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Novel Therapeutic Options for Management of Electrolyte Disorders

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Electrolyte disorders are a key component of chronic kidney disease (CKD) management, and adequate and timely treatment is vital to the well being and outcome of this patient population. As any newly minted nephrologist or seasoned practitioner knows, nephrologists are often consulted for managing electrolyte abnormalities, such as hyponatremia, hyperkalemia, hyperphosphatemia, and metabolic acidosis. Therefore, awareness of current guidelines and emerging therapies to correct these disorders that can further prevent morbidity and mortality is vital. CKD patients with hyponatremia had a higher mortality rate than those with normal serum sodium level, irrespective of the presence or absence of heart failure[1] and chronic mild hyponatremia has also been associated with increased falls and impaired attention.[2] Although neurological deficits are often the most feared complication of hyponatremia, cardiac arrhythmias confer increased risk of death in those with untreated hyperkalemia. Even mild hyperkalemia would preclude the use of renoprotective agents, which could then hasten kidney disease progression.[3] Excess hydrogen ion production or increased bicarbonate loss can lead to metabolic acidosis, and chronic metabolic acidosis is linked to adverse outcomes affecting bones, heart, and kidneys.[4] Hyperphosphatemia develops as kidney function declines and is associated with adverse cardiovascular outcomes. Although calciphylaxis is considered much less common than the other electrolyte disturbances, it is associated with two to three times higher mortality risk. Its prevalence ranges from 1 to 4% in dialysis patients but is often underreported and undiagnosed.[5] Hence, raising awareness of how to diagnose early and treat this disorder appropriately could decrease the morbidity and mortality of these fragile patients.

In this issue of *Current Opinion in Nephrology and Hypertension*, we are excited to introduce a unique group of articles by expert authors addressing above discussed electrolyte disorders and emerging therapeutic options to effectively manage them. Hoorn and Spasovski provided refreshing updates on management options for acute and chronic hyponatremia. They compare the use of hypertonic saline boluses versus infusions in correcting serum sodium at an appropriate rate, highlight the utility of vasopressin receptor antagonists, and examine the evidence behind using urea to correct hyponatremia. Further, they also review other nontraditional therapies, such as fludrocortisone, interleukin-6 inhibitors, and albumin, in disease-specific causes of hyponatremia.[6] One disease-specific cause of hyponatremia is malignancy, which is being addressed in detail by Kitchlu and Rosner.[7] Hyponatremia is the most common electrolyte disorder in malignancy, most often seen in those with lung, prostate, pancreatic, and liver cancer, and is associated with higher mortality if left untreated. The syndrome of inappropriate antidiuretic hormone, intractable vomiting/diarrhea, reduced solute intake, polydipsia, hypothyroidism, organ failure (heart, liver, or kidney), renal tubular injury, and concomitant diuretic use are all common causes of hyponatremia in this population. Accurately diagnosing and treating these patients is critical to allow for subsequent chemotherapy cycles and potentially reduce hospitalizations.

Lopes *et al.*[8] have provided us with a comprehensive overