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Novel intestinal dialysis interventions and microbiome modulation to control uremia

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Purpose of review
In patients with chronic kidney disease (CKD), the gut plays a key role in the homeostasis of fluid and electrolyte balance and the production and disposal of uremic toxins. This review summarizes the current evidence on the gut-targeted interventions to control uremia, fluid overload, hyperkalemia and hyperphosphatemia in CKD.

Recent findings
Studies have emerged that support the concept of intestinal dialysis, such as colonic perfusion with a Malone antegrade continence enema stoma or colonic irrigation with a rectal catheter, as a promising adjuvant approach to control uremia in CKD, although most findings are preliminary. The use of AST-120, an oral adsorbent, has been shown to reduce circulating levels of indoxyl sulfate and p-cresol sulfate and have potential renoprotective benefits in patients with advanced CKD. Diarrhea or inducing watery stools may modulate fluid retention and potassium and phosphorus load. Accumulating evidence indicates that plant-based diets, low-protein diets, and pre-, pro-, and synbiotic supplementation may lead to favorable alterations of the gut microbiota, contributing to reduce uremic toxin generation. The effects of these gut-targeted interventions on kidney and cardiovascular outcomes are still limited and need to be tested in future studies including clinical trials.

Summary
Interventions aimed at enhancing bowel elimination of uremic toxins, fluid and electrolytes and at modulating gut microbiota may represent novel therapeutic strategies for the management of uremia in patients with CKD.

Keywords
chronic kidney disease, gut microbiota, intestinal dialysis, uremia, uremic toxins

INTRODUCTION

Chronic kidney disease (CKD) has been a significant public health problem worldwide due to its increasing prevalence and strong association with poor outcomes, contributing to a substantial global burden of morbidity and mortality and consuming a disproportionate amount of financial resources [1]. The accumulation of various uremic toxins associated with reduced kidney function (i.e., uremia) is one of the major factors for the excess risk of morbidity and mortality in CKD, through the deleterious effects of uremic toxins on various tissues and organs [2,3]. Over the past decades, considerable efforts have been made to reduce the uremic load in patients with CKD, particularly among those with end-stage renal disease (ESRD), primarily by optimizing therapeutic modalities, improving dialysis adequacy, reducing protein intake, and administering oral adsorbents [4,5]. These efforts, however, have had little success, and the substantial disease burden attributable to uremic toxins remains unresolved.

It is well known that antiquity medicine often resorted to the use of enemas or rectoclysis to 'free' the body of the 'poisons' believed to originate in the gut and cause diseases [6]. A large number of studies in modern medicine have now provided proof of

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KEY POINTS

- Intestinal dialysis with colonic perfusion/irrigation may be an effective supplementary therapy to control uremia, fluid overload, hyperkalemia and hyperphosphatemia in CKD.
- AST-120, an oral adsorbent, can reduce circulating levels of indoxyl sulfate and p-cresol sulfate and has renoprotective benefits in patients with advanced CKD.
- Plant-based and low-protein diets and prebiotic, probiotic, and synbiotic supplementation represent novel gut microbiota-targeted strategies for the management of uremia in CKD.

this theory, demonstrating the major role of the gut in the disposal of nitrogenous waste products generated primarily in the large intestine [7]. Furthermore, with recent scientific and technological advances in the field of microbiome research, mounting evidence points to the pivotal role of the gut microbiota in uremic toxin production [8], which in turn has brought unprecedented attention to gut microbiota-targeted strategies in the management of uremia in CKD [9▪]. Herein, we provide a narrative review of the history, recent evidence, and therapeutic potential of bowel elimination (e.g., intestinal dialysis) and gut microbiota modulation to control uremia in CKD.

