



Review

Gut–Kidney Crosstalk in Acute Kidney Injury: Gut as a Modifier of AKI

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Abstract

Growing recognition of the gut–kidney axis has revealed that gut dysbiosis and altered mucosal immunity are intimately intertwined with acute kidney injury (AKI). Gut changes following AKI, including dysbiosis and associated altered metabolites, barrier disruption, and maladaptive immune responses, affect post-AKI outcomes in a bidirectional manner. Therefore, the gut is increasingly recognized as a previously underappreciated modifier of AKI, and recent research is beginning to dissect the causal relationships between microbial perturbations and AKI, as well as the mechanisms underlying these complex interactions. However, relevant data remain limited, underscoring the need for further mechanistic and translational studies to fully elucidate key pathways for the development of novel, gut-targeted therapeutics. In this review, we summarize the mechanisms by which gut dysbiosis contributes to AKI outcomes and discuss gut-based therapeutic options based on experimental and clinical studies as well as future perspectives.

Keywords: acute kidney injury; gut microbiome; kidney–gut crosstalk

1. Introduction

Acute kidney injury (AKI) is a serious clinical syndrome characterized by a rapid decline in renal function, with an incidence of approximately 10–15% among hospitalized patients and exceeding 50% in critically ill patients in intensive care units [1–3]. AKI arises from diverse etiologies, broadly categorized as prerenal (intravascular volume depletion, hemodynamic compromise), intrinsic renal (ischemia–reperfusion injury [IRI], nephrotoxin exposure, sepsis), and postrenal (urinary obstruction) causes. Prerenal and acute tubular necrosis (ATN) are common subtypes of AKI, and they exist with a pathophysiological continuum: sustained hypoperfusion from sepsis or uncorrected volume depletion can progress from reversible prerenal AKI to established ATN. This continuum is especially relevant in gut-related conditions such as IBD or colonic surgery, where volume depletion, hypotension, gut-derived nephrotoxic cytokines, and nephrotoxic medications act in concert to precipitate AKI. Despite advances in renal replacement therapy and supportive care, mortality associated with severe AKI remains unacceptably high, and survivors face substantially elevated risks of incomplete renal recovery, progression to chronic kidney disease (CKD), and long-term cardiovascular morbidity. AKI pathogenesis involves complex interactions between tubular epithelial and endothelial cells and innate and adaptive immune systems. Among them, inflammation caused by both the migration of circulating



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leukocytes or the activation of resident immune cells in the kidney have been demonstrated to regulate not only the pathogenesis of the kidney injury but also the repair process. However, despite advancements in our understanding of the pathogenetic mechanisms, little progress has been made in the development of therapies, and thus, mortality associated with AKI still remains high.

Over the last two decades, the gut microbiome has emerged as an important modifier of mammalian health and pathology. Accumulating evidence has shown that alterations in the gut microbiome, referred to as dysbiosis, can trigger or aggravate numerous immune-mediated or metabolic disorders, including various kidney diseases [4–6]. Preclinical studies have clearly demonstrated a bidirectional relationship between the kidney and gut in AKI. The present review summarizes our current understanding of kidney–gut crosstalk in AKI, with a focus on the underlying mechanisms and proposes future directions for the development of novel microbiome-targeted therapeutics.

2. Bidirectional Relationship Between the Kidney and Gut in AKI

The gut harbors more than 100 trillion microbial cells and is in a state of dynamic interaction with the host, participating in multiple physiological functions, including development, metabolism, the maintenance of barrier integrity, and immune modulation. A large body of evidence indicates that perturbations in the structure or function of the gut microbiota (i.e., dysbiosis) are associated with the development and progression of many immune-mediated or metabolic disorders, including chronic kidney disease (CKD). Uremic toxins, gut edema, prolonged transit times, reduced dietary fiber intake, frequent use of antibiotics, and other factors can contribute to gut dysbiosis, aggravating kidney fibrosis via altered metabolites and immune dysfunction. Although studies focused on crosstalk between the kidney and gut in AKI are still limited, we can obtain some clues from previous studies involving patients with inflammatory bowel disease (IBD) or those undergoing colorectal surgery (Table 1). In recent published epidemiological studies, patients with chronic inflammatory bowel disease had an approximately two-fold increased risk of AKI [7–10]. Despite the use of various criteria to define AKI, it is evident that AKI remains closely associated with the presence of multiorgan dysfunction, especially gut dysfunction [11–14]. Postoperative ileus persisting beyond three days following colorectal surgery is independently associated with a more than six-fold increased risk of AKI, likely reflecting the combined effects of prolonged prerenal states due to delayed volume resuscitation and ileus-induced gut microbiota dysbiosis, both of which may act in concert to precipitate renal injury [15]. The renal implications of immunomodulatory therapies used in IBD—including anti-TNF agents, anti-interleukin therapies, JAK inhibitors, and conventional immunosuppressants—remain incompletely understood. While these agents may confer renal protection by attenuating systemic inflammation and cytokine-mediated tubular injury, they may equally carry nephrotoxic potential through drug-induced interstitial nephritis or direct tubular toxicity. Further studies are warranted to clarify the renal impact of these therapies, particularly in IBD patients at high risk of AKI. All these data suggest that the gut might be an important modifier of the AKI (Table 1).

