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Novel Therapeutic Approaches in Chronic Kidney Disease and Uremia Management:

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With the worldwide epidemic of chronic non-communicable diseases, chronic kidney disease (CKD) is one of the growing public health problems and can progress to kidney failure, also known as the end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) in form of maintenance dialysis or kidney transplantation. Dialysis therapy is often associated with decreased quality of Life (QoL) and high morbidity and mortality [1] in addition to economic burden and high costs [2].

In addition to CKD epidemic, increasing number of geriatric population leads to aging epidemic [3]. The majority of non-dialysis dependent (NDD) CKD patients will die, especially from cardiovascular disease (CVD), before their kidney function progress to ESRD [4–6]. The incidence of ESRD has been growing all throughout the world, and mortality of patients with ESRD under dialysis therapy is even greater than NDD-CKD patients. The more advanced is the CKD stage, the more increased is the risk of mortality [4]. Therefore, reduction of CKD progression to ESRD and avoidance of dialysis therapy may lower morality in CKD population while it may also improve QoL and mitigate cost burden. Several therapeutic strategies are well established to slow progression of CKD. In this special edition of the Current Opinion in Nephrology and Hypertension, we present a series of Novel Therapeutic Approaches in CKD and Uremia Management, that may help

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Conflicts of interest:

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prevent CKD progression and manage uremic symptoms using non-traditional approaches. These strategies are not limited to places with resource and budget constraints such as underdeveloped nations. They are indeed the areas of unmet need for most developed communities with easy access to dialysis, where the patients and providers as well as the government seek to entertain novel approaches in leu of or as compliment to the traditional dialysis.

Volume overload due to fluid retention is common in advanced CKD and may not be commonly accounted for as one of the modifiable factors leading to progression of CKD to ESRD and high burden of cardiovascular (CV) mortality. A vicious cycle of kidney-heart relationship as so-called cardiorenal syndrome is not only via uncontrolled blood pressure (BP), but also systemic inflammation from intestinal edema and ischemia contributes to CKD progression. Elevated intrarenal venous pressure from right sided heart failure is also a mechanism discussed [7]. Overall, diuretic, dietary sodium restriction, vasopressin 2 receptor antagonist are discussed in a practical way. Although uncommon practice, peritoneal dialysis for volume removal in diuretic resistant patients especially heart failure individuals is an option.

Electrolyte disturbance commonly occurs in advanced CKD is hyperkalemia. Potassium homeostasis and mechanism of hyperkalemia in CKD and kidney transplant recipients are reviewed. Renin-angiotensin aldosterone blockade is commonly used for anti-proteinuric modulation in CKD patients. However, its use is commonly limited due to hyperkalemia in CKD patients who are at risk for hyperkalemia. This conflict of using RAAS inhibition in CKD patients who generally have benefit from antiproteinuria, but also at risk of hyperkelamia leads to a need for therapeutic options to prevent hyperkalemia. Efficacy and safety of three potassium binders currently available including sodium polystyrene sulfonate, patiromer, and sodium zirconium cyclosilicate are reviewed. Particularly, with several evolving evidence of the clinical utility of the last two agents, the limited use of RAAS agents due to hyperkalemia can be mitigated or eliminated.

Three emerging contributors that cause stress to the kidneys and lead to CKD progression are H^+ stress (metabolic acidosis), intestinal stress (gut-derived toxins from dysbiosis of gut microbiome), and oxidative stress. These provide opportunity to slow CKD progression by non-pharmacologic and novel pharmacologic interventions as well as dietary selection be incorporated in interventions for all of these stresses. RAAS blockade which is on pathogenesis pathway of CKD progression may be intervened by a decrease in H+ diet and medications blocking this pathway e.g. angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), and mineralocorticoid receptor antagonist as well as Na +-based alkali. Vegan or plant-based diet is a proposed dietary intervention for dysbiosis of gut microbiome apart from pre- and pro-biotics in order to reduce gut-derived uremic toxins especially p-Cresyl sulfate and indoxyl sulfate. These gut-derived toxin interventions decrease renal and cardiovascular risks. Oxidative stress reduction to slow CKD progression by intervening modifiable factors such as smoking cessation and plant-based dietary protein intake is reviewed.

CKD leads to not only fluid, electrolyte, and metabolic disarrangement, but also dysbiosis of gut microbiome, another emerging and more recognized pathogenesis of CKD, so called "Gut-Kidney Axis" [8]. Gut microbiome adds more complexity in a vicious pathway of CKD progression; however, it opens therapeutic opportunity to preserve renal function by involving dietary and nutritional intervention as well as pharmacological therapies. Genetic engineering of microorganisms such "smart bacteria" is another therapeutic option for uremic dysbiosis; although, more studies are required. Similarly, fecal microbiome transplantation (FMT), which is indicated for recurrent *Clostridium diffucile* colitis, may be another treatment for dysbiosis in CKD, but additional strong evidence of its clinical utility is needed.

