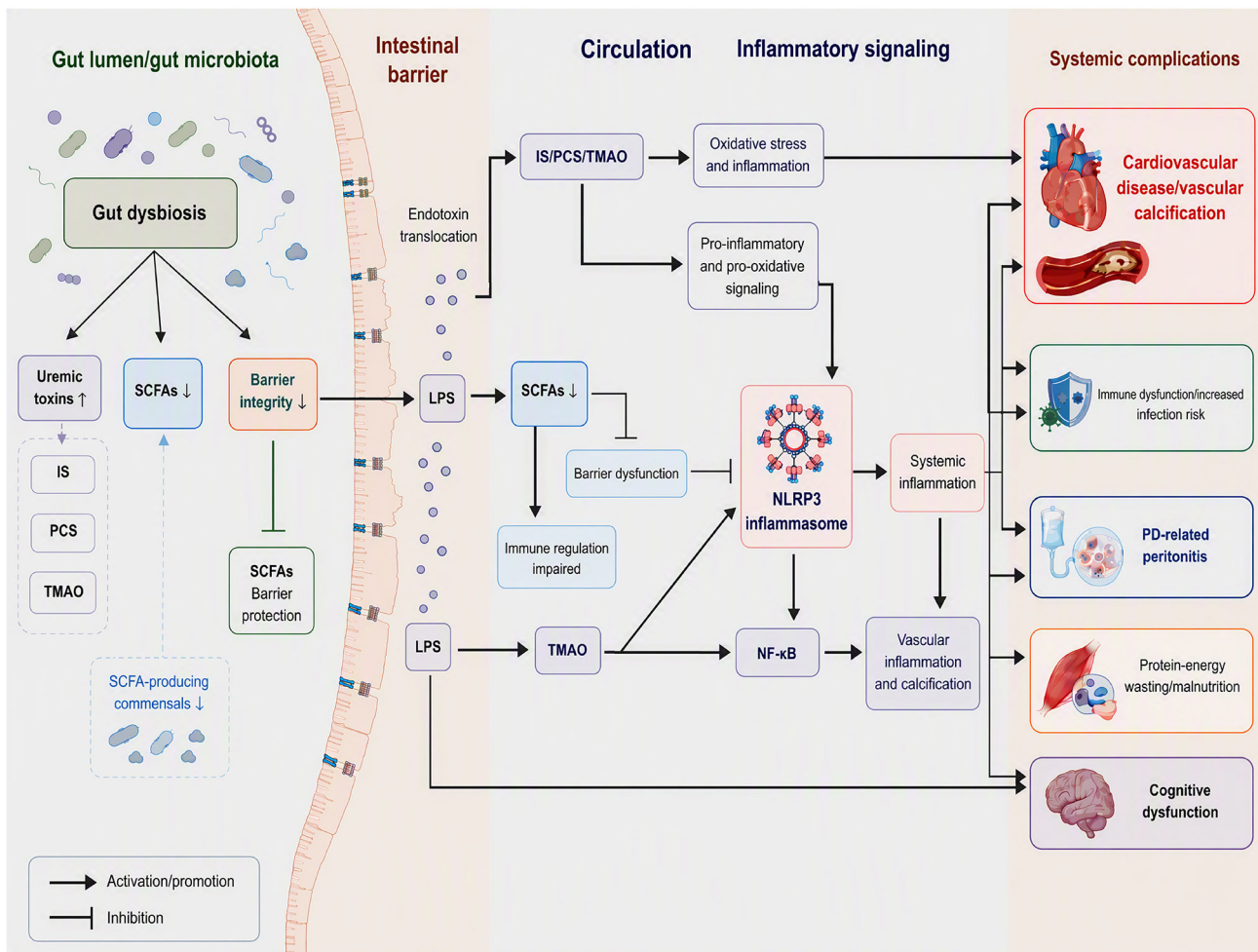


Figure 2. Schematic illustrating pathophysiological cascades linking gut dysbiosis to systemic complications in patients receiving dialysis. Uremia induces gut microbial shifts, such as the overproduction of protein-bound uremic toxins (for example, IS, PCS and TMAO) and depletion of protective SCFAs. Diminished SCFA-mediated mucosal protection and uremic damage disrupts intestinal tight-junctions, increasing gut permeability and enabling LPS translocation into circulation. Circulating microbial metabolites and endotoxins trigger oxidative stress and activate the NLRP3 inflammasome-NF- κ B inflammatory axis. Persistent systemic inflammation drives major dialysis-associated adverse outcomes, including cardiovascular disease and vascular calcification, immune dysfunction, PD-related peritonitis, protein-energy wasting and cognitive dysfunction via the kidney-gut-brain axis. Solid arrows indicate process activation/promotion; bar-ended lines represent inhibition. IS, indoxyl sulfate; PCS, p-cresyl sulfate; TMAO, trimethylamine-N-oxide; SCFAs, short-chain fatty acids; LPS, lipopolysaccharide; NLRP3, NOD-like receptor family pyrin domain containing 3; PD, peritoneal dialysis.

probiotic supplementation modulates inflammatory markers in patients with CKD, providing proof-of-concept that targeting gut microbiota can attenuate systemic inflammation. Longitudinal evidence from Lin *et al* (12) revealed that gut dysbiosis predicts mortality in patients receiving HD, with inflammatory pathways mediating this association. The mechanistic underpinnings were further elucidated by Holle *et al* (53), demonstrated that in pediatric patients with CKD gut dysbiosis and metabolite imbalance drive inflammation through integrin-mediated signaling. More recently, Mafra *et al* (54) specifically examined the link between gut microbiota and NLRP3 inflammasome activation in patients receiving HD, identifying that microbial alterations associate with increased caspase-1 activity and IL-1 β production. Samaan *et al* (55) reported that Ramadan fasting modulates inflammatory markers and gut bacterial endotoxins in patients receiving HD, suggesting that dietary patterns influence endotoxin burden. Collectively, these studies establish endotoxemia as a mechanistic bridge between gut dysbiosis and the systemic inflammatory state observed in dialysis populations.

NLRP3 inflammasome as an integrative hub. Emerging evidence positions the NLRP3 inflammasome as a central molecular integrator linking gut microbial alterations to sterile inflammation in patients receiving dialysis. Zhang *et al* (46) first demonstrated that TMAO promotes vascular calcification through NLRP3 activation, establishing a direct pathway from gut microbial metabolite to inflammatory cascade. The relevance to dialysis populations was confirmed by Mafra *et al* (54), who showed that NLRP3 inflammasome components are upregulated in patients receiving HD with pronounced gut dysbiosis. Guo *et al* (56) demonstrated that sodium butyrate exerts neuroprotective effects in Parkinson's disease models by restoring gut microbiota and inhibiting Toll-like receptor 4 signaling, suggesting that SCFAs may counterbalance inflammasome activation. Qu *et al* (57) further established that SCFAs modulate α -synuclein aggregation and neuroinflammation via the G protein-coupled receptor 43 (GPR43)-NLRP3 signaling pathway, wherein SCFA binding to GPR43 inhibits NLRP3 inflammasome activation and downstream inflammatory cascades; this mechanism is

potentially relevant to the kidney-gut-brain axis in patients undergoing dialysis. Liu *et al* (58) recently reported that *Bacteroides coprocola* protects dopaminergic neurons through inhibition of the NLRP3 signaling pathway, highlighting that specific commensals may modulate inflammasome activity. Together, these findings suggest that NLRP3 may represent a potential molecular target for interventions aimed at breaking the dysbiosis-inflammation cycle in patients receiving dialysis.

Interplay with host signaling systems. Gut dysbiosis interacts with host signaling systems beyond canonical inflammatory pathways, including the renin-angiotensin system (RAS) and immune checkpoint regulators. Wu *et al* (34) demonstrated that phosphate binders differentially modulate gut microbiota composition, suggesting that medications targeting mineral metabolism indirectly influence host-microbe signaling. The RAS connection was explored by Li *et al* (59), who showed that uremic clearance granules affect p38 mitogen-activated protein kinase/NF- κ B signaling pathways in rats receiving PD, with concurrent alterations in microbial and metabolic profiles. Zhang *et al* (60) demonstrated that TMAO increases peritoneal inflammation and peritonitis risk in patients receiving PD, establishing a link between gut microbial metabolism and local host responses in the peritoneal cavity. The programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) immune checkpoint axis has also been implicated, with Chen *et al* (61) showing that Prevotellaceae produces butyrate to alleviate PD-1/PD-L1 inhibitor-related toxicity via the peroxisome proliferator-activated receptor α -cytochrome P450 family 4 subfamily X member 1 axis in colonic macrophages. Wang *et al* (62) further demonstrated that Fushen Granule modulates gut microbiota to prevent chronic renal failure, with effects partly mediated through host metabolic pathways. These observations indicate that gut dysbiosis exerts pleiotropic effects on host signaling networks, with therapeutic implications for personalized microbiome-based care.

Collectively, the pathophysiological evidence suggests that gut dysbiosis may contribute to systemic complications through a convergent triad of mechanisms: Microbial metabolite imbalance (excess uremic toxins, deficient SCFAs), barrier disruption with endotoxin translocation and NLRP3 inflammasome-mediated sterile inflammation. These pathways are not mutually exclusive but operate synergistically, with microbial metabolites directly activating inflammatory cascades while simultaneously compromising barrier integrity, creating a self-reinforcing cycle of dysbiosis, inflammation and tissue injury.

4. Major complications associated with gut dysbiosis in dialysis

Gut dysbiosis in patients receiving dialysis is associated with systemic complications through interconnected pathways involving microbial metabolite imbalance, intestinal barrier disruption and sustained inflammation. The clinical impact extends beyond traditional cardiovascular disease to encompass immune dysfunction, PD-related peritonitis, protein-energy wasting and cognitive impairment. These complications collectively contribute to poor clinical outcomes and increased mortality, supporting a potential role for the gut microbiome in

the prognosis of patients receiving dialysis. Table I illustrates the major complications linked to gut dysbiosis and their underlying mechanistic connections.

Cardiovascular disease and vascular calcification. Cardiovascular disease remains the leading cause of mortality in patients receiving dialysis, and accumulating evidence implicates gut-derived uremic toxins in vascular pathology. Zhang *et al* (46) demonstrated that TMAO promotes vascular calcification through activation of NLRP3 inflammasome and NF- κ B signaling pathways, providing mechanistic evidence linking gut microbial metabolism to arterial pathology. Extending these findings to clinical outcomes, He *et al* (20) reported that higher serum TMAO levels are independently associated with increased abdominal aortic calcification in patients receiving HD. Bao *et al* (19) further reported a notable relationship between gut microbiota composition and vascular calcification severity, identifying specific bacterial taxa associated with calcification risk. The protein-bound toxins IS and PCS also contribute to cardiovascular injury. In the aforementioned study, higher abundances of bacteria in the *Escherichia-Shigella* and *Ruminococcus* groups were positively associated with vascular calcification, whereas lower abundances of *Ruminococcus*, *Adlercreutzia*, *Alistipes* and *Ruminococcaceae* were negatively associated with calcification severity. In terms of relative contribution to calcification risk as determined by importance ranking analysis, *Escherichia-Shigella* exerted the greatest influence, followed by *Ruminococcus* and *Butyrivibrio*. Velasquez *et al* (63) reviewed the role of gut microbiota in cardiovascular uremic toxicities, emphasizing that these metabolites promote endothelial dysfunction and oxidative stress. Kanitsoraphan *et al* (64) conducted a systematic evaluation demonstrating that elevated TMAO levels are associated with increased cardiovascular risk and mortality across populations with CKD. Mechanistically, the persistence of these toxins despite conventional dialysis reflects inadequate clearance of protein-bound solutes, as highlighted by Gryp *et al* (47), who characterized PCS as a prototypical gut-derived cardiovascular toxin. Collectively, these findings support a potential role for gut dysbiosis in the accelerated cardiovascular pathology observed in patients receiving dialysis, although prospective interventional studies targeting the microbiome to reduce cardiovascular events remain limited.

However, despite these mechanistic and observational data, establishing causality in humans remains challenging. Most evidence for direct vascular injury derives from *in vitro* and animal models, whereas human studies are predominantly cross-sectional or prospective observational, which are susceptible to residual confounding by dietary intake and comorbid conditions (19,20). Furthermore, whether reducing these metabolites through gut modulation translates into decreased cardiovascular events has not been established in adequately powered randomized trials. In the evidence hierarchy, the current data support strong associations and plausible mechanistic pathways, but definitive causal proof would require demonstration that microbiome-targeted interventions specifically reduce cardiovascular events through toxin-dependent mechanisms (14). This distinction is not merely semantic; it has direct implications for clinical trial

Table I. Major complications associated with gut microbiota dysbiosis in patients receiving dialysis: Clinical manifestations and mechanistic pathways.

Complication	Key clinical manifestations	Gut microbiota-related mechanisms	Primary microbial metabolites/ pathways involved	(Refs.)
Cardiovascular disease and vascular calcification	Accelerated atherosclerosis, arterial stiffness, abdominal aortic calcification and increased cardiovascular mortality	Endotoxemia, NLRP3 inflammasome activation, NF- κ B signaling and oxidative stress	TMAO, IS, PCS and LPS	(46,20,19,63)
Immune dysfunction and infection risk	Susceptibility to bacterial infections, reduced vaccine response, T cell dysregulation, high sepsis-related mortality	Increased intestinal permeability, bacterial translocation, chronic low-grade inflammation, altered Treg/Th17 balance	LPS, zonulin, IS, PCS	(53,65,49,66)
Peritoneal dialysis-related peritonitis	Recurrent or refractory peritonitis, increased catheter removal, technique failure, hospitalization	Gut-peritoneal translocation of pathogenic bacteria, antibiotic-induced dysbiosis, loss of commensal <i>Bifidobacterium</i>	TMAO, <i>Escherichia coli</i> enrichment, reduced SCFAs	(41-43,60,68)
Protein-energy wasting and malnutrition	Loss of muscle mass, low serum albumin, poor nutritional status, reduced quality of life	Reduced SCFA production, increased proteolytic fermentation, chronic inflammation, altered appetite regulation	Depletion of butyrate-producing genera (such as <i>Faecalibacterium</i> and <i>Roseburia</i>) and increased uremic toxins	(72)
Cognitive dysfunction and kidney-gut-brain axis	Mild cognitive impairment, executive dysfunction, memory decline, potential progression to dementia	Neuroinflammation, blood-brain barrier disruption, microglial activation, altered neurotransmitter metabolism	IS, PCS, TMAO, reduced SCFAs, tryptophan/tyrosine pathway metabolites	(23,74-77)

TMAO, trimethylamine-N-oxide; IS, indoxyl sulfate; PCS, p-cresyl sulfate; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; NLRP3, NOD-like receptor family pyrin domain containing 3; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; Treg, regulatory T cell; Th17, T helper 17 cell.

design and the interpretation of intervention studies that show metabolite reduction without corresponding improvements in hard clinical outcomes.

Immune dysfunction and increased infection risk. Patients receiving HD exhibit heightened susceptibility to infections and experience disproportionately high mortality following septic events, with gut microbiota dysregulation increasingly recognized as a contributing mechanism. Holle *et al* (53) demonstrated in pediatric patients with CKD that gut dysbiosis and metabolite imbalance drive inflammation through integrin-mediated signaling, establishing a mechanistic link between microbial alterations and immune dysfunction. Lv *et al* (65) recently performed 16S ribosomal RNA (16S rRNA) sequencing-based analysis of gut flora and T cell profiles in patients receiving maintenance HD, revealing that immune-microbiota dysregulation characterized by reduced regulatory T cell populations associates with specific taxonomic shifts. The translocation of bacterial products across a compromised intestinal barrier perpetuates systemic inflammation that impairs host defense. Ficek *et al* (49) established associations among plasma zonulin (a marker of intestinal permeability), bacterial LPS and inflammatory markers in patients receiving HD, indicating an association between gut barrier dysfunction and immune activation. Glorieux *et al* (66) reviewed the role of gut-derived metabolites in immune dysfunction in CKD, emphasizing that protein-bound uremic toxins suppress phagocytic function and alter lymphocyte responses. Furthermore, Al Khodor and Shatat (67) described the bidirectional relationship between gut microbiome and kidney disease, noting that dysbiosis-induced inflammation creates a vicious cycle that further compromises immune competence. While observational associations support a relationship, causality remains to be definitively established, and whether microbiome-targeted interventions can reduce infection risk in patients receiving dialysis requires prospective validation.

PD-related peritonitis. Gut microbiome dysbiosis has been associated with peritonitis in patients receiving PD, creating a clinically actionable connection between intestinal microbial health and infectious outcomes of the peritoneal cavity. Zhang *et al* (43) performed risk factor assessment and microbiome analysis in PD-related peritonitis, demonstrating that cumulative antibiotic exposure was independently associated with loss of commensal *Bifidobacterium* species and that gut microbiota composition predicted peritonitis risk. Zhou *et al* (41,42) explored the association between intestinal flora and PD-related peritonitis in two complementary studies, identifying an association between prior antibiotic courses and dysbiosis characterized by reduced microbial diversity and overgrowth of pathogenic Enterobacteriaceae, with specific enrichment of *Escherichia coli* in culture-positive cases. The gut microbial metabolite TMAO also contributes to peritoneal inflammation. Zhang *et al* (60) demonstrated that TMAO increases peritoneal inflammation and peritonitis risk in patients receiving PD, establishing a link between gut microbial metabolism and local host responses in the peritoneal cavity. Xu *et al* (68) recently provided a new perspective on gut microbiome and peritoneal inflammation,

proposing that microbial metabolite profiling could identify patients at elevated peritonitis risk before clinical infection manifests. Conversely, traditional risk factors such as hydration status also modulate peritonitis susceptibility, as Santhakumaran *et al* (69) demonstrated that fluid overload measured by bioimpedance spectroscopy represents a modifiable risk factor for peritonitis. These observations suggest that integrated approaches combining microbiome assessment with conventional risk stratification may optimize peritonitis prevention strategies.

Malnutrition and PEW. PEW affects a substantial proportion of patients receiving dialysis and has been associated with gut microbial alterations through bidirectional interactions. Lin and Hung (31) demonstrated that malnourished patients receiving HD harbored reduced abundances of beneficial butyrate-producing genera, establishing an association between nutritional status and gut microbiota composition. Bakinowska *et al* (70) comprehensively reviewed the pathogenesis of sarcopenia in CKD, identifying gut dysbiosis as a contributing factor through inflammation-mediated muscle catabolism and metabolic dysregulation. The relationship between nutritional status and the microbiome is further complicated by reduced dietary fiber intake, which reduces substrate availability for saccharolytic commensals and shifts microbial metabolism toward proteolytic fermentation pathways that generate nephrotoxic metabolites. March *et al* (71) conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) examining prebiotic, probiotic and synbiotic supplementation in patients receiving dialysis, finding that these interventions significantly reduced circulating levels of gut-derived metabolites, including endotoxin [standardized mean difference (SMD), -0.61; 95% confidence interval (CI), -1.03 to -0.20], indoxyl sulfate (SMD, -0.34; 95% CI, -0.64 to -0.04) and p-cresyl sulfate (SMD, -0.34; 95% CI, -0.61 to -0.07), but noting inconsistent effects on nutritional parameters. Pan *et al* (72) performed a RCT demonstrating that probiotic supplementation improved malnutrition and health-related quality of life in patients receiving PD, suggesting that targeting gut microbiota may improve nutritional outcomes. Nevertheless, Azamian *et al* (73) reported that synbiotic supplementation reduced advanced glycation end products and cardiovascular risk factors in patients receiving HD without notable improvements in nutritional indices, suggesting that the effects on PEW may be indirect and require longer intervention periods. The heterogeneity of outcomes across studies highlights the need for larger, adequately powered trials with standardized nutritional endpoints.

Nevertheless, it remains unresolved whether gut dysbiosis is a primary driver of PEW or a consequence of the malnourished state itself. A short-term RCT showed improvement in nutritional parameters (72), whereas another reported no significant improvement in nutritional indices (73), and the heterogeneity in definitions of PEW and intervention protocols prevents definitive conclusions regarding a causal relationship.

Cognitive dysfunction and the kidney-gut-brain axis. Brain dysfunction in patients receiving maintenance HD has been increasingly linked to the kidney-gut-brain axis, with gut

microbiota disorders and intestinal mucosal damage constituting key components of a systemic communication network extending beyond the traditional gut-kidney framework. Zhu *et al* (74) performed a single-center observational study identifying abnormalities in gut microbiota and serum metabolites in patients receiving HD with mild cognitive decline, demonstrating that reduced abundances of SCFA-producing genera associated with poorer cognitive performance. Wang *et al* (75) extended these findings to patients receiving PD, showing that gut microbiome composition associates with cognitive impairment and that specific taxa including *Lactobacillus* and *Bifidobacterium* were depleted in patients with worse cognitive scores. Yu *et al* (23) comprehensively reviewed research progress on the kidney-gut-brain axis in brain dysfunction in patients receiving maintenance HD, proposing that microbial metabolites including IS and PCS cross the blood-brain barrier and promote neuroinflammation. The mechanistic underpinnings were elucidated by Shah *et al* (76), who demonstrated that PCS causes cerebrovascular damage through EGF receptor activation, providing direct experimental evidence linking gut-derived metabolites to neurological injury. Martín-del-Campo *et al* (77) recently reported that gut microbiome composition is related to cognitive impairment in patients receiving PD, identifying that reduced microbial diversity and depletion of *Faecalibacterium prausnitzii* were independently associated with lower Mini-Mental State Examination scores. Furthermore, Gao *et al* (78) employed combined 16S ribosome DNA and shotgun metagenome sequencing to analyze intestinal flora and cognitive function in patients receiving maintenance HD, revealing that specific metabolic pathways including tryptophan and tyrosine metabolism were enriched in patients with cognitive decline. Collectively, these findings position the gut microbiome as a potential therapeutic target for preserving cognitive function in patients receiving dialysis, although longitudinal studies tracking microbiota changes before and after the onset of cognitive decline are needed to establish temporality and causality.

Across these five complication domains, common mechanistic threads emerge, including microbial metabolite excess (IS, PCS and TMAO), SCFA depletion or endotoxin-mediated inflammation. The strength of causal evidence varies considerably, with cardiovascular disease supported by extensive mechanistic studies, whereas cognitive impairment and PEW remain predominantly associative. This pattern highlights the need for mechanism-targeted interventions and suggests that microbiome modulation may offer a unified strategy for mitigating multiple complications simultaneously.

5. Therapeutic modulation of the gut microbiome in dialysis: Current evidence

A growing armamentarium of gut-targeted interventions offers potential avenues for mitigating dysbiosis in patients receiving dialysis, although the evidence base remains at an early stage. These strategies include probiotics, prebiotics, synbiotics and dietary modifications, phosphate binders and fecal microbiota transplantation. Table II provides a comparative overview of these therapeutic approaches and key clinical findings in dialysis populations.

Probiotics, prebiotics and synbiotics. Probiotic, prebiotic and synbiotic supplementation represents the most extensively investigated class of microbiome-targeted interventions in patients receiving dialysis, although trial results have been heterogeneous. Soleimani *et al* (79) conducted a randomized trial in patients with diabetes receiving HD, demonstrating that probiotic supplementation produced beneficial metabolic effects including reduced fasting blood glucose and improved lipid profiles. Borges *et al* (52) further showed that probiotic supplementation in patients with CKD modulated inflammatory markers, providing early proof-of-concept for anti-inflammatory effects. However, subsequent studies have yielded inconsistent findings regarding uremic toxin reduction. In a pilot study, Borges *et al* (80) reported that probiotic supplementation did not significantly lower TMAO plasma levels in patients receiving HD, suggesting that single-strain or multi-strain formulations may have limited impact on this specific metabolite.

The combination of probiotics with prebiotics as synbiotics has shown more promising results in certain contexts. Lopes *et al* (81) demonstrated that a synbiotic meal decreased uremic toxin levels in individuals receiving HD compared with placebo. Similarly, Mirzaeian *et al* (82) conducted a double-blind, randomized clinical trial showing that synbiotic supplementation reduced protein-bound uremic toxins and systemic inflammation in patients receiving HD. Nevertheless, Zhou *et al* (83) recently reported that probiotic treatment induced changes in intestinal microbiota but did not alter SCFA levels in patients receiving PD, highlighting that microbial composition shifts do not necessarily translate into functional metabolic changes. Pan *et al* (72), who demonstrated in a RCT that probiotic supplementation improved malnutrition and health-related quality of life in patients receiving PD. Additionally, Wang *et al* (84) recently showed that enhanced sleep quality and reduced IS levels following probiotic supplementation were linked to gut microbiota modulation in patients receiving HD. Abdelnasier *et al* (85) prospectively demonstrated that probiotic use reduced gut leakage measured by zonulin and decreased PCS levels and inflammation in patients receiving HD, providing mechanistic evidence for barrier-stabilizing effects. Collectively, these studies indicate that while probiotics and synbiotics hold promise, response heterogeneity across trials likely reflects differences in strains, doses, dialysis modalities and patient populations, necessitating larger, adequately powered trials with standardized endpoints.

The discrepancy in outcomes across these RCTs highlights issues, including variations in bacterial strains, treatment duration and the lack of baseline microbiome stratification (52,79,80,83). Furthermore, the consistent observation that changes in microbial composition do not necessarily translate into altered functional metabolites underscores a gap in understanding the taxonomy-function relationship, indicating that current evidence is insufficient to support broad clinical recommendations (83).

Dietary interventions. Dietary modulation, particularly through plant-based diets and resistant starch supplementation, has emerged as a physiologically rational approach to reshape gut microbial metabolism in patients receiving dialysis.

Table II. Summary of microbiome-targeted therapeutic strategies in patients receiving dialysis.

First author, year	Intervention	Specific strategy	Dialysis modality	Key findings in dialysis populations	Key limitation/note	(Refs.)
Dai <i>et al.</i> , 2020	Phosphate binders	Sevelamer	Mixed HD/PD	Associated with higher levels of gut-derived uremic toxins	Potential drug-microbiome interaction; observational	(36)
Borges <i>et al.</i> , 2018	Probiotics	Probiotic supplementation	HD	Modulated inflammatory markers; reduced PCS	TMAO unchanged; small sample size	(52)
Pan <i>et al.</i> , 2021	Probiotics	Probiotic supplementation	PD	Improved malnutrition and health-related quality of life	Long-term clinical outcomes not assessed	(72)
Soleimani <i>et al.</i> , 2017	Probiotics	Multi-strain probiotics	HD	Improved metabolic profiles (fasting glucose, lipids) in patients with diabetes receiving HD	Uremic toxin levels not reported	(79)
Borges <i>et al.</i> , 2019	Probiotics	Probiotic supplementation	HD	No significant reduction in TMAO levels	Pilot study	(80)
Lopes <i>et al.</i> , 2019	Synbiotics	Synbiotic meal	HD	Decreased uremic toxins	Single-meal design; not long-term	(81)
Mirzaeian <i>et al.</i> , 2020	Synbiotics	Synbiotic supplementation	HD	Reduced serum IS, PCS and systemic inflammation	Double-blind but moderate sample size	(82)
Zhou <i>et al.</i> , 2024	Probiotics	Probiotic treatment	PD	Induced intestinal microbiota changes	No effect on SCFA levels despite compositional shifts	(83)
Wang <i>et al.</i> , 2025	Probiotics	Probiotic supplementation	HD	Enhanced sleep quality and reduced indoxyl sulfate linked to gut microbiota modulation	Observational component; causality not proven	(84)
Abdelnasier <i>et al.</i> , 2026	Probiotics	Probiotic use	HD	Reduced gut leakage (zonulin), PCS and inflammation	Prospective controlled but not randomized	(85)
Stanford <i>et al.</i> , 2021	Dietary intervention	Plant-based diet quality	HD	Higher adherence associated with lower gut-derived uremic toxins	Cross-sectional; causality unclear	(86)
Li <i>et al.</i> , 2020	Prebiotics	Inulin-type fructans	PD	Restricted increase in gut-generated indole	Crossover design; short intervention	(87)
He <i>et al.</i> , 2022	Prebiotics	Inulin-type prebiotics	PD	Reduced serum uric acid levels via gut microbiota modulation	Effects on protein-bound toxins not evaluated	(88)
Li <i>et al.</i> , 2024	Prebiotics	Inulin-type prebiotics	PD	Exerted arsenic-lowering effect	Specific to arsenic; generalizability limited	(89)
Esgalhado <i>et al.</i> , 2018	Prebiotics	Resistant starch	HD	Reduced IS and PCS levels; attenuated inflammation	Small pilot; needs larger confirmation	(90)

Table II. Continued.

First author, year	Intervention	Specific strategy	Dialysis modality	Key findings in dialysis populations	Key limitation/note	(Refs.)
Azevedo <i>et al</i> , 2020	Prebiotics	Resistant starch	HD	Reduced plasma indole-3-acetic acid and AhR mRNA expression	Secondary analysis of pilot trial	(91)
de Paiva <i>et al</i> , 2020	Prebiotics	Resistant starch	HD	Attenuated inflammation	Pilot study	(92)
Rocchetti <i>et al</i> , 2020	Emerging approach	Divinylbenzenic resin	HD	Removed IS and PCS <i>in vitro</i> and in a pilot <i>in vivo</i> study	Pilot <i>in vivo</i> ; limited number of patients	(101)

HD, hemodialysis; PD, peritoneal dialysis; ESKD, end-stage kidney disease; IS, indoxyl sulfate; PCS, p-cresyl sulfate; TMAO, trimethylamine-N-oxide; SCFA, short-chain fatty acid; AhR, aryl hydrocarbon receptor; mRNA, messenger ribonucleic acid.

Stanford *et al* (86) examined associations among plant-based diet quality, uremic toxins and gut microbiota profile in adults undergoing HD, demonstrating that higher adherence to plant-based diets was associated with lower circulating levels of gut-derived toxins. The prebiotic effects of inulin-type fructans have been rigorously evaluated in PD populations. Li *et al* (87) conducted a randomized crossover study demonstrating that inulin-type fructan intervention restricted the increase in gut microbiome-generated indole in patients receiving PD. Extending these findings, He *et al* (88) showed that inulin-type prebiotics reduced serum uric acid levels via gut microbiota modulation in a randomized controlled crossover trial in patients receiving PD. Furthermore, Li *et al* (89) recently reported that inulin-type prebiotics exerted an arsenic-lowering effect in patients with end-stage renal disease (ESRD), suggesting additional detoxification benefits.

Resistant starch represents another promising prebiotic approach. Esgalhado *et al* (90) conducted a pilot RCT showing that resistant starch supplementation improved inflammatory and oxidative stress biomarkers in patients receiving HD, although uremic toxin levels were not notably altered. Azevedo *et al* (91) further demonstrated that resistant starch supplementation reduced plasma indole-3-acetic acid and aryl hydrocarbon receptor mRNA expression in patients receiving HD. De Paiva *et al* (92) reported that resistant starch supplementation attenuated inflammation in patients receiving HD, corroborating the anti-inflammatory effects observed in earlier studies. However, the optimal formulation and duration of dietary interventions remain unclear, and head-to-head comparisons between different prebiotic agents are lacking. Nevertheless, these dietary approaches offer the advantage of targeting fundamental substrate availability rather than merely modifying microbial composition, positioning them as potential components of integrated microbiome-directed care in patients receiving dialysis.

Phosphate binders as microbiome modulators. Phosphate binders, prescribed to control hyperphosphatemia in patients receiving dialysis, have been increasingly recognized for their unintended but potentially beneficial effects on gut microbial ecology; however, not all binders exert equivalent effects. Dai *et al* (36) reported that sevelamer use in patients with ESKD was associated with higher levels of gut-derived uremic toxins, raising the possibility of detrimental drug-microbiome interactions. This finding contrasts with the expected benefit of phosphate control and suggests that sevelamer may alter gut microbial composition or function in ways that promote toxin generation. Conversely, iron-based binders have shown more favorable microbiome profiles (34), although comparative trials directly evaluating binder effects on clinical outcomes remain limited. These observations highlight that medication selection in patients receiving dialysis may have previously unrecognized consequences for gut microbial homeostasis, warranting prospective comparative effectiveness studies.

Fecal microbiota transplantation (FMT). FMT is used in the treatment of recurrent *Clostridioides difficile* infection and is being explored across various disease states, although its application in dialysis populations remains limited. Studies in other fields have established the feasibility and safety of

FMT. Baruch *et al* (93) demonstrated that FMT promoted response in immunotherapy-refractory patients with melanoma, while Davar *et al* (94) showed that FMT overcame resistance to anti-PD-1 therapy in patients with melanoma. In Parkinson's disease, several randomized trials have evaluated FMT with mixed results. Scheperjans *et al* (95) conducted a RCT of FMT for Parkinson's disease, and Zhang *et al* (96) recently reported that gut microbiota modulation via repeated donor FMT improved motor and gastrointestinal symptoms in drug-naïve patients with Parkinson's disease. However, no published RCT has specifically evaluated FMT in patients receiving dialysis. Challenges include safety concerns related to immune dysfunction, infection risk from donor material and the absence of standardized protocols for this vulnerable population. While FMT holds theoretical promise for restoring a healthy gut ecosystem in patients receiving dialysis, rigorous phase I and II trials are essential before clinical adoption can be considered. For phase I trials in patients receiving dialysis, proposed safety endpoints should include monitoring for bacteremia, peritonitis in patients receiving PD and febrile reactions within 72 h post-FMT, alongside standard adverse event reporting. Donor stool should be rigorously screened for multidrug-resistant organisms and potential pathogens, with particular attention to cytomegalovirus and Epstein-Barr virus status given the immune dysfunction in patients receiving dialysis (97,98). Patient selection for initial trials should prioritize clinically stable individuals without active infections or recent antibiotic exposure, with gradual dose escalation to assess tolerability (99).

Emerging approaches. Novel strategies beyond traditional probiotics and prebiotics are being investigated. Colon-targeted adsorbents represent an approach that removes gut-derived toxins without altering living microbial communities. Messaoudene *et al* (100) demonstrated in a phase I trial in healthy volunteers that the DAV132 colon-targeted adsorbent did not interfere with plasma concentrations of antibiotics but prevented antibiotic-related dysbiosis, offering a paradigm for toxin sequestration rather than microbial modification. Rocchetti *et al* (101) evaluated the efficacy of divinylbenzenic resin in removing IS and PCS in patients receiving HD through *in vitro* and pilot *in vivo* studies, showing proof-of-concept for adsorption-based strategies. Additionally, engineered microbiota approaches and postbiotic formulations targeting specific metabolite pathways are emerging from preclinical models. Collectively, these approaches may enable more precise, mechanism-based interventions compared with traditional probiotic supplementation, although clinical translation in dialysis populations remains distant.

In summary, the evidence for microbiome-targeted therapies in dialysis remains preliminary, with probiotics and synbiotics showing the most promise but also the greatest heterogeneity. Several consistent themes emerge: Responses vary substantially across individuals, microbial composition changes do not reliably predict functional metabolic improvements and no single intervention has demonstrated consistent efficacy across studies. These observations collectively indicate that successful therapeutic modulation may require personalized approaches guided by baseline microbial

profiling and metabolomic phenotyping rather than uniform supplementation protocols.

6. Multi-omics approaches to characterizing dysbiosis in dialysis

Multi-omics technologies have transformed the investigation of gut microbiota alterations in patients receiving dialysis, enabling taxonomic, functional and metabolic characterization of dysbiosis beyond traditional culture-based methods. However, the heterogeneity of sequencing platforms, analytical pipelines and population characteristics has generated divergent findings that complicate cross-study comparisons. Table III provides an integrated overview of key multi-omics discoveries in dialysis-associated dysbiosis, highlighting methodological considerations and major biological insights.

16S rRNA and metagenomic sequencing. Taxonomic profiling using 16S rRNA sequencing has consistently identified reduced microbial diversity and compositional shifts in patients receiving dialysis. Crespo-Salgado *et al* (102) performed a pediatric study demonstrating that patients with ESRD exhibit decreased abundances of Lactobacillaceae and Bifidobacteriaceae compared with healthy controls. Similarly, Li *et al* (103) reported that patients with CKD stage 5 receiving maintenance HD showed enrichment of pathogenic Enterobacteriaceae and depletion of butyrate-producing *Roseburia* and *Faecalibacterium*, with these changes being positively associated with serum IS levels. Hu *et al* (48) extended these findings using high-throughput sequencing, revealing that patients with ESRD had markedly lower abundances of SCFA producers compared with those in patients with CKD and healthy controls. Notably, Luo *et al* (17) directly compared patients receiving HD with those receiving PD, demonstrating that PD was associated with greater preservation of beneficial commensals, although both modalities exhibited marked dysbiosis relative to healthy controls. Chen *et al* (27) later reported that patients receiving HD showed enrichment of Proteobacteria and Firmicutes, whereas transplant recipients displayed more diverse and eubiotic profiles. Collectively, these 16S-based studies support a reproducible core dysbiosis signature, yet the substantial variability in reported taxa across cohorts underscores the influence of geographic, dietary and medication-related confounders.

Metagenomic shotgun sequencing provides functional insights beyond taxonomic assignment. Shi *et al* (15) identified notable alterations in gut microbial pathways and virulence factors in patients receiving HD, with enrichment of LPS biosynthesis and bacterial secretion systems that may exacerbate systemic inflammation. Zhang *et al* (104) performed metagenome-wide analysis in patients with ESRD and uncovered taxon-specific functional signatures, including enhanced urease and indole-producing pathways in *Escherichia coli* and *Klebsiella* species. More recently, Lv *et al* (65) integrated 16S sequencing with T cell profiling, revealing that immune-microbiota dysregulation characterized by reduced regulatory T cell populations associates with specific taxonomic shifts in patients receiving maintenance HD. Qin *et al* (105) reported a paradoxical decrease in *Escherichia-Shigella* in patients with ESKD undergoing HD, contrasting with earlier reports,

Table III. Multi-omics characterizations of gut microbiota dysbiosis in patients receiving dialysis: Key findings from 16S rRNA sequencing, metagenomics, metabolomics and integrative analyses.

First author, year	Population	Dialysis modality	Omics technology/platform	Key microbial and metabolite findings	(Refs.)
Shi <i>et al.</i> , 2022	24 patients receiving HD, 16 controls	HD	Shotgun metagenomics	Enrichment of LPS biosynthesis pathways and bacterial secretion systems	(15)
Luo <i>et al.</i> , 2021	25 patients receiving HD, 25 patients receiving PD, 25 controls	HD vs. PD	16S rRNA sequencing (V3-V4)	PD associated with greater preservation of beneficial commensals; both modalities showed marked dysbiosis relative to controls	(17)
Hu <i>et al.</i> , 2020	16 patients with ESRD, 16 patients with CKD, 20 controls	Not specified	16S rRNA high-throughput sequencing (V3-V4)	Reduced abundance of SCFA producers (such as Lachnospiraceae and Ruminococcaceae) in patients with ESRD compared with patients with CKD and controls	(48)
Lv <i>et al.</i> , 2025	45 patients receiving MHD, 30 controls (HD-LI vs. HD-NLI)	MHD	16S rRNA sequencing (V3-V4) + T cell profiling	Reduced SCFA-producing bacteria in immunodeficient state; <i>Prevotella copri</i> , <i>Bacteroides vulgatus</i> and <i>Agathobacter</i> depleted; <i>Escherichia-Shigella</i> , <i>Blautia</i> and <i>Citrobacter</i> enriched	(65)
Zhu <i>et al.</i> , 2020	77 patients receiving MHD (classified as NCF or MCD) and 30 healthy controls	MHD	16S rRNA sequencing + serum metabolomics	Reduced SCFA-producing genera (<i>Lachnospira</i> , <i>Roseburia</i> , <i>Faecalibacterium</i>) in cognitively impaired patients; altered tryptophan and tyrosine metabolites associated with cognitive decline	(74)
Gao <i>et al.</i> , 2024	36 patients receiving MHD, 18 controls	MHD	16S rDNA + shotgun metagenome sequencing	<i>Roseburia</i> reduced by both methods; <i>Faecalibacterium</i> , <i>Megamonas</i> and <i>Bifidobacterium</i> positively associated with cognitive function; enriched KEGG pathways (oxidative phosphorylation, photosynthesis and riboflavin metabolism) in cognitively impaired patients	(78)
Li <i>et al.</i> , 2019	26 patients with CKD stage 5, 20 controls	Maintenance HD	16S rRNA sequencing (V3-V4)	Enrichment of pathogenic Enterobacteriaceae, depletion of butyrate-producing <i>Roseburia</i> and <i>Faecalibacterium</i> ; positive association between toxin-producing taxa and serum indoxyl sulfate levels	(103)
Zhang <i>et al.</i> , 2023	378 patients with ESRD receiving HD, 290 controls	HD	Deep metagenomic sequencing + MAG reconstruction	348 differentially abundant species, including ESRD-elevated <i>Blautia</i> , <i>Dorea</i> , Eggerthellaceae, and depleted <i>Prevotella</i> , <i>Roseburia</i> ; gut microbial composition predicted serum uremic toxin (IS, PCS, PAG, TMAO) concentrations	(104)
Qin <i>et al.</i> , 2025	20 patients receiving MHD, 20 controls	MHD	16S rRNA sequencing (ASV-based)	Decrease in <i>Escherichia-Shigella</i> abundance; 19 differentially abundant genera identified in patients receiving MHD compared with controls	(105)

Table III. Continued.

First author, year	Population	Dialysis modality	Omics technology/platform	Key microbial and metabolite findings	(Refs.)
Bao <i>et al</i> , 2022	Patients receiving PD (number not specified in the original study)	PD	16S rRNA sequencing (V3-V4) + serum metabolomics	Reduced <i>Lactobacillus</i> and <i>Bifidobacterium</i> abundances associated with higher serum PCS	(108)
James <i>et al</i> , 2025	Adults initiating PD	PD	Metagenomic sequencing + serum LC-MS/MS	Baseline microbial composition predicted subsequent uremic toxin elevations; serum IS, PCS, TMAO, PAG levels	(109)
Manokasemsan <i>et al</i> , 2025	Patients receiving PD	PD	LC-MS/MS metabolomics + 16S rRNA sequencing	Microbial compositional shifts associated with histidine metabolism; elevated imidazole propionate and other gut-derived metabolite alterations; histidine metabolism identified as previously underappreciated pathway	(110)
Kuo <i>et al</i> , 2025	85 patients receiving HD	HD	16S rRNA sequencing + targeted serum metabolomics	Distinct gut microbiota signatures associated with serotonin pathway metabolites; serum serotonin pathway metabolites (tryptophan, 5-HIAA, 5-HTP) associated with specific taxa (<i>Eubacterium eligens</i> , <i>Roseburia hominis</i>)	(111)
Li <i>et al</i> , 2024	73 patients receiving CAPD (different dialysis vintages)	CAPD	16S rRNA sequencing + untargeted metabolomics	Fungal signatures discriminated patients with different dialysis vintages; microbiome-derived metabolites associated with dialysis vintage	(112)
Krukowski <i>et al</i> , 2026	130 (metagenomics) + 4,420 (cross-study)	Mixed (dialysis and non-dialysis)	Quantitative fecal metagenomics	Host factors (diet, medications and socioeconomic status) explain more variance in gut microbiome composition than eGFR	(106)
Wang <i>et al</i> , 2024	Patients with ESRD receiving PD (sample size not specified in the available data)	PD	Metagenomic sequencing (shotgun)	PD promoted microbial-driven biosynthesis pathways of sesquiterpenes and triterpenes; sesquiterpene and triterpene metabolites with immunomodulatory properties	(117)

16S rDNA, 16S ribosomal DNA; 16S rRNA, 16S ribosomal RNA; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HTP, 5-hydroxytryptophan; ASV, amplicon sequence variant; CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis; HD-LI, maintenance hemodialysis patients with low immunity; HD-NLI, maintenance hemodialysis patients with normal immunity; IS, indoxyl sulfate; KEGG, Kyoto Encyclopedia of Genes and Genomes; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LPS, lipopolysaccharide; MAG, metagenome-assembled genome; MCD, mild cognitive decline; MHD, maintenance hemodialysis; NCF, normal cognitive function; PAG, phenylacetylglutamine; PCS, p-cresyl sulfate; PD, peritoneal dialysis; SCFA, short-chain fatty acid; TMAO, trimethylamine N-oxide; V3-V4, variable regions 3 and 4 of the 16S rRNA gene.

suggesting that disease severity and dialysis vintage may differentially impact specific taxa. These functional metagenomic approaches suggest that the enzymatic capacity for toxin synthesis, rather than taxonomic composition *per se*, may be an important determinant of circulating uremic toxin burden in patients receiving dialysis.

Despite these consistent findings, methodological heterogeneity, including differences in DNA extraction, primer selection and bioinformatic pipelines, complicates direct cross-study comparisons (17,27,48). Additionally, as demonstrated by Krukowski *et al* (106), host factors such as diet and socioeconomic status account for substantial variance in gut microbiome composition, often exceeding the effect of kidney function itself, suggesting that simple disease-centered interpretations of dysbiosis may be oversimplified.

Metabolomics and microbial metabolites. Metabolomic profiling directly captures the functional output of gut microbial communities and has identified specific metabolite signatures associated with clinical complications in dialysis populations. Li *et al* (107) performed targeted metabolomics of serum bile acids in patients receiving HD, demonstrating distinct profiles of primary and secondary bile acids that associated with inflammatory markers. Zhu *et al* (74) combined 16S sequencing with serum metabolomics in patients receiving HD with mild cognitive decline, identifying that reduced SCFA-producing genera associated with altered tryptophan and tyrosine metabolites. Bao *et al* (108) specifically examined gut-derived PCS in patients receiving PD, showing that serum levels were associated with reduced abundances of *Lactobacillus* and *Bifidobacterium*. James *et al* (109) recently characterized associations between uremic toxins and gut microbiota in adults initiating PD, finding that baseline microbial composition predicted subsequent toxin elevations. Manokasemsan *et al* (110) employed liquid chromatography-tandem mass spectrometry to identify elevated imidazole propionate and other gut-derived metabolite alterations in patients receiving PD, highlighting histidine metabolism as a previously underappreciated pathway. Kuo *et al* (111) identified gut microbiome signatures associated with the serotonin pathway in tryptophan metabolism of patients receiving HD, linking microbial metabolites to neurobehavioral complications. A critical observation from these metabolomic studies is that circulating toxin levels do not always associate with the abundance of their cognate biosynthetic taxa, indicating that pathway activity, substrate availability and host clearance mechanisms collectively determine metabolite concentrations.

Emerging dimensions: Mycobiome, virome and transkingdom interactions. While most studies have focused on bacterial communities, emerging evidence suggests that non-bacterial components of the gut ecosystem contribute to dysbiosis in patients receiving dialysis. Li *et al* (112) performed integrated microbiome and metabolome analysis in patients receiving continuous ambulatory PD, noting that fungal signatures discriminated patients with different dialysis vintages, although the mycobiome remains largely unexplored. Regarding host factors that shape the microbiome, Krukowski *et al* (106) recently demonstrated that host genetics and lifestyle factors dictate gut microbiome alterations in CKD more strongly

than kidney function itself, a finding that challenges simplistic disease-centered interpretations of dysbiosis. Additionally, the urogenital microbiome, which may interact with the gut reservoir, was characterized by Araujo *et al* (113) in patients receiving PD, revealing that specific taxa enriched in the urinary tract associate with peritonitis risk. These transkingdom and multi-compartment investigations remain in their infancy, yet they point to a more complex microbial ecology than bacterial-focused analyses can capture. A standardized framework for integrating fungal, viral and bacterial datasets in dialysis populations is currently lacking, representing a priority for future research.

Integrative multi-omics for mechanistic discovery. Integrating metagenomic and metabolomic datasets has enabled the investigation of potential mechanistic links between specific microbial functions and clinical phenotypes. Wu *et al* (114) developed a gut microbiota-based diagnostic tool that mirrored disease progression and circulating nephrotoxin levels in CKD, achieving high predictive accuracy for distinguishing mild from advanced disease. Zhou *et al* (115) characterized gut microbiota in patients receiving HD with sarcopenia and subsequently demonstrated that FMT from these patients induced muscle dysfunction in mice, providing causal evidence for the microbiota-sarcopenia axis. Similarly, Tang *et al* (116) showed that the gut microbiota from patients with sarcopenia receiving HD influenced muscle function in germ-free mice, providing experimental support for this association. Gao *et al* (78) combined 16S and shotgun metagenome sequencing to analyze intestinal flora and cognitive function in patients receiving HD, revealing that specific metabolic pathways including tryptophan and tyrosine metabolism were enriched in cognitively impaired individuals. Wang *et al* (117) demonstrated that PD promoted microbial-driven biosynthesis pathways of sesquiterpenes and triterpenes, metabolites with previously unrecognized immunomodulatory properties. These integrative approaches have moved beyond descriptive cataloging toward hypothesis-driven mechanistic interrogation, yet the majority of studies remain cross-sectional, limiting causal inference. Prospective longitudinal multi-omics studies tracking patients from dialysis initiation through complication development are urgently needed.

Methodological challenges and standardization needs. Despite the power of multi-omics approaches, substantial technical and interpretative challenges hinder progress in dialysis microbiome research. Mortelé *et al* (118) optimized an *in vitro* gut microbiome biotransformation platform, demonstrating that fecal sample processing and storage conditions affect measured microbial activity, a finding with direct implications for clinical study design. Lockwood *et al* (119) assessed the acceptability and feasibility of fecal microbiome and serum metabolite sample collection in patients receiving HD, reporting high patient compliance but noting logistical barriers that may introduce bias. Methodological heterogeneity across studies includes differences in DNA extraction kits, primer selection for 16S amplification, sequencing platforms (Illumina vs. nanopore), bioinformatic pipelines (QIIME2 vs. mothur) and metabolite extraction protocols. Furthermore, Krukowski *et al* (106) demonstrated that host

factors such as diet, medication adherence and socioeconomic status explain more variance in gut microbiome composition than estimated glomerular filtration rate, emphasizing that observational studies without rigorous covariate adjustment may yield spurious associations. The absence of standardized positive and negative controls across dialysis microbiome studies limits meta-analytic synthesis. Future investigations should adopt minimum reporting guidelines including shotgun metagenomic depth, metabolite quantification limits and comprehensive covariate documentation to enable meaningful cross-study comparisons.

While integrative multi-omics analyses have identified associations between microbial functions and clinical phenotypes (114,116), these findings remain largely correlational. Establishing causality requires prospective longitudinal sampling to determine temporality, coupled with functional validation in animal models, which still have limited translatability to the human uremic condition. Standardized reporting protocols for multi-omics studies should include shotgun metagenomic sequencing depth (minimum 5 million reads per sample), metabolomic quantification limits with internal standards and comprehensive documentation of demographic, dietary, medication and dialysis vintage data (106,118). Harmonized bioinformatic pipelines and reference databases are also essential to enable cross-study comparisons (13).

Integrative multi-omics frameworks and systems biology approaches. Moving beyond descriptive cataloging toward mechanistic inference requires integrative frameworks that synthesize metagenomic, metabolomic and clinical data into coherent biological models (106,120). Multi-omics integration can be conceptualized at three levels: Parallel analysis of separate datasets, correlation-based integration identifying statistical associations between omic layers and mechanistic integration inferring causal relationships through network modeling, longitudinal tracking or intervention studies (106,114). Most dialysis microbiome studies currently operate at the first two levels. Network-based approaches provide a powerful integration framework; microbial co-occurrence networks reveal ecological relationships disrupted in dysbiosis (107), while host-microbe correlation networks link specific microbial features to clinical parameters and circulating metabolites (114). Wu *et al* (114) demonstrated that gut microbiota correlation networks mirrored disease progression and nephrotoxin levels in CKD, achieving high predictive accuracy, while Mansour *et al* (121) constructed association networks between gut-derived uremic toxins and bile acid dysregulation.

Causal inference represents a critical frontier. While cross-sectional multi-omics studies generate hypotheses, establishing causality requires integration with longitudinal data or experimental manipulation. Zhou *et al* (115) characterized gut microbiota in patients with sarcopenia receiving HD, and Tang *et al* (116) subsequently showed that fecal transplantation from these patients induced muscle dysfunction in mice. Machine learning enables data-driven integration for patient stratification and biomarker discovery; Zhang *et al* (104) employed random forest classification to identify gut microbiota biomarkers of CKD progression, while Liu *et al* (122) proposed a diet-microbiota-kidney axis framework leveraging

machine learning to integrate dietary, microbial and metabolic data for precision nutrition. Pathway-level integration aggregates multiple omic features into functional units. Clinical translation of integrative findings requires rigorous covariate adjustment for host factors (diet, medications and socioeconomic status) that substantially influence gut microbiome composition (107), standardization of analytical protocols (118) and prospective validation in independent cohorts (120). Despite these challenges, integrative multi-omics frameworks hold promise for transforming dialysis microbiome research from descriptive association studies toward mechanistic, predictive and prescriptive approaches that can inform personalized care.

Taken together, multi-omics approaches have transformed gut microbiota research in dialysis from descriptive taxonomic cataloging toward functional, mechanistic and systems-level understanding. However, the translation of multi-omics discoveries into clinical practice faces persistent challenges, including methodological heterogeneity, lack of standardized protocols and the substantial influence of host factors on microbial composition. A potential path forward involves integrative frameworks that combine metagenomic, metabolomic and clinical data with network-based modeling and machine learning to generate testable hypotheses and ultimately guide personalized interventions.

Addressing inconsistencies across studies. Despite a reproducible core dysbiosis signature in patients receiving dialysis, several notable inconsistencies emerge across studies. For example, some reports found enrichment of *Escherichia-Shigella* in patients receiving HD (65), whereas others reported a paradoxical decrease (105). *Bifidobacterium* depletion has been associated with both cognitive impairment (75) and peritonitis risk (43), yet the specific species affected and the magnitude of depletion vary considerably. Regarding dialysis modality, Stadlbauer *et al* (26) reported that PD was associated with greater alterations in microbial diversity than HD, whereas Luo *et al* (17) found greater preservation of beneficial commensals in patients receiving PD. These discrepancies are not necessarily contradictory but likely reflect true biological variation across populations and methodological differences.

Multiple factors contribute to inter-study heterogeneity. Geographic location and dietary habits shape baseline gut microbiota composition (106). Medication use, including phosphate binders, proton pump inhibitors and antibiotics, exerts substantial and differential effects on microbial communities (35-37). Dialysis vintage may also influence microbial profiles, as Qin *et al* (105) suggested that disease severity and treatment duration differentially impact specific taxa. Furthermore, methodological heterogeneity across sequencing platforms (16S vs. shotgun metagenomics), DNA extraction kits, primer selection, bioinformatic pipelines and metabolite quantification protocols complicates cross-study comparisons (118). Studies also vary in sample size, inclusion criteria and covariate adjustment, with numerous lacking rigorous control for confounders that were demonstrated by Krukowski *et al* (106) to explain more variance in gut microbiome composition than kidney function itself.

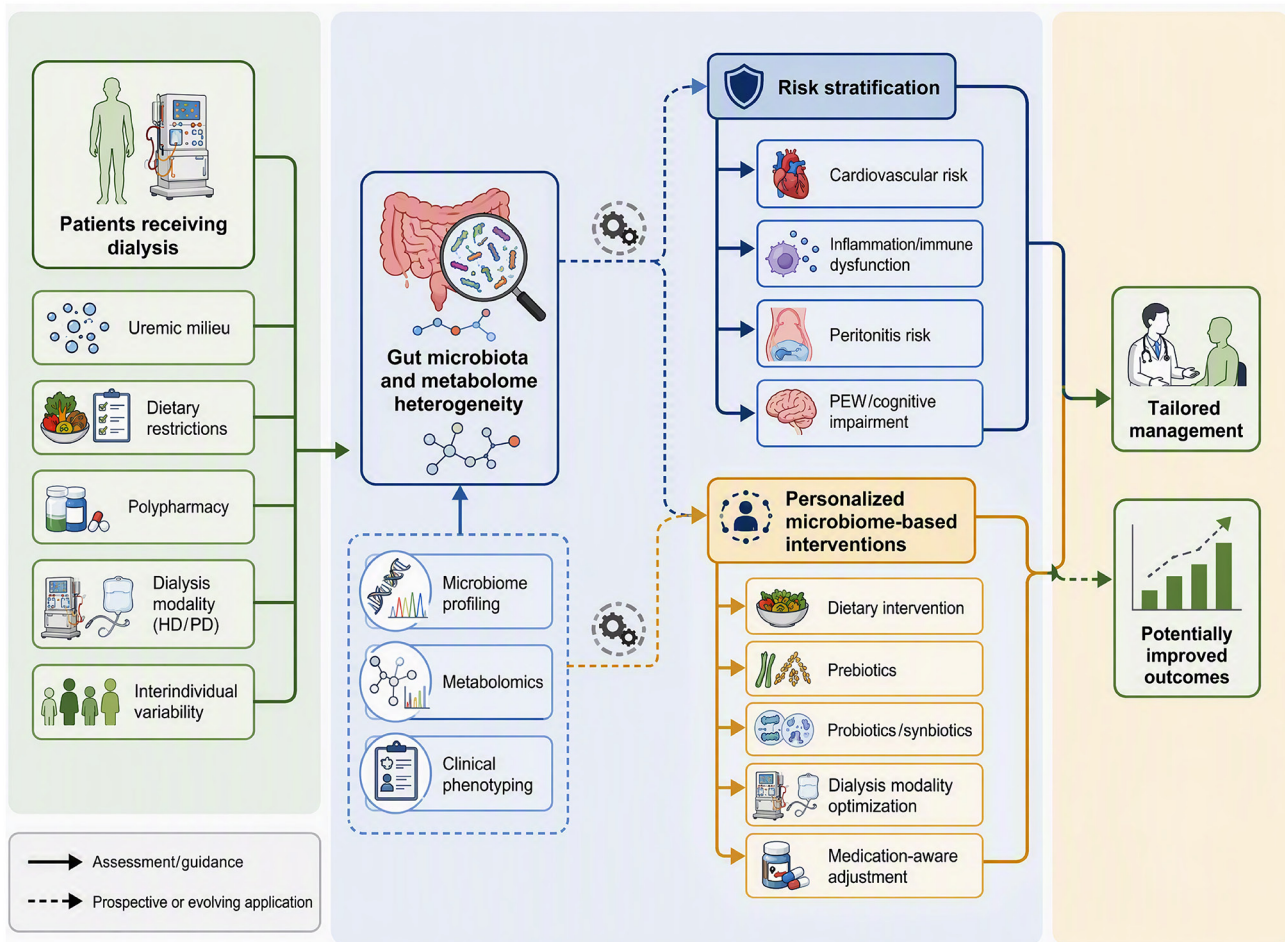


Figure 3. Translational roadmap for personalized microbiome-based care among patients receiving dialysis. Baseline factors including uremic milieu, dietary restrictions, polypharmacy, dialysis modality (HD/PD) and inter-individual variation drive gut microbiome-metabolome heterogeneity. Integrated assessments comprising microbiome profiling, metabolomics and clinical phenotyping feed into machine-learning-assisted risk stratification, which stratifies patients by their individual risk of cardiovascular events, inflammation-immune defects, peritonitis, PEW and cognitive impairment. Stratified subgroups receive tailored interventions, including dietary adjustment, prebiotics, probiotics/synbiotics, dialysis modality optimization and medication adjustments considering drug-microbiome interactions. Longitudinal follow-up enables adaptive management to improve clinical outcomes. Solid arrows represent assessment and clinical guidance; dashed arrows denote prospective, evolving translational applications. HD, hemodialysis; PD, peritoneal dialysis; PEW, protein-energy wasting.

Acknowledging these sources of heterogeneity is essential for interpreting the literature and designing future studies. The field would benefit from standardized reporting guidelines that include detailed documentation of demographic, dietary and medication data, along with harmonized analytical pipelines to enable meaningful meta-analyses (118). Rather than viewing discrepant findings as problematic, they should be recognized as opportunities to identify patient subgroups, geographical or environmental influences and intervention-specific responses that may ultimately inform personalized approaches (106).

7. Toward personalized microbiome-based care in dialysis

Personalizing microbiome-based interventions in patients receiving dialysis requires moving beyond one-size-fits-all strategies. Accumulating evidence from randomized trials on prebiotics, probiotics, synbiotics and dietary fibers reveals marked heterogeneity in therapeutic responses. This variability may reflect differences in baseline microbiota composition, dialysis modality, concomitant medications

and host metabolic profiles. A roadmap integrating clinical phenotyping, microbial profiling and metabolomic biomarkers is therefore essential to guide individualized selection of microbiome-targeted therapies (Fig. 3).

Dietary and prebiotic strategies. Dietary modulation represents a foundational approach to reshape gut microbiota in patients receiving dialysis. Increased intake of dietary fiber has been associated with lower levels of gut-derived uremic toxins, although adherence remains suboptimal (123,124). Among prebiotics, inulin-type fructans have been investigated. Li *et al* (87) conducted a randomized crossover trial in patients receiving PD and found that inulin-type fructan supplementation notably restricted the increase in serum indole, a microbiota-generated uremic toxin. Similarly, in a controlled crossover trial in patients receiving PD, inulin-type prebiotics reduced serum uric acid levels via gut microbiota modulation (88); however, the effects on protein-bound solutes such as IS and PCS have been less consistent. A pilot study of inulin supplementation in patients receiving HD reported

altered microbiota composition but no significant changes in circulating IS or PCS (125), suggesting that baseline microbial composition or dialysis modality may influence responses.

Resistant starch (RS) has emerged as another prebiotic. In patients receiving HD, RS type-2 enriched cookies markedly reduced plasma IS and PCS levels while attenuating inflammation (92,126). A subsequent RCT further demonstrated that RS supplementation increased the proportion of *Faecalibacterium*, a butyrate-producing genus with anti-inflammatory properties (127). However, a recent double-blind controlled trial reported that pea hull fiber supplementation did not modulate uremic metabolites in adults receiving HD (128), highlighting that not all fibers confer equivalent benefits. Collectively, these data indicate that prebiotic efficacy is fiber-type specific and likely depends on baseline dysbiosis severity, necessitating personalized selection based on individual microbial profiles.

Probiotic and synbiotic interventions. Probiotic supplementation has been extensively evaluated in dialysis populations, albeit with heterogeneous outcomes. Soleimani *et al* (79) demonstrated that a multi-strain probiotic improved metabolic profiles in patients with diabetes receiving HD. Subsequently, Borges *et al* (52,80) reported that probiotic supplementation reduced plasma PCS and inflammatory markers but did not notably lower TMAO levels. In a larger randomized trial, Liu *et al* (129) showed that probiotics altered gut microbiota composition in patients receiving HD, yet changes in uremic toxins did not reach statistical significance. More recently, Zhou *et al* (83) found that probiotic treatment induced intestinal microbiota changes but did not alter SCFA levels in patients receiving PD. These discrepancies may be explained by differences in probiotic strains, dosing regimens, treatment duration and patient characteristics.

Synbiotics, which combine probiotics with prebiotics, have shown benefits. A randomized trial by Mirzaeian *et al* (82) reported that synbiotic supplementation markedly reduced serum IS and PCS along with systemic inflammation in patients receiving HD. Similarly, Lopes *et al* (81) demonstrated that a synbiotic meal decreased uremic toxins in individuals receiving HD. In patients receiving PD, synbiotics alleviated gut indole load and dysbiosis (130). A recent 2025 randomized trial by Climent *et al* (131) revealed that psychobiotic-containing nutritional supplements improved mood and gastrointestinal symptoms in patients receiving HD, extending benefits beyond metabolic endpoints. Despite these results, the lack of head-to-head comparisons and standardized outcome measures precludes definitive recommendations, and future trials should incorporate baseline microbiome profiling to identify responders.

Novel and adjunctive approaches. Beyond classical prebiotics and probiotics, emerging strategies offer additional avenues for personalization. SCFA supplementation, particularly sodium propionate, improved inflammatory parameters and reduced gut-derived uremic toxins in a pilot study in patients receiving HD (132). Oral vancomycin-induced gut microbiome perturbation lowered plasma IS and PCS concentrations in patients with ESRD (133), providing proof-of-concept that targeted antimicrobial modulation can be effective, albeit with safety concerns regarding resistance

and dysbiosis. Another approach involves oral administration of engineered microbial cocktails. Zheng *et al* (134) developed an orally delivered microbial formulation that effectively removed nitrogenous waste in animal models of kidney failure, representing a potential synthetic biology strategy for future clinical translation.

Phosphate binders, routinely used in dialysis, may exert unintended microbiome-modulating effects. Sevelamer use was associated with poor vitamin K status and elevated gut-derived uremic toxins, suggesting a drug-microbiome interaction (36). Conversely, sucroferic oxyhydroxide showed differential impacts on the oral and intestinal microbiome compared with calcium acetate (35,135). These observations raise the possibility of selecting phosphate binders based on their collateral microbiome effects. Furthermore, FMT has been explored in small studies. A pilot trial in children on kidney replacement therapy demonstrated the feasibility of FMT for recurrent *Clostridium difficile* infection (97), but its application for uremic toxin reduction remains investigational and requires rigorous safety evaluation.

Microbiome-based patient stratification and multi-omics integration. A step toward personalization is systematic stratification of patients receiving dialysis into distinct microbial subtypes, or microbiotypes, based on compositional and functional profiles. Enterotype-based stratification has been explored in CKD populations, with patients with CKD stages 3-5 categorized into distinct enterotypes whose formation showed weak dependence on environmental factors, suggesting that microbial stratification may offer insights beyond traditional clinical classification (106). In dialysis populations, distinct microbial communities distinguish patients receiving PD from those receiving HD despite similar overall diversity, and specific taxonomic shifts, such as depletion of *Bifidobacterium adolescentis*, have been linked to nutritional risk (17).

Beyond enterotyping, integrative clustering approaches that combine fecal microbiome data with urinary peptidome profiles have been applied to explore patient clustering in CKD (120). Extending such multi-omics clustering to dialysis populations could enable identification of patient subgroups with shared microbial dysbiosis patterns, thereby guiding selection of targeted interventions. For instance, patients with predominant depletion of SCFA producers may benefit more from prebiotic fiber supplementation, whereas those with overrepresentation of proteolytic toxin-generating taxa might require different approaches such as adsorbents or dietary protein modification.

Metabolite-guided therapeutic selection represents another dimension of personalization. Serum metabolomics has identified gut-derived uremic toxins and bile acid dysregulation associated with CKD severity (121), and baseline microbial composition has been shown to predict subsequent uremic toxin elevations in patients initiating PD (110). Such predictive capacity could inform preemptive selection of interventions targeting specific metabolite pathways. For example, patients with elevated baseline TMAO may be candidates for strategies specifically aimed at reducing TMAO production, while those with high IS or PCS might benefit from adsorbent-based approaches or dietary tryptophan restriction (101).

The integration of multi-omics data, including metagenomics, metabolomics and metatranscriptomics, is essential for moving beyond descriptive taxonomy toward functional personalization (120). Metagenome-wide analyses have uncovered taxon-specific functional signatures in ESRD (104), and combined 16S and shotgun metagenome sequencing has revealed metabolic pathway enrichment associated with specific clinical phenotypes such as cognitive impairment (78). However, integrating these disparate data types into clinically actionable frameworks remains challenging. Krukowski *et al* (106) demonstrated that host factors including diet, medications and socioeconomic status explain more variance in gut microbiome composition than estimated glomerular filtration rate, emphasizing that patient-level covariates must be incorporated into any personalization algorithm.