Experimental studies have also shed light on the potentially important interaction of the gut and kidney in AKI. For example, germ-free mice (GFM) show exacerbated injury with increased CD8⁺ T cells in the kidneys following ischemia/reperfusion injury (IRI) [16]. Park et al. have shown that kidney IRI provokes the release of preformed IL-17A from the small-intestinal Paneth cells, mediating kidney injury, as well as concomitant gut and liver injury [17]. This landmark study demonstrated that gut-derived IL-17A enters the systemic circulation and serves as a critical mediator of multiorgan dysfunction, including sepsis-like AKI. Notably, depletion of Paneth cells or neutralization of IL-17A significantly

attenuated renal tubular apoptosis and inflammation. IL-17A may act either as an upstream trigger or as a downstream inflammatory amplifier, although these roles cannot yet be clearly distinguished. In addition, the administration of short-chain fatty acids (SCFAs), metabolites exclusively produced by the colonic bacterial fermentation of indigestible dietary fiber, attenuates IRI and is associated with decreased systemic inflammation and oxidative stress, as well as increased mitochondrial biogenesis [18,19]. All these data show the potentially important, previously unrecognized interaction between the gut and kidney in AKI.

Table 1. Clinical studies of acute kidney injury in inflammatory bowel disease and colorectal surgery.

Author, Year	n.	Study Design	Population	AKI Definition	Outcome
Surgery-associated AKI					
Lim et al. 2016 [15]	288	Retrospective single center	Elective colorectal surgery	AKIN criteria: 0.3 mg/d or a 50% increase in the SCr from the baseline value within 48 h or a urine output < 0.5 mL/kg/h for 6 h	Postoperative ileus is a risk factor for AKI (HR 6.75, 95% CI 1.5–28.78, $p = 0.01$) AKI was associated with longer hospital stay (16 days vs. 26 days, $p = 0.04$), more dialysis requirement (0 vs. 2, $p = 0.001$), increased mortality (0 vs. 2, $p = 0.001$)
Marcotte et al. 2018 [14]	132	Retrospective, Propensity matched cohort comparison	Elective colorectal surgery	KDIGO criteria	ERAS with lower AKI rate (11.4 vs. 2.3%, $p < 0.01$) AKI induced more postoperative AKI (AKI 46% vs. no AKI 16%, $p = 0.01$)
Slagelse et al. 2019 [13]	6580	Prospective observational cohort	Colorectal cancer surgery	50% increase in PCr, initiation of RRT within 7 days after surgery or an absolute increase in creatinine of 26 $\mu\text{mol/L}$ within 48 h.	AKI occurred 20.3% AKI was associated with increased 30 d mortality (aHR 4.01, 95% CI 3.11–5.17), 90 d mortality (aHR 2.08, 1.60–2.69)
IBD-associated AKI					
Liu et al., 2023 [7]	4201	prospective, observational, population-based cohort	2940 ulcerative colitis, 1261 Crohn's disease	ICD-10 code, N17 for AKI	AKI, HR 1.70 (95% CI 1.51–1.91) CKD, HR 1.32 (95% CI 1.15–1.51)
Achit et al., 2022 [12]	94,363	Retrospective national insurance database review	ICD-10 code IBD	ICD-19 code, N00, N01, N04, N10, N141, N142, N144, N17, Drug-related kidney biopsy and withholding medication records	AKI without monitoring (HR 3.7, (95% CI 3.0–4.6, $p < 0.01$)
Yang et al. 2024 [9]	82,051	nationwide cohort study	biopsy-proven IBD	Receiving a diagnosis of acute nephritis or acute renal/kidney failure, enriched with procedural codes of acute dialysis therapy.	AKI developed in 2556 patients (3%) Colectomy was a risk factor for AKI (HR 2.37, 95% CI 2.17–2.58) Total colectomy worse than partial colectomy
Yang et al. 2024 [8]	10,117	nationwide cohort study	biopsy-proven IBD	Receiving a diagnosis of acute nephritis or acute renal/kidney failure, enriched with procedural codes of acute dialysis therapy.	AKI (HR 1.97 [95% CI 1.70–2.29])

Table 1. Cont.

Author, Year	n.	Study Design	Population	AKI Definition	Outcome
Saha et al. 2024 [10]	57,121	Retrospective population-based cohort study	IBD	ICD-9 code with AKI, AKI requiring dialysis	In -hospital AKI incidence 13% AKI OR 1.27 (95% CI 1.23–1.31 vs. general population)
Nguyen et al. 2026 [11]	140,482	7 retrospective cohort studies systematic review and meta-analysis	IBD	-	IBD is associated with AKI OR 1.87 (95% CI 1.53–2.29)

Recently, the most common cause of AKI in intensive care units is septic AKI [2]. Sepsis is a life-threatening illness triggered by a dysregulated host immune response against pathogens, resulting in multiple organ dysfunction including AKI. Gut dysbiosis characterized by decreased alpha diversity, imbalance between Firmicutes/Bacteroidetes, as well as increased relative abundance of Enterobacteriaceae, Enterococcus, and decreased abundance of Lactobacillus has been demonstrated in human sepsis [20–22]. Multiple factors including increased permeability provoked by systemic inflammation, the nonselective depletion of commensal bacteria by the prolonged use of broad-spectrum antibiotics, intestinal ischemia caused by septic shock, gastrointestinal dysfunction, and prolonged fasting are thought to be major drivers of dysbiosis in sepsis [23,24]. Similar to IRI, a leaky gut with endotoxin translocation, altered metabolites and immune phenotype has been demonstrated to be important in organ dysfunction. In addition, emerging evidence suggests that gut microbiota signatures such as an increased relative abundance of Enterococcus might be useful as a predictive biomarker for patient outcomes.

2.1. AKI Provokes Gut Changes

Experimental studies have clearly demonstrated the rapid development of gut dysbiosis one day after kidney IRI or four days after cisplatin administration [25,26]. Gut dysbiosis after kidney IRI was characterized by increases in the relative abundance of Enterobacter and Escherichia, and decreases in the abundance of Lactobacillus and Ruminococcus. In addition to dysbiosis, these studies demonstrated that gut dysbiosis was associated with increased permeability and bacterial translocation, which can potentiate systemic inflammation. Fecal levels of short-chain fatty acids, which are important in immune modulation as well as colonocyte survival were decreased significantly. AKI also provoked potent gut inflammation, characterized by increased neutrophil and proinflammatory macrophage infiltration, as well as an increased percentage of IL-17A+ Th 17 cells in both the small and large intestines. These data show altered gut microenvironmental changes, including a leaky gut, bacterial translocation, and gut inflammation after AKI, might have profound effects on post-AKI outcomes.

2.2. Gut as a Previously Unrecognized Modifier of AKI

Despite epidemiological studies showing an increased risk of AKI in patients with IBD or those undergoing colorectal surgeries, the role of the gut as a possible modifier of AKI remained unclear. In an experimental model of IRI-induced AKI, Yang et al. clearly demonstrated this role by using GMF receiving fecal microbiota transplantation (FMT) [25]. They demonstrated that GFM receiving FMT from mice subjected to IRI developed more severe functional deterioration, more pronounced kidney damage, and more severe kidney inflammation than GFR receiving FMT from sham-operated mice. These data clearly show

that gut dysbiosis and the accompanying barrier disruption/inflammation are not only consequences of kidney IRI but also represent important modifiers of post-ischemic kidney outcomes, further supporting the gut as a novel therapeutic target in AKI.

3. Proposed Temporal Sequence of Kidney-Gut Crosstalk in AKI

Despite a lack of data, we suggest that following kidney IRI, (1) the injury triggers systemic inflammation and hemodynamic compromise, leading to gut ischemia and mucosal injury within hours; (2) intestinal barrier disruption ensues, allowing the translocation of bacteria and endotoxins into the portal and systemic circulation; (3) the activation and migration of gut immune cells further amplify systemic inflammation; and (4) these gut-derived inflammatory mediators feed back to the injured kidney, worsening tubular injury and delaying recovery.

4. Mechanisms by Which the Gut Affects AKI Causation and Outcomes

Considering that gut changes might be a novel therapeutic target, it is important to understand the mechanisms linking the gut to kidney injury. Bacteria or endotoxins that migrate via a leaky gut, altered bacterial metabolites, and immune-cell activation/trafficking are potential mediators of kidney injury in AKI.

4.1. Bacteria and Endotoxins

Endotoxins from Gram-negative bacteria mediate septic AKI by provoking systemic inflammation, oxidative stress, and ischemia via renal vasoconstriction. By using two-photon microscopy, Kalakeche nicely demonstrated that fluorescein-labeled endotoxins are freely filtered through the glomerulus and subsequently taken up by S1 proximal tubular cells in a Toll-like receptor four-dependent manner and promote oxidative stress in neighboring S2 tubular cells [27]. Therefore, endotoxemia from increased gut permeability after kidney IRI is likely to contribute to the potentiation of tubular injury in AKI even in the absence of overt sepsis. Likewise, circulating endotoxins were demonstrated to be closely associated with increased cardiovascular risk in CKD patients. However, the role of endotoxins in other disease models, including unilateral ureteral obstruction (UUO) or glomerulonephritis, is not certain. The impact of endotoxins on AKI progression remains understudied and warrants further investigation. The possible contribution of circulating endotoxins to cardiovascular events has been studied in CKD and hemodialysis patients rather than in AKI [28,29].

4.2. Metabolites

In addition to endotoxins, gut bacterial metabolites can mediate kidney injury. Gut bacteria produce diverse metabolites via the breakdown of food components, such as fiber, protein, or host substances, which are important for maintaining homeostasis, including metabolic balance, gut barrier integrity, and immunity. Gut dysbiosis following AKI inevitably leads to alterations in metabolite levels, with potential effects on kidney injury [30]. Among the various metabolites, SCFAs are mainly produced by the fermentation of indigestible dietary fibers and participate in a variety of processes, such as colon epithelial cell survival, metabolic regulation, and immune modulation, specifically the induction of Tregs rather than Th17 cells and the inhibition of neutrophil activation [31]. Preclinical data have shown that levels of fecal acetate and butyrate decrease one day after kidney IRI and also have demonstrated the beneficial effect of acetate in mitigating kidney injury via decreased systemic inflammation and oxidative stress and increased mitochondrial biogenesis, strongly suggesting that decreased levels of SCFAs contribute to AKI [18,25,32]. In particular, SCFAs function via binding to G-protein-coupled receptors (GPRs) or the

inhibition of histone deacetylases (HDAC) [33–38]. Four GPRs (i.e., GPR41, GPR43, olfactory receptor (Olfr) 78, and GPR109A) are known to be present in the kidneys [39–41]. A recent study has shown that SCFAs directly exert anti-inflammatory effects on podocytes and tubular epithelial cells in a GPR43- and GPR109A-dependent manner in a diabetic nephropathy model [42]. SCFAs enhance organic anion transport 1 (OAT1) activity in kidney proximal tubule cells, not via a GPR-dependent pathway but via the inhibition of HDACs [43]. Given the important role of SCFAs in the maintenance of barrier integrity and colon epithelial cell survival, decreased levels of these metabolites could aggravate systemic inflammation via bacterial transmigration. However, despite promising data, substantial differences in the type, dose, route and timing of administration remain major hurdles for translation.

Another gut bacterial metabolite potentially linking the gut to kidney injury is trimethylamine N-oxide (TMAO), a fermentation product from dietary phosphatidylcholine and carnitine. TMAO is associated with the dysregulation of bile acid and cholesterol metabolism, leading to oxidative stress, endothelial dysfunction, and inflammation; plasma levels of TMAO are strongly correlated with atherosclerotic cardiovascular diseases [44–51]. Several recent studies have shown that TMAO may be involved in kidney diseases. Lee et al. observed that the plasma levels of TMAO increased and could predict the AKI-to-CKD transition in 61 patients who survived three months following the initiation of continuous kidney replacement therapy in intensive care units [52]. TMAO promotes tubular cell apoptosis, G2-M arrest, and inflammation via NADPH oxidase 2 (NOX2)-dependent mechanisms in cultured tubular cells. Given that persistent gut dysbiosis might lead to increased production, decreased renal clearance might also be responsible for elevated plasma levels of TMAO during AKI-to-CKD transition. In addition, TMAO was recently found to facilitate M2-macrophage polarization in a macrophage–tubular cell coculture experiment [53]. Based on an observed increase in urine TMAO levels in mice with unilateral ureteral obstruction, the authors demonstrated that TMAO excreted through the kidneys disrupts pyruvate metabolism, leading to the production of lactic acid. The accumulated lactic acid in tubule cells promotes adjacent macrophage M2 polarization.

4.3. Gut-Derived Immune Cells

The gut is the largest immune organ in the body, housing the greatest number of immune cells, including macrophage/dendritic cells and T and B lymphocytes in the lamina propria or gut-associated lymphoid tissues (GALT), such as Peyer's patch. These cells play critical roles in maintaining the balance between immunologic tolerance to innocuous materials and robust immune responses against harmful pathogens. The possible mechanism underlying AKI's effect on the kidney involves a series of gut changes, including proinflammatory mediators, volume overload and uremic toxins among others. Shortly after kidney injury, the number and function of gut immune cells are substantially altered, potentially aggravating systemic and kidney inflammation and injury. We have previously shown that neutrophils start to appear and macrophages increase in number [25]. In addition, macrophages show altered phenotypes with increases in the percentage of proinflammatory CX3CR1^{intermediate} Ly6⁺ cells in the lamina propria of the colon, along with increased proinflammatory cytokines. Mononuclear phagocytes, including monocytes/macrophages and dendritic cells, are the most abundant and heterogeneous leukocyte subset in the gut and are constantly replenished from circulating monocytes [54–57]. CX3CR1^{high} macrophages are mature resident macrophages with an anti-inflammatory phenotype, while CX3CR1^{intermediate} cells represent recently migrated monocytes with a proinflammatory phenotype in the inflamed gut [57]. In addition to alterations in innate immune cells, gut T cells also change following AKI. Using flow cytometry, we have shown that