Given pathogenesis of CKD and CKD progression from dysbiosis of gut microbiome and conservative management in advanced CKD patients who are not a candidate for RRT including dialysis and kidney transplantation (KT), intestinal dialysis is one option for conservative management by removing small molecule such as urea and middle molecule such as p-cresyl sulfate and indoxyl sulfate. History and effective evidence of intestinal dialysis are reviewed. Although with limited clinical data, some published cases and studies showed an effectiveness of intestinal dialysis with complications such as hyperchloremia. In addition, induced diarrhea and colonic dialysis are reviewed. In addition to be therapeutic option to overcome barriers to traditional dialysis or KT, intestinal dialysis may reduce economic burden of costly traditional renal replacement therapy.

Followed the uremic dysbiosis of gut microbiome in CKD, uremic pruritus is another related and overlapped topic in terms of pathogenesis and therapeutic modalities. QoL is one of the main factors in caring CKD and ESRD patients. Not only medical burdens to regularly follow up with nephrologists or have dialysis, symptoms related to uremia can significantly interfere daily activities. Pruritus is a very common uremic-related symptom which is oftentimes ignored and undertreated by providers caring kidney patients. Since the pathogenesis of pruritus remains unclear and the effectiveness of available therapeutic options is varied, further studies are in an urgent need. The emerging uremic toxin, indoxyl sulfate and p-Cresyl sulfate from dietary protein and gut microbiota, respectively provide further therapeutic options for uremic toxin-related pruritus from both dietary protein restriction, probiotics, oral charcoal therapies and charcoal in extracorporeal techniques.

CVD is the most common cause of mortality in CKD population. Several pathogenic mechanism involve this poor outcome in CKD. Epidemiologic studies demonstrate association between surrogate markers commonly occur in CKD and renal and patient outcomes. Alkaline phosphatase (ALP) has been showed to be associated with poor outcomes in CKD [9]. Given its ubiquitous presence, ALP is discussed as a target for epigenetic modulation in CKD. It extensively involves in biomineralization such as arterial calcification, bone mineralization, fibrosis both in cardiac and pulmonary fibrosis, inflammation, oxidative stress, hypertension, cognitive impairment, and chronic kidney disease. Regulation of ALP gene expression, epigenetic regulation of ALP which may indicate gene dysregulation in some diseases. Novel therapies with epigenetic modulators such as microRNA which is dysregulated in chronic kidney disease-mineral and bone disorder (CKD-MBD), apabetalone treatment, a bromodomain and extraterminal (BET)

inhibitor in improvement in renal function, and BET inhibition in metabolic bone disorders are reviewed.

Although RRT both dialysis and KT is a treatment for advanced CKD patients, it may not provide benefits in terms of survival and QoL. Particularly CKD patients who is not suitable, ready, or unlikely to receive benefits from, but rather potentially encounter complications of dialysis or KT such as elderly patients with multiple unacceptable comorbidities. It is still controversial whether non-RRT can be generalized as one of the options for advanced CKD patients; however, it is reasonable to be an option or even ultimate and appropriate treatment for some patients. Particularly there are novel medications which can correct or avoid complications of worsening renal function such those discussed in previous aforementioned article regarding novel medications for chronic hyperkalemia for CKD. Preservative management to maintain residual renal function longer is proposed as one part of conservative management. Although there are growing areas of potential benefits than harm for conservative management in some population, the practice needs to be justified and precision medicine to individualized care is warranted. Moreover, fluid and electrolyte management by means of inducing and modulating perspiration is an old concept that may regain momentum in conservative management of advanced CKD.

Lastly, since KT is still a treatment of the first choice for an appropriate advanced CKD and ESRD patients [10], every effort should be implemented to prolong renal allograft function. Renal transplant recipient (RTR) will ultimately encounter with continuously worsening renal allograft which is proposedly defined as “failing renal allograft (FRG)”. Immunological and non-immunological factors are both contributing to FRG. Although it seems to be complex in pathogenesis, several contributing factors open opportunities to intervene both pharmacological and non-pharmacological interventions. However, the lack of robust evidences for some of these therapeutic interventions leads to controversial in clinical practice and implementation of these interventions should be individualized. Although these strategies may slow FRG, renal allograft failure is inevitably ultimate outcome. Therefore, concomitant preparation for the return to dialysis should also be carefully planned in advance, while managing FRG by taking immunosuppressive medication into the consideration in order to increase possibility of the next KT without unnecessarily over immunosuppression.

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Abbreviations

ALP	alkaline phosphatase
BET	bromodomain and extraterminal

BP	blood pressure
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease-mineral and bone disorder
CV	cardiovascular
CVD	cardiovascular disease
ESRD	end-stage renal disease
FMT	fecal microbiome transplantation
KT	kidney transplantation
QoL	quality of life
RAAS	renin-angiotensin aldosterone system
RRT	renal replacement therapy

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