INTESTINAL DIALYSIS

The first recorded use of bowel elimination as a means of treating kidney disease dates back to 40 B.C. in Dioscorides' Materia Medica, in which terra sigillata was advocated for multiple disorders, including diseases of the kidney [10]. Subsequently, a large number of attempts have been made to treat kidney disease and its complications by utilizing intestinal lavage/perfusion (i.e., intestinal dialysis) or drainage of bowel fluid (i.e., induced diarrhea) until the mid to late 1900s, when modern renal replacement therapy (RRT) (i.e., hemodialysis, peritoneal dialysis (PD), or kidney transplantation) was introduced [7,11▪▪].

Intestinal dialysis – historical approach

The application of clinically effective intestinal dialysis for uremia was first reported by Kolff in 1947 [12]. An isolated intestinal loop was created by a double-ended ileostomy in a 57-year-old man with uremia. Perfusion with warmed dialysate in the loop removed urea at a rate of 0.48 g/h, resulting in marked clinical improvement. Subsequently in 1951, Twiss and Kolff reported the case of a 36-year-old uremic man treated with intestinal dialysis by daily perfusion of rinsing fluid (at a flow rate of 500–2,100 mL/h for 8–10 h/day) through a 2.5-m isolated loop of mid-intestine, which removed an average of 8.6 g/day of urea over 16 consecutive days [13]. Following these seminal studies, several trials of intestinal dialysis were initiated in desperate attempts to forestall death in uremia, and researchers were becoming convinced of its beneficial effects on water, electrolyte, and acid-base balance in uremic patients [12–15]. However, with the advent and development of modern RRT in the late 1900s, the need for and interest in intestinal dialysis has waned. Furthermore, the limited long-term survival benefit of intestinal dialysis could no longer justify the extensive surgery required to create an isolated intestinal loop, which halted further exploration of this method to treat uremia [10,16].

Induced diarrhea

The benefit of induced diarrhea for the treatment of uremia was discovered serendipitously while designing a fluid replacement regimen for dehydration in acute cholera [17]. A key discovery was the recognition of the substantial loss of nitrogenous waste products in the voluminous diarrheal stools in cholera [18]. In the late 1970s, when the side effect of saline-induced diarrhea (i.e., sodium and fluid retention) had been overcome by incorporating mannitol in the solution, diarrhea therapy was introduced as a simple, inexpensive, and less invasive method to alleviate uremia. In 1979, Young *et al.* reported 17 uremic patients in Taipei (creatinine clearance of 2.1–7.3 mL/min) treated with thrice-weekly diarrhea therapy at home [19]. The patients were instructed to drink 7 L of a warmed mannitol-saline solutions at the rate of 200 mL every 5 min for 3 h. When their endogenous creatinine clearance decreased to 1.0–2.0 mL/min and their uremic symptoms, such as nausea, vomiting, and fluid overload, reappeared, the therapy was discontinued and switched to either peritoneal or hemodialysis. Over a mean follow-up of 6.8 (with a range of 1.3–16) months, all patients experienced improvements in appetite, pruritus, and weakness and demonstrated good tolerance to the strenuous regimen of diarrhea therapy. During each diarrhea session, urea and creatinine clearances were 27.8 and 7.4 mL/min, respectively [19]. Later in 1991, Miskowiak reported a case of uremic patient treated with diarrhea therapy by oral administration of 1.0–1.5 L of polyethylene glycol or mannitol every 4 h in one day (up to 15 or 7 h, respectively), with a 10-day interval [20]. The procedure was well-tolerated, and the diarrhea was induced without abdominal cramping. The patient's intestinal clearances for

creatinine, uric acid, and phosphate were 6.0–10.4, 4.0, and 10.7–15.4 mL/min, respectively, which were comparable to those obtained from 12 h weekly hemodialysis. Despite these findings, to date no randomized controlled clinical trials of diarrhea therapy have been conducted, and the safety and efficacy of this therapy for the management of uremia remain unclear.

Recent advances in intestinal dialysis

Colonic perfusion with a Malone antegrade continence enema stoma

After earlier reports and endeavors for the development of intestinal dialysis, the beneficial effects of this therapy have been periodically rediscovered, as exemplified by a few recent basic and clinical studies. In a recent animal study using uremic rats with a Malone antegrade continence enema (MACE) stoma, the researchers evaluated the effect of colonic dialysis on blood urea nitrogen (BUN) and plasma creatinine levels by perfusing two different (i.e., low vs. high osmolar) PD solutions through the stoma [21]. Mannitol and activated charcoal were added to both PD solutions in this study. Compared with uremic controls without colonic dialysis, uremic rats with colonic dialysis had consistently lower levels of BUN and plasma creatinine and showed better survival. They also found that colonic dialysis with a high (vs. low) osmolar PD solution resulted in better laboratory outcomes and was more suitable for effective BUN and creatinine clearance [21]. In humans, on the other hand, the MACE stoma (a.k.a. appendicostomy; Fig. 1a) has been used primarily to treat unremitting functional constipation or idiopathic fecal incontinence [22,23], but its application to uremic patients has also been suggested. In a case report of a 20-year-old uremic woman who had a MACE stoma at the age of 11 years for her severe constipation due to sacral agenesis, a colonic dialysis was selected as an alternative RRT because of her refusal to receive any type of conventional RRT [24]. On admission, her blood pressure was 190/100 mmHg and her BUN and serum creatinine were 29 and 6.5 mg/dL, respectively. By changing the colonic irrigation solution to 2L of standard PD solution with 10 g of activated charcoal and 100 mL of 10% mannitol, the colonic dialysis was continued at home by perfusing the solution in ~3 h, 2 or 3 cycles/day, for 2 years until she received kidney transplantation. During the 2 years of follow-up, the mean levels of her BUN and serum creatinine were 10.7 and 2.8 mg/dL, respectively, and her blood pressure and biochemical parameters remained within the normal range except for two episodes of mild hypokalemia.

Colonic irrigation with a rectal catheter

Nowadays, the practice of colonic irrigation (a.k.a. colon hydrotherapy or cleansing; Fig. 1b) has been rooted primarily in beauty centers where a slogan

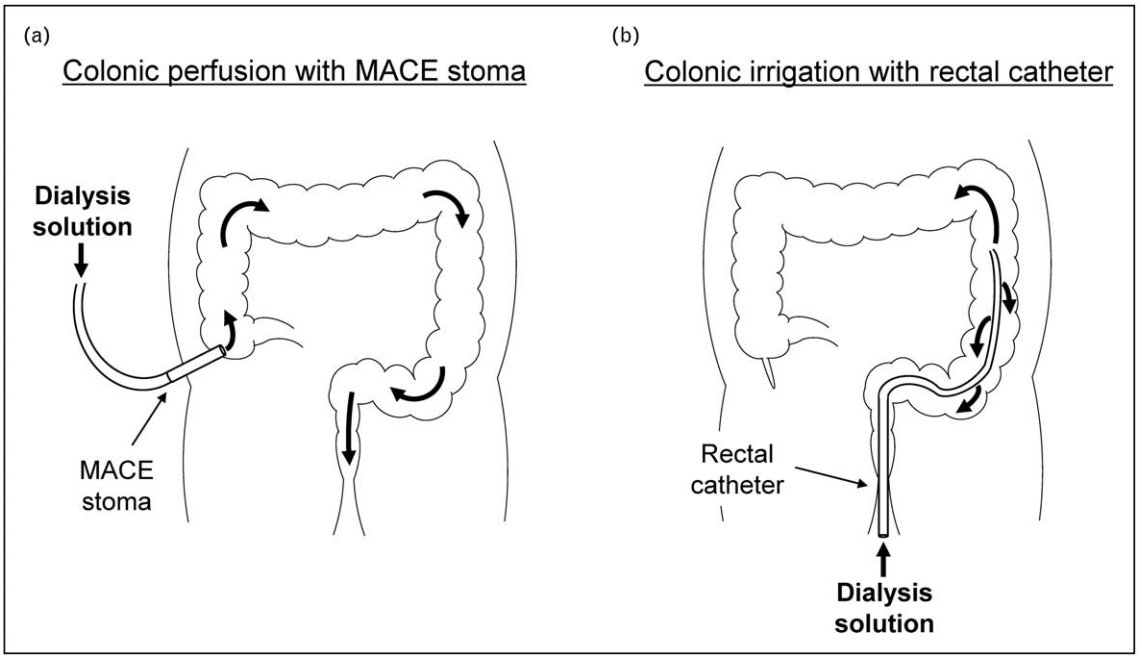

FIGURE 1. Schematic representation of intestinal dialysis: (a) colonic perfusion with MACE stoma and (b) colonic irrigation with rectal catheter. MACE, Malone antegrade colonic enema.

like 'clean on the inside, beautiful on the outside' has gained popularity [6]. In the scientific community, however, there has been a heated debate with harsh criticism over this procedure, largely due to the lack of sufficient scientific evidence supporting its clinical benefits vs. harms [25,26]. Nevertheless, evidence has accumulated suggesting the effectiveness of colonic irrigation for patients with severe defecation disorders [27–32], and even in those with CKD [33▪]. This colonic dialysis does not require surgical creation of an isolated bowel loop, which was utilized in historical intestinal dialysis as described above. In a recent retrospective study of 178 patients with CKD stages G3-G5 in China, Dai *et al*. investigated the association between the use of simplified colonic dialysis (or colonic irrigation) and risk of CKD progression (≥50% decrease in estimated glomerular filtration rate [eGFR] or initiation of RRT) with a follow-up of 36 months [33▪]. For the colonic irrigation, patients were instructed to lie left lateral position, bent knees and relax. A disposal catheter was inserted through the patient's anus to the colon (up to 65–75 cm), and warmed hemodialysis solutions were perfused into the colon for 10 s, followed by a drainage period of 18–20 s, which was repeated for ∼1 h (with a total dialysate volume of 15–16 L), 3 times per week. Results showed that the use (vs. no-use) of colonic irrigation was significantly associated with a lower risk of CKD progression (adjusted hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.20–0.69), which was evident in subgroups of patients with CKD stages G4 and G5 [33▪]. In a follow-up study, fecal 16S rRNA sequencing demonstrated that colonic dialysis mitigated CKD-associated gut microbial dysbiosis, with species richness more similar to healthy subjects [34]. Although uremic toxins were not measured in this study, the results suggest that colonic irrigation could be an effective supplementary therapy to retard CKD progression in advanced CKD, perhaps by reducing gut-derived uremic toxins.

Colon cleansing with laxatives

In line with the concept of intestinal dialysis, active control of defecation (or colon cleansing) with laxatives may also be an appealing 'bowel elimination' strategy for the management of uremia, in a less invasive, more readily applicable, and perhaps more tolerable manner than colonic perfusion/irrigation. This may also be supported by the facts of high prevalence of constipation (up to ∼90%) in patients with advanced CKD [35,36], enhanced production of uremic toxins in slow colonic transit [37], and adverse clinical outcomes associated with constipation [38,39]. The theoretical safety concerns about the use of laxatives (e.g., dehydration, progressive loss of kidney function, and hypokalemia) may be alleviated by recent evidence on the associations of laxative use with clinically negligible change in eGFR and with no risk of hypokalemia in patients with advanced CKD [40,41].

Fluid and electrolyte balance in intestinal dialysis

Fluid balance

Volume overload is one of the common and potentially life-threatening conditions in patients with CKD, particularly among those with ESRD [42]. Current strategies to prevent or treat volume overload include restrictions of fluid and salt intake and the use of low sodium dialysate, which unfortunately are often not very successful [43,44]. In this context, intestinal dialysis and induced diarrhea using nonabsorbable solutions may be an effective strategy to improve fluid control in these patients, as shown in several previous studies [19,20,24,45]. In a recent prospective study of 35 hemodialysis patients, oral administration of 2L polyethylene glycol solution successfully reduced the inter-dialytic weight gains without inducing any adverse effects including worsening of thirst sensation [46].

Hyperkalemia

Under physiologic circumstances, intestinal potassium excretion is quite constant at approximately 10% of total potassium excretion, whereas the remaining 90% is accounted for by renal excretion [47]. However, when the kidney function declines and the dietary potassium load cannot be fully excreted by the kidneys, the gut becomes especially important for maintaining potassium balance primarily by enhancing potassium secretion via the large conductance calcium-activated potassium channel subunit-α1 (a.k.a. BK channel) expressed on the apical surface of colonic epithelial cells [48,49]. In hemodialysis patients, for example, a series of potassium balance studies have demonstrated that potassium excretion in stool was three times higher than in healthy controls, reaching approximately 80% of dietary potassium (up to 3000 mg/d) for some patients [50]. It is therefore conceivable that conditions with faster intestinal transit time induced by intestinal dialysis or induced diarrhea can enhance intestinal potassium excretion and perhaps reduce intestinal potassium absorption, helping to prevent hyperkalemia in CKD [24,46,51,52]. A recent observational study showing the association of laxative use (vs. nonuse) with lower risk of hyperkalemia in advanced CKD may also support the clinical utility of

'gastrointestinal potassium wasting' as a therapeutic tool for hyperkalemia management in CKD [41].

Hyperphosphatemia

In advanced CKD with limited urinary phosphate excretion capacity, reducing intestinal phosphate absorption is pivotal in preventing hyperphosphatemia. Intestinal phosphate absorption occurs via active transcellular transport (mostly mediated by sodium phosphate cotransporter 2b [NaPi-2b] in the brush border membrane of enterocytes) and passive paracellular transport [53]. Of interest, recent studies have demonstrated that intestinal phosphate absorption efficiency is maintained even at low $1,25(OH)_2D$ levels (and thus low NaPi-2b expression), suggesting the importance of paracellular phosphate absorption in phosphate balance in CKD [54,55]. In addition, while it is widely recognized that the small intestine is responsible for most phosphate absorption, several studies have reported a significant involvement of the colon in paracellular phosphate transport [56,57], as exemplified by the findings that phosphate-containing enemas can induce hyperphosphatemia [58–62]. Therefore, reducing intraluminal phosphate concentrations in the colon by means of intestinal dialysis or induced diarrhea may be a reasonable approach to mitigate hyperphosphatemia in patients with CKD.

ORAL ADSORBENTS

The oral administration of adsorbents, a group of agents with the ability to adsorb uremic solutes, is one of the bowel elimination strategies for uremia [63]. Since the late 1900s, several adsorbents have been developed and tested for use in advanced uremia, including charcoal [64], oxycellulose [65], locust bean gum (a mannose polymer derived from seeds of the ceratonia siliqua tree) [66], and microcrystalline carbon [67]. Among these, porous microcrystalline carbon with an oxygen complex, AST-120, has been most extensively studied and widely used for the management of uremia in CKD.

AST-120

AST-120 (Kremezin, Kureha Chemical Co., Tokyo, Japan) consists of fine spherical particles that are approximately 0.2–0.4 mm in diameter and composed of porous microcrystalline carbon with an oxygen complex including a surface oxide [68]. It is insoluble in water and common organic solvents and differs from activated charcoal in its uniform composition [69]. It has a lower adsorption ability for amylase, pepsin, lipase, and chymotrypsin than charcoal, but adsorbs hydrophobic uremic substances, such as indole and p-cresol, in the gut and excretes these substances into feces [69]. Both indole and p-cresol are precursors of two major uremic toxins, indoxyl sulfate and p-cresyl sulfate, respectively, and hence, their excretion from the gastrointestinal tract attenuates the accumulation of uremic toxins (Fig. 2).

In an earlier study including 26 hemodialysis patients with elevated levels of serum indoxyl sulfate, those with (vs. without) oral administration of AST-120 (6 g/day for 12 weeks) had significantly lower serum concentrations of indoxyl sulfate at as early as 2 weeks after the administration, without experiencing any side effects [69]. In another study including 35 patients with nondialysis-dependent CKD (NDD-CKD), those with (vs. without) oral administration of AST-120 (6 g/day for 6 months) demonstrated a significant reduction in both serum and urine indoxyl sulfate levels (from 2.0 to 1.7 mg/dL and from 66.8 to 43.4 mg/day, respectively) [70]. Similar to the earlier study from hemodialysis patients, a significant reduction in indoxyl sulfate was observed within 1 month of the AST-120 administration in this study. In addition, the study showed a significant negative correlation between changes in urine indoxyl sulfate levels and the slope of 1/serum creatinine-time plot, which led to subsequent larger randomized clinical trials to validate the effectiveness of AST-120 on CKD progression.

In two multinational, randomized, double-blind, placebo-controlled trials (EPPIC-1 and EPPIC-2), when AST-120 was added to standard therapy in adults with moderate to severe CKD, the results failed to show a benefit toward slowing CKD progression [71]. However, the high pill burden of AST-120 (30 capsules per day) in these trials might have affected drug adherence, and hence it remains unclear if proper administration of this or other similar adsorbents could be renoprotective. In fact, a recent post-hoc analysis of the EPPIC trials showed a renoprotective benefit in the subgroup of patients with high proteinuria and hematuria [72]. Of interest, a recent animal study suggested the influence of AST-120 on the gut microbiota, which may explain its preferential reduction of p-cresyl sulfate (rather than indoyl sulfate) via decreasing the abundance of *Erysipelotrichaceae* and *Clostridium* species which express a gene involved in p-cresol production [73].

GUT MICROBIOTA MODULATION

Gut microbiota and uremic toxins

Under physiologic conditions, the gut microbiota participates in a variety of metabolic activities and

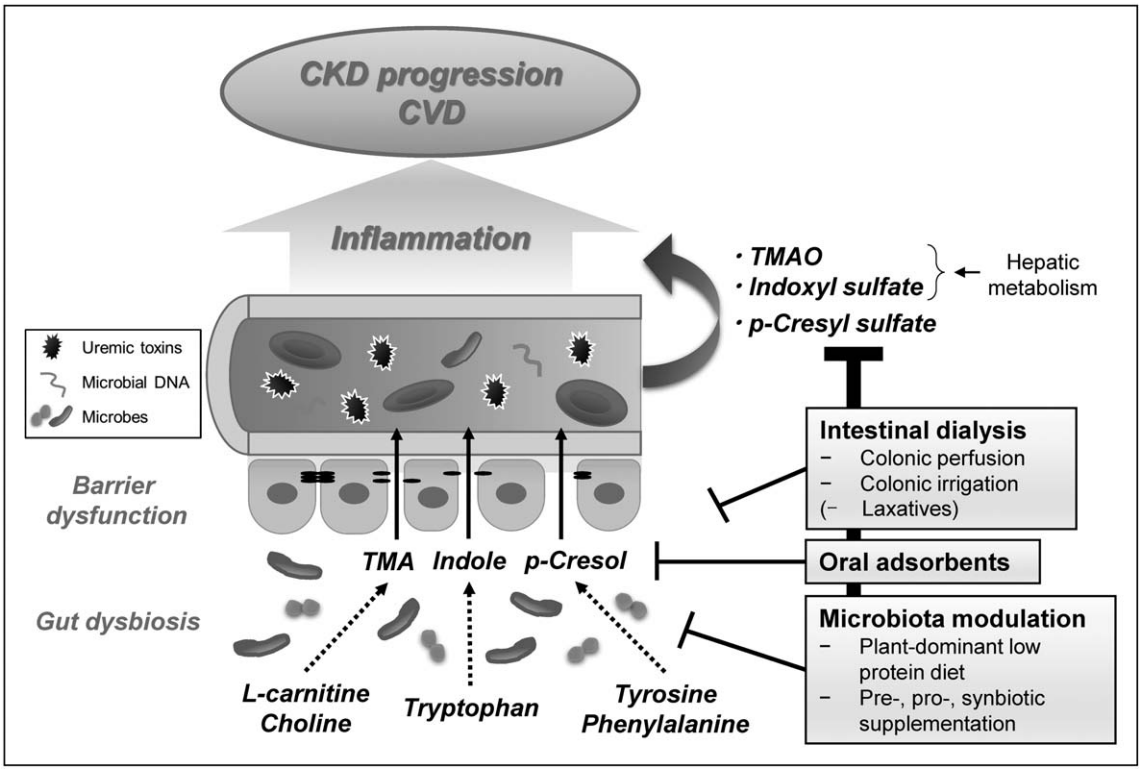

FIGURE 2. Potential mechanistic links between gut dysbiosis, uremia, and adverse outcomes and therapeutic targets by intestinal dialysis, oral adsorbents, and microbiota modulation. CKD, chronic kidney disease; CVD, cardiovascular disease; TMA, trimethylamine; TMAO, trimethylamine N-oxide.

thus can be considered as a metabolically active endogenous organ in itself [74]. One of such activities of the gut microbiota is protein fermentation, which generates precursors of the two major gut-derived uremic toxins, indoxyl sulfate and p-cresyl sulfate [75]. Certain intestinal bacteria, such as *Escherichia coli*, have tryptophanase that converts tryptophan to indole, which is subsequently absorbed into the systemic circulation and metabolized by the liver to indoxyl sulfate [76]. Meanwhile, p-cresyl sulfate is a 188-Da protein-bound solute that originates from the sulfation of p-cresol, which is a colonic fermentation product of the amino acid tyrosine and phenylalanine [76,77]. Trimethylamine-N-oxide (TMAO) is another toxic gut-derived metabolite, which is a circulating organic compound derived from the metabolism of dietary L-carnitine and choline by intestinal bacteria [78,79] (Fig. 2).

Gut dysbiosis and uremic toxins in chronic kidney disease

Significant alterations of the gut microbiota (a.k.a. gut dysbiosis) have been reported in CKD, which is often characterized by the shift from a saccharolytic (carbohydrate-fermenting) to a more proteolytic phenotype [37]. The proteolytic bacteria dominating in CKD accelerate protein fermentation, in particular the amino acids prevalent in animal-derived proteins, contributing to the excessive production of uremic toxins [8]. Further, these uremic toxins impair gut barrier function, allowing translocation of uremic substances and other gut-derived products (e.g., endotoxins, microbial DNA fragments, and intact microbes) into the systemic circulation [80]. The uremic toxins that cannot be fully secreted by the impaired kidneys and thus accumulate in the blood exert deleterious effects on various tissues and organs, such as renal tubular cell damage, endothelial dysfunction, leukocyte activation, coagulation disturbances, insulin resistance, and cardiac fibrosis and hypertrophy [2,3], collectively contributing to the excess morbidity and mortality in patients with CKD [81–84] (Fig. 2).

Gut microbiota modulation for uremia

Vigorous efforts have been devoted to develop therapeutic strategies targeting the gut microbiota to control uremia [9▪,74]. These include dietary modifications (e.g., plant-based diet and low-protein diet [LPD]) [85▪,86,87] and dietary supplementation of prebiotics (i.e., nondigestible food ingredients that

Table 1. Mechanisms of action and potential challenges of gut-targeted interventions for uremia in CKD

Interventions	Mechanisms of action	Potential challenges	Suggested types of patients for implementation
Intestinal dialysis			
Colonic perfusion with a Malone antegrade colonic enema stoma	Cleanse the entire colon and increase excretion of uremic toxins, fluid, potassium and phosphate into feces Potentially modulate the gut microbiota	Need for stoma surgery Stoma-related complications (e.g., site infection) Bowel perforation Dehydration Hypokalemia Nutrient malabsorption	ESRD patients with failure of dialysis access ESRD patients with severe functional constipation or idiopathic fecal incontinence ESRD patients who refuse conventional dialysis therapies
Colonic irrigation with rectal catheter	Cleanse the left colon and increase excretion of uremic toxins, fluid, potassium and phosphate into feces Potentially modulate the gut microbiota	Need for colonic irrigation device Limited physical activities during treatment Bowel perforation Dehydration Hypokalemia Nutrient malabsorption	CKD and ESRD patients with chronic constipation ESRD patients with failure of dialysis access ESRD patients with limited access to conventional dialytic modalities Advanced CKD patients who refuse conventional dialysis therapies
Laxatives	Enhance gut motility and increase excretion of uremic toxins, fluid, potassium and phosphate into feces Potentially modulate the gut microbiota	Gastrointestinal discomfort (e.g., diarrhea, abdominal pain, and bloating) Hypokalemia due to drug-induced diarrhea Drug toxicity Nutrient malabsorption	CKD and ESRD patients with chronic constipation ESRD patients with limited access to conventional dialytic modalities
Oral adsorbents	Selectively adsorb uremic toxin precursors and increase their excretion into feces Potentially modify the gut microbiota	High pill burden Low adherence Gastrointestinal complications (e.g., constipation and nausea)	CKD patients at high risk of disease progression (e.g., those with high proteinuria) CKD patients with uremic symptoms
Plant-based and low-protein diet	Reduce production of uremic toxins by modulating the gut microbiota through high fiber and low protein intake	Risk of protein-energy wasting Inadequate essential amino acids High potassium load Low palatability and adherence	CKD patients at high risk of disease progression (e.g., those with high proteinuria) CKD patients with uremic symptoms Advanced CKD patients who choose conservative nondialytic care
Prebiotic, probiotic, and synbiotic supplementation	Reduce production of uremic toxins by modulating the gut microbiota	Gastrointestinal discomfort (e.g., abdominal bloating, flatulence, and diarrhea)	CKD and ESRD patients with uremic symptoms CKD and ESRD patients with chronic constipation

CKD, chronic kidney disease; ESRD, end-stage renal disease.

induce specific modifications in the composition and/or activity of the gut microbiota) [88], probiotics (i.e., live microorganisms which confer health beneficial effects when administered in adequate amounts to the host) [89], and synbiotics (i.e., both probiotics and prebiotics) [90].

In a recent study evaluating associations among diet quality, serum uremic toxins, and the gut microbiota profile in patients on hemodialysis, higher adherence to plant-based diet was significantly associated with lower serum indoxyl sulfate levels and lower relative abundances of bacteria that were related to elevated indoxyl sulfate levels [91]. Similarly, a study of NDD-CKD patients undergoing LPD for 6 months demonstrated that those who adhered (vs. did not adhere) to the LPD had significantly lower levels of serum p-cresyl sulfate, along with the change in the gut microbiome profile [92]. A favorable effect of pre-, pro-, and synbiotic supplementations on uremic toxins has also been reported in some studies [93,94], although a recent systematic review and meta-analysis of clinical trials showed low certainty of evidence to support the overall treatment effect of these supplementations on uremic toxins. Of note, similar therapeutic properties (i.e., change in the gut microbiota and reduction in circulating uremic toxins) have also been reported in colonic irrigation [34,95] and certain types of laxatives, such as lactulose, chloride channel activator, and guanylate cyclase C agonist [96–99].

CONCLUSION

With growing recognition of the importance of the gut and the gut microbiota in health and disease, evidence is accumulating that supports the concept of intestinal dialysis and gut microbiota modulation as promising adjuvant approaches to the management of CKD. While acknowledging the challenges (Table 1), given the substantial disease burden associated with uremia, fluid overload, and electrolyte disturbances and the limited ability of conventional dialysis therapy to reduce the consequences of these conditions, perhaps the time has come to further explore the clinical application of gut-targeted interventions and confirm their effectiveness on uremia and relevant clinical outcomes through well designed clinical trials. Some of these interventions may be especially useful in parts of the world with limited access to conventional dialytic modalities.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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