the percentage of IL-17A+ T cells increases significantly in both the small intestine and colon shortly after kidney IRI [25]. IL-17A is a proinflammatory cytokine that induces chemokines, thereby recruiting neutrophils and other immune cells to sites of inflammation, playing important roles in many inflammatory and autoimmune diseases. Numerous pre-clinical studies have demonstrated the important role of IL-17A or IL-17C in various models of AKI. A higher serum level of IL-17 at the time of AKI diagnosis or intensive care unit admission is independently associated with hospital mortality and major adverse kidney events, supporting the possible important role of IL-17 in human AKI [58]. Given that Th17 cells are the main source of IL-17A and are primarily located in the gut, the migration of gut Th17 cells into the injured kidney in AKI may aggravate kidney injury. Despite the lack of studies on AKI, Krebs et al. have demonstrated the migration of gut-derived Th17 cells in a crescentic glomerulonephritis model [59]. They used Kaede transgenic mice showing a color change from green to red fluorescence upon near-UV irradiation. Following the selective exposure of the small intestine to irradiation, an increased number of IL-17A+ red cells were identified in inflamed glomeruli, showing that gut-derived Th 17 cells ultimately migrate and contribute to glomerular injury [59]. Recently, in a unilateral ureteral obstruction mouse model, Liang and Bonventre demonstrated that type 3 innate lymphoid cells (ILC3), as well as T cells, B cells, monocytes, and neutrophils from the gut accumulate rapidly in the injured kidney via the CXCR6-CXCL16 axis and contribute to kidney fibrosis [60]. In addition to an increased percentage of gut mucosal Th17 cells, an earlier study also demonstrated the important role of preformed IL-17A released from the Paneth cells in mediating kidney, liver and intestinal injury in an AKI model. Depletion of Paneth cells or neutralization of IL-17A significantly attenuated tubular cell apoptosis and inflammation, showing that the release of preformed IL-17A from the Paneth cells might act as an upstream trigger that potentiates kidney injury and inflammation.

5. Potential Therapeutic Strategies Targeting the Gut

Alterations in the gut microbiota and associated gut microenvironment, comprising barrier disruption, subsequent bacterial transmigration, altered metabolites, and the activation and migration of gut-derived immune cells, are thought to be important modifiers of post-AKI outcomes, such as AKI severity and progression to CKD. This suggests that the gut is a target for the prevention and treatment of AKI. There are several potential approaches to achieve this, including directly targeting the gut microbiota or their metabolites, as well as modulating gut-derived immune cells.

5.1. Modulation of the Gut Microbiota

Several interventions directly targeting the gut microbiota have been proven to have therapeutic potential, mostly in preclinical models. Pretreatment of mice with a combination of oral antibiotics resulted in the depletion of the gut microbiota and conferred a substantial protective effect against IRI [25,52,61–63]. Gut microbiota depletion by an antibiotic cocktail led to gut barrier protection, as well as decreased IL-17A+ cells in the small intestine, while the percentage of Tregs increased, shifting the Th17/Treg balance toward immune modulation [25]. Moreover, these changes in the gut led to the suppression of kidney inflammation and injury. Similarly, the protective effect of gut microbiota depletion via an increase in the ratio of Tregs/Th17 cells in the gut has also been demonstrated in an ischemic stroke model [64], where gut microbiota depletion led to decreased infarct size. Recently, Gharaie et al. have shown that amoxicillin administered in drinking water after unilateral IRI substantially mitigated interstitial fibrosis, accompanied by increased gut microbiota diversity, decreased gut and kidney IL-17A+ cells, and increased CD8+ T cell infiltration in the kidney [63]. In the same study, amoxicillin did not accelerate repair

in GFM, and FMT from amoxicillin-treated mice to GFM reduced kidney fibrosis, clearly showing that amoxicillin-induced protective effects are mediated by the gut microbiota. Another approach directly targeting the gut microbiota is the use of prebiotics and probiotics. *Bifidobacterium bifidum* (BGN4), administered two weeks before injury, confers a substantial protective effect against IRI, accompanied by an increased gut Treg/Th17 ratio [65]. Interestingly, BGN4-immune cell culture leads to the expansion of Tregs and CD103+ regulatory dendritic cells. The effect of probiotics in a cisplatin-induced AKI model has also been demonstrated [26]. *Lactobacillus salivarius* BP121, isolated from the feces of newborns, attenuates cisplatin-induced kidney injury and decreases serum levels of indoxyl sulfate and *p*-cresol sulfate. In addition, H₂O₂-induced tight junction protein damage is reduced in Caco-2 cells treated with the BP121 culture supernatant, demonstrating the direct barrier protective effect of BP121. Zhu et al. have demonstrated that *Lactobacillus casei* Zhang has a beneficial effect on the AKI-to-CKD transition, and this effect is mediated via SCFA- and nicotinamide-induced anti-inflammatory effects [66].

However, despite promising preclinical data, data supporting the effect of probiotics and microbial depletion via antibiotics in human AKI are still limited. In addition, there are unanswered concerns regarding the potential risks of antibiotics or probiotics, including microbiome disruption, an increased risk of infection, and the emergence of antibiotic resistance. In a double-blind, randomized, controlled clinical trial involving 92 septic-AKI patients, seven consecutive days of probiotic administration showed a significantly lower blood urea level but no benefits in the kidney failure rate nor mortality at 6 months [67]. The selective decontamination of the digestive tract (SDD) with an antibiotic mixture in a human study has shown conflicting results so far. A systematic review and meta-analysis with 32 RCTs, including 24,389 adults in the ICU, revealed that SDD was associated with lower hospital mortality [68]. The SuDDICU trial investigated whether SDD—consisting of oral colistin, tobramycin, and nystatin combined with intravenous antibiotics—could improve mortality in mechanically ventilated ICU patients. However, the study did not meet its primary outcome; among the 5982 enrolled patients, SDD failed to significantly reduce in-hospital mortality compared to standard care [69]. The SuDDICU group extended their study to a multi-national large population cohort in which 9289 patients were randomized. However, SDD did not result in lower in-hospital mortality [70]. A retrospective cohort study showed that exposure to anti-anaerobic antibiotics could be a risk factor for sepsis-associated AKI [71]. Antibiotic administration in the clinical setting has several limitations, and the infection risk and antimicrobial resistance have not been adequately evaluated. Given the well-established risk of *Clostridium difficile* infection associated with broad antibiotic use—which itself perpetuates gut barrier injury and sustains the gut–kidney vicious cycle—the adoption of SDD as a widespread standard of care should be approached with considerable caution.

The transfer of a healthy microbiota might be a strategy to change the course of AKI. FMT, an established treatment for recurrent *Clostridium difficile* infection with a success rate exceeding 90%, has the potential to rebuild the gut microbiota structure and diversity, thereby establishing dynamic homeostasis and ultimately modifying post-AKI outcomes. However, FMT also carries concerns regarding safety, donor screening and diverse regulatory challenges that need to be overcome. Current expert reviews and clinical practice guidelines generally consider conditions such as sepsis or systemic inflammatory response system, severe intestinal barrier disruption, and marked immunodeficiency as high-risk settings or relative contraindications for FMT, in which the procedure should be avoided or undertaken only with extreme caution. Most critically ill AKI patients would face these risks due to compromised gut barrier integrity and systemic inflammation. Fecal donor screening criteria have not yet been established. Finally, establishing regulatory

frameworks that can appropriately validate and recognize the clinical efficacy of FMT represents one of the key remaining challenges in translating this therapy into routine clinical practice for AKI patients. To date, no clinical trial has directly tested fecal microbiota transplantation as an intervention in patients with AKI, although early trials in CKD subtypes and other systemic diseases suggest that FMT can safely reshape gut dysbiosis and may confer renoprotective potential.

5.2. Modulation of Gut Microbial Metabolites

SCFAs, bacterial metabolites with pleiotropic functions, have potential as novel therapeutics. An early study by Oliveira et al. has shown that acetate attenuates kidney IRI leading to decreased systemic inflammation and oxidative stress, and increased mitochondrial biogenesis [18]. Propionate and butyrate were also shown to help prevent kidney damage and the subsequent transition to CKD [72]. In transcriptional analyses, 103 genes involved in inflammatory processes/immune cell activation triggered by TNF- α in HK-2 cells were downregulated by propionate/butyrate, indicating a potent anti-inflammatory effect. Tian et al. have also recently shown that butyrate attenuates kidney injury and inflammatory cell infiltration by regulating NLRP3 inflammasome-mediated pyroptosis and suppressing the STING-GSDMD (Gasdermin D) signaling pathway [73]. Al-Harbi et al. also demonstrated that acetate exerts renoprotective effects in a murine model of sepsis-induced AKI [74]. Acetate corrected the oxidant–antioxidant imbalance in splenic CD4+ T cells by suppressing NOX2 subunit expression (gp91phox, p47phox) and intracellular ROS production, while restoring SOD, catalase, and glutathione levels through the inhibition of HDAC activity in T cells. However, chronic systemic elevation of SCFAs could induce T cell-mediated ureteritis and kidney hydronephrosis via mTOR activation, dysbiosis and renal tissue inflammation [75].

Another approach targeting microbial metabolites is the inhibition of TMAO. Given that the gut bacterial TMAO is linked to AKI and the progression to CKD via oxidative stress and inflammation, strategies targeting TMAO are promising. An observational study has reported increased plasma TMAO levels accompanied by reduced urinary TMAO excretion in patients with AKI [76]. Targeted inhibition of TMAO with iodomethylcholine blocks the choline diet-induced elevation in TMAO levels, leading to reduced tubulointerstitial fibrosis and improved kidney function in a murine model of CKD [77]. The protective effect of TMAO inhibition also improves cardiac function and remodeling in heart failure [78].

5.3. Immune Modulators

Given that gut is a potent amplifier of systemic and kidney inflammation following AKI, strategies targeting gut immune cells, their receptors, or their migration might be beneficial in AKI. However, relevant data are still limited and largely experimental. Data showing that IL-17A-knockout mice are protected from septic AKI (in a cecal ligation and puncture model) suggest that monoclonal antibodies to IL-17A (e.g., secukinumab) and IL-17 receptor (brodalumab) have some therapeutic potential [79]. Similarly, targeting the CXCR6-CXCL16 pathway, which inhibits the migration of CXCR6+ gut-derived immune cells to the injured kidney, is also promising [60]. These therapeutic experiments are summarized in Table 2 and Figure 1.

Table 2. Summary of exploring therapeutic approaches in AKI.

Author, Year	Model	Method	Result
Ischemic reperfusion injury AKI model			
Jang HR et al. 2009 [16]	GFM vs. conventional SPF mice (6 week old)	Exposed to normal bacteria for 5 week (=conventionalized GFM, CV-GF); bilateral warm IRI	GFM kidneys had more NKT cells and lower IL-4 at baseline; post-IRI GF mice showed greater CD8 T cell infiltration, worse renal function and structural injury vs. controls; CV-GF mice were equivalent to normal controls in injury severity, T cell phenotype, and cytokine profile → early microbial exposure shapes renal immune environment and modulates IRI outcomes.
Andrade-Oliveira V et al. 2015 [18]	C57BL/6 mice	Bilateral IRI model, Acetate, propionate, butyrate independently diluted in PBS administration intraperitoneal dose (200 mg/kg) 30 min before and at the moment of reperfusion	SCFAs improved renal function after IRI. SCFA treatment reduced local and systemic levels of pro-inflammatory cytokines and chemokines vis NF-κB suppression. In vitro: SCFAs reduced DC maturation and CD4+/CD8+ T cell proliferation, kidney epithelial cell injury via mitochondrial biogenesis. Bacteria-treated mice showed reduced AKI severity.
Emal et al. 2017 [61]	C57BL/6 mice	Bilateral IRI, microbiota-depletion with oral broad-spectrum antibiotics for 2 weeks prior to IRI and FMT	Gut microbiota depletion significantly reduced renal tubular necrosis, NGAL expression, plasma creatinine, and urea after I/R injury. Remote organ injury was attenuated: lower plasma LDH, ALAT, ASAT; reduced F4/80+ macrophage staining in liver and spleen. FMT erased protective effect of microbiota depletion.
Nakade et al. 2018 [30]	C57BL/6 mice, GFM, serine racemase knock out: D-amino acid oxidase-overexpressing mice	Unilateral IRI (40 min)	AKI (IRI) induced gut dysbiosis. Gut-derived D-serine is transported to the kidney via circulation. Oral D-serine administration mitigated IRI in both models.
Yang et al. 2020 [25]	C57BL/6 mice and GFM	Bilateral IRI, microbiota-depletion with oral broad-spectrum antibiotics 2 weeks prior to IRI, GFM with post-AKI FMT	IRI caused colonic barrier disruption with dysbiosis GFM with post-AKI FMT showed worse IRI severity, these results showed the interplay between gut and kidney with bidirectional relationship. Renoprotective effect of microbiota depletion was associated with Th17, Treg, M2 alteration.
Zhu et al. 2021 [66]	C57BL/6 mice Human CKD 3–5 patients vs. placebo	Bilateral IRI, Cisplatin-induced AKI, LPS-induced AKI with oral administration of probiotics (Lac.z or L. acidophilus)	Probiotics restore the microbiota in AKI, serum and kidney levels of SCFAs and nicotinamide were increased. Oral probiotics dampen kidney function deterioration.
Sun et al. 2022 [19]	Male Sprague-Dawley rats Kidney transplantation recipients	Unilateral IRI model, oral administration of butyrate (100 mg/kg) via tail vein injection 30 min prior to IRI Serum SCFA measurement	SCFA attenuated IRI severity. Post transplantation serum SCFAs were significantly increased.
Gharaie et al. 2023 [63]	C57BL/6 mice	Bilateral and unilateral IRI, microbiota-depletion with oral broad-spectrum antibiotics, GFM, CD-4 deficient mice, CD-8 deficient mice and all with microbial depletion 2 weeks prior IRI, FMT	Antibiotics altered gut microbiota. Antibiotics with intact microbiome and CD8+ T cells were required for kidney protective effect. Antibiotics pretreatment protected against IRI but not cisplatin AKI

Table 2. Cont.

Author, Year	Model	Method	Result
Lee J et al. 2024 [52]	C57BL/6 mice AKI hospitalized ICU requiring dialysis	Unilateral IRI, microbiota-depletion with oral broad-spectrum antibiotics 2 weeks prior IRI plus 2 weeks after IRI	TMAO is a key metabolite associated with the AKI-to-CKD transition, and NOX2 activation was identified as a key regulator of TMAO-related AKI-to-CKD transition
Sepsis-induced AKI model			
Al-Harbi et al. 2018 [74]	BALB/c mice	LPS (10 mg/kg) intraperitoneal injection, acetate 200 mmol/L diluted in drinking water for 7 days before injury	Acetate attenuated kidney injury via inhibiting HDAC in T cell, NOX2 subunit expression

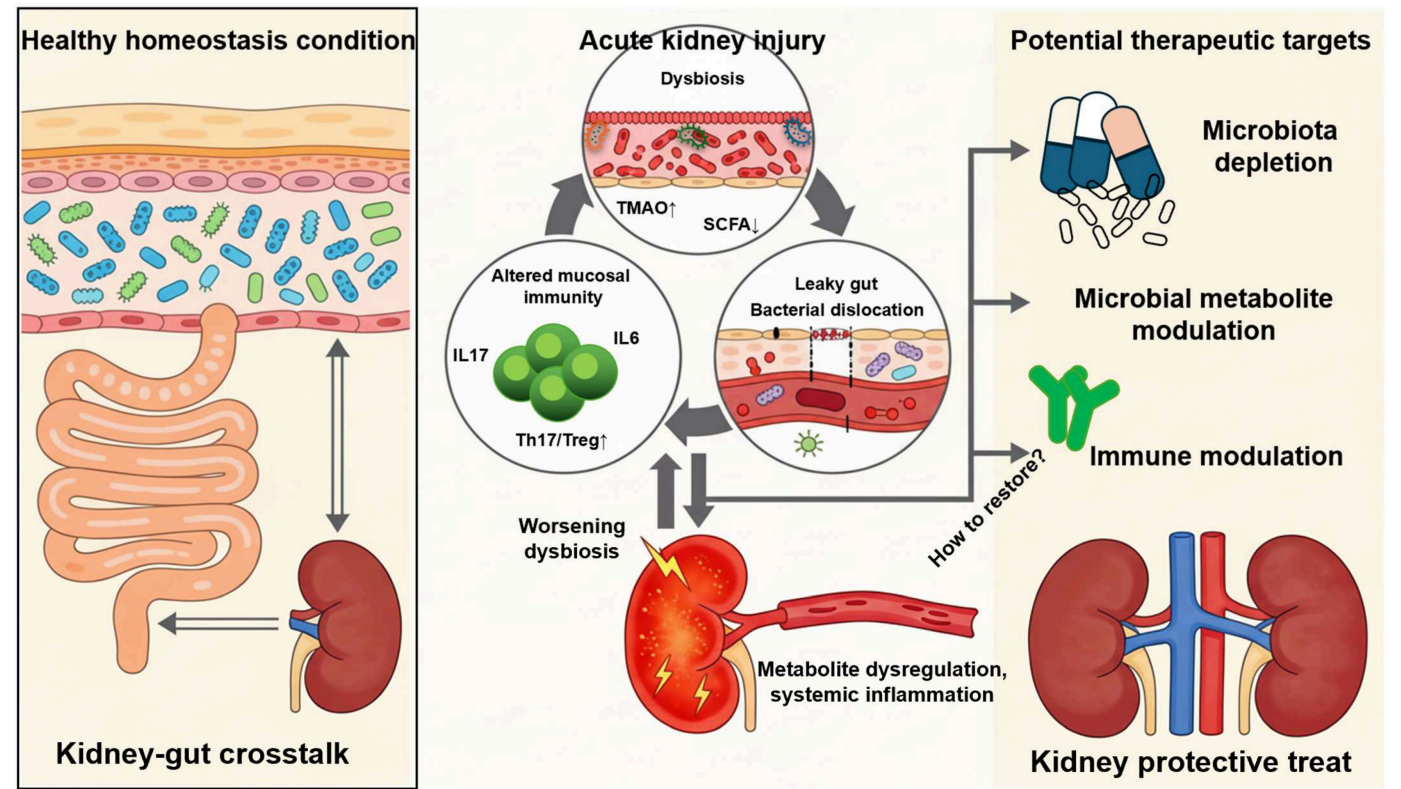


Figure 1. The kidney–gut axis, mechanistic pathways, and therapeutic strategies.

6. Conclusions and Future Direction

Gut dysbiosis and associated gut microenvironmental changes, comprising leaky gut, altered metabolites, and gut inflammation, are thought to be substantial modifiers of AKI outcomes. Although research is still in an early stage, preclinical data have indicated that targeting the gut might be a novel therapeutic strategy. These strategies may involve modifying the gut microbiota via antibiotics, prebiotics, and probiotics, or FMT, as well as modifying bacterial metabolites or utilizing immune modulation. However, for the development of targeted interventions, further studies providing mechanistic insights are definitely needed, and recent studies are transitioning from associative interactions to mechanistic ones. In the future, a better understanding of the mechanisms underlying kidney–gut crosstalk is urgently needed to facilitate human clinical trials testing various gut-targeted interventions.

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Abbreviations

AKI; acute kidney injury, CI; confidence interval, CKD; chronic kidney disease, GALT; Gut associated lymphoid tissue, GFM; germ0free mice, FMT; fecal microbiota transplantation, GPR; G-protein coupled receptor, HDAC; Histone deacetylase, HR; hazard ratio, IBD; inflammatory bowel disease, ICU; intensive care unit, ILC3; type 3 innate lymphoid cells, IRI; ischemia/reperfusion injury, LPS; lipopolysaccharide, NOX2; NADPH oxidase 2, OAT; organic anion transport, Olfr; olfactory receptor, OR; odd ratio; TMAO; trimethylamine N-oxide, SCFA; short-chain fatty acids

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