Predictive modeling and artificial intelligence (AI). Machine learning and AI are emerging as tools for translating multi-omics data into personalized recommendations. In HD populations, machine learning has been applied to investigate how patient characteristics, medications and clinical parameters affect gut microbiome diversity over time (122). Random forest classification and other machine learning approaches have validated key microbial alterations associated with disease, and gut microbiota biomarkers of CKD progression have been identified using 16S ribosomal DNA sequencing combined with machine learning (114).

The application of AI to the gut-kidney axis has been comprehensively reviewed, with AI utilized for multi-omics analysis to better understand CKD pathogenesis (122). In PD, multi-omics and AI have been proposed to enhance personalized nutritional management by processing datasets from continuous glucose monitoring, genetic, metabolic and microbiome profiles. AI can identify patterns and predict outcomes that may be difficult for humans to detect, enabling personalized recommendations for diet, medication and dialysis management. More recently, the diet-microbiota-metabolite-kidney axis framework has been proposed, identifying AI-assisted dietary planning as a potential direction for precision nutrition (122).

Predictive modeling of clinical outcomes using microbial signatures is also advancing. Specific taxa such as Bifidobacteriaceae have been identified as potential markers for predicting skeletal muscle mass decline and PEW (70). Ongoing clinical trials are actively developing AI models for early cardiovascular risk prediction in patients receiving HD using gut microbiome multi-omics data (122). These developments underscore the potential for AI-driven predictive models to inform clinical decision-making, although prospective validation in real-world dialysis settings remains limited.

Roadmap to personalization. Accumulating evidence indicates that a one-size-fits-all approach is unlikely to succeed in microbiome-based care for patients receiving dialysis. Host factors, including diet, medications and genetic background, shape gut microbiota notably more than kidney function itself (106). Longitudinal multi-omics profiling integrating metagenomics, metabolomics and clinical parameters will be essential to stratify patients into distinct microbiotypes. For instance, serum metabolomics has identified gut-derived

uremic toxins and bile acid dysregulation associated with CKD severity (121), and guild-level signatures of gut microbiome have been linked to diabetic kidney disease (136). Machine learning models incorporating baseline microbiota and metabolome data could predict individual responses to specific interventions, enabling algorithm-driven prescription of prebiotics, probiotics or dietary regimens (122). Additionally, dynamic monitoring during follow up would allow adaptive modifications. The practical implementation of such a framework will require standardized protocols for sample collection and processing, development of clinically validated algorithms and integration with electronic health records to enable real-time decision support. Realizing this vision requires large-scale, well-phenotyped cohort studies with multi-omics characterization and standardized interventional protocols. Until then, pragmatic attempts at personalization should consider dialysis modality, residual kidney function, dietary habits, concomitant medications (such as proton pump inhibitors and phosphate binders) and baseline toxin levels as initial stratification variables.

Clinical translation: Feasibility, barriers and future opportunities. Translating microbiome research into dialysis clinical practice requires addressing several practical considerations. The feasibility of microbiome profiling in patients receiving dialysis has been assessed in a pilot study, with Lockwood *et al* (119) reporting high patient compliance in fecal sample collection, although logistical barriers including sample processing, storage and shipping remain challenging (118). Potential biomarkers for risk stratification include gut-derived uremic toxins (IS, PCS and TMAO) measured by serum metabolomics (121), specific taxa such as Bifidobacteriaceae for predicting muscle mass decline (70) and microbial diversity indices associated with cognitive impairment (78) and mortality risk (12). However, none of these biomarkers have been validated in prospective interventional trials for clinical decision-making.

Barriers to clinical implementation include a lack of standardized analytical protocols across institutions, which limits cross-study comparability (106,118); the substantial influence of host factors (diet, medications and socioeconomic status) on microbiome composition, complicating interpretation of individual patient profiles (106); the absence of clinically validated thresholds for microbiome-based risk stratification; and limited evidence that microbiome-targeted interventions improve hard clinical outcomes. Despite these barriers, future opportunities include integration of microbiome profiling with electronic health records to enable real-time decision support, development of point-of-care metagenomic testing and AI-assisted algorithms for predicting treatment responses based on baseline microbial profiles (122). Pragmatic initial steps may include using baseline toxin levels and dialysis modality as stratification variables while standardized protocols are being developed (14).

8. Future perspectives

Despite substantial progress in characterizing gut dysbiosis in patients receiving dialysis, the field remains at a stage where observational associations must be translated into

mechanism-based interventions. Several knowledge gaps warrant attention. First, the causal relationship between specific microbial taxa and clinical outcomes remains incompletely established. Krukowski *et al* (106) demonstrated that host factors including diet, medications and socioeconomic status explain more variance in gut microbiome composition than estimated glomerular filtration rate, challenging simplistic disease-centered interpretations of dysbiosis. Similarly, Holle *et al* (53) showed in pediatric patients with CKD that gut dysbiosis and metabolite imbalance drive inflammation through integrin-mediated signaling, yet whether similar mechanisms operate in dialysis populations requires direct validation. These findings collectively suggest that future studies must incorporate rigorous covariate adjustment and preferably employ longitudinal designs to disentangle cause from consequence. To move from association to causation in dialysis microbiome research, the field requires a stepwise approach: Prospective longitudinal cohorts that document microbial changes before and after complication development to establish temporality; mechanistic validation in animal models with human-derived microbial transplants to test candidate causal pathways (115,116); and RCTs of microbiome-targeted interventions that demonstrate both modulation of specific microbial functions and corresponding improvement in clinical outcomes (14). Currently, most evidence in patients receiving dialysis remains at the first level of this hierarchy, with only limited progress toward the second and third levels. The substantial heterogeneity in treatment responses observed in probiotic and prebiotic trials may partly reflect unrecognized differences in baseline microbial composition and metabolic capacity, underscoring the need for baseline microbiome stratification in future RCTs (83).

Emerging multi-omics technologies offer opportunities for mechanistic discovery. Wu *et al* (120) employed integrated metagenomic, metabolomic and deep immune profiling to uncover complex host-microbe interactions in chronic kidney disease, demonstrating the power of multi-omics approaches for patient stratification. Extending this approach, Mansour *et al* (121) identified gut-derived uremic toxins and bile acid dysregulation associated with CKD severity using serum metabolomics, suggesting that metabolite signatures may outperform taxonomic markers for risk stratification. Notably, Liu *et al* (122) proposed a diet-microbiota-kidney axis reprogramming framework emphasizing that microbial metabolite-driven precision nutrition represents a potential avenue for personalized care. Nevertheless, Lockwood *et al* (119) reported high patient compliance but noted logistical barriers in fecal sample collection from patients receiving HD, highlighting that methodological standardization remains a prerequisite for clinical implementation.

FMT has emerged as a potential approach, although evidence in patients receiving dialysis remains sparse. Samaey *et al* (97) conducted a pilot study demonstrating the feasibility of FMT for recurrent *Clostridioides difficile* infection in children on kidney replacement therapy, but no trial has specifically evaluated FMT for uremic toxin reduction in dialysis populations. Conversely, Arteaga-Muller *et al* (137) reported changes in CKD progression following FMT, while

Zhong *et al* (138) showed that washed microbiota transplantation improved renal function in patients with renal dysfunction. However, Liu *et al* (98) cautioned that gut dysbiosis in kidney injury requires careful patient selection for FMT, given potential safety concerns related to immune dysfunction in patients receiving dialysis. A recent case report by Marasco *et al* (99) described FMT for *Clostridioides difficile* infection in a patient receiving PD, but larger controlled trials are needed. These mixed findings underscore that FMT protocols must be optimized specifically for dialysis populations before clinical adoption.

Beyond FMT, novel therapeutic paradigms are rapidly evolving. Xie *et al* (139) reported that alteration of gut microbiota contributes to peritoneal fibrosis through increased production of TMAO, identifying a previously unrecognized mechanism linking dysbiosis to peritoneal membrane injury. Furthermore, Ban *et al* (140) employed multi-omics to demonstrate that *Akkermansia muciniphila* confers renal protection in CKD, suggesting that single-organism supplementation may represent a more targeted approach than whole-community transplantation. The application of AI to predict individual responses represents another area of investigation, with Mahdavi (141) advocating for precision nutritional genomics integrating gut microbiota data with machine learning algorithms to guide personalized interventions.

Advancing the field from observational associations to microbiome-guided dialysis care will therefore require several coordinated efforts. Prospective longitudinal multi-omics studies tracking patients from dialysis initiation through complication development are needed, as are adequately powered RCTs of FMT and next-generation probiotics with standardized endpoints. Moreover, integration of host genetic, dietary and medication data into predictive models of treatment response will be essential for realizing personalized approaches, alongside the development of regulatory frameworks for microbiome-based therapeutics specifically tailored to the dialysis population. Until these goals are achieved, pragmatic personalization should incorporate dialysis modality, residual kidney function and baseline toxin profiles as stratification variables for interventional studies.

9. Conclusions

Gut dysbiosis in patients receiving dialysis may contribute to systemic complications through metabolite imbalance, barrier disruption and inflammation. Conventional therapies inadequately address this cycle. Personalized microbiome-based care that integrates multi-omics profiling, dietary modulation and targeted interventions holds promise. Practical translation will require overcoming barriers in analytical standardization, biomarker validation and clinical integration, with pragmatic initial steps focusing on baseline toxin stratification and dialysis modality-specific approaches. Future research must establish causality and optimize strategies to improve clinical outcomes in this population.

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Authors' contributions

CJ conducted the literature search, extracted and synthesized the published literature, and drafted the manuscript. YW conceived the review and critically revised the manuscript. Both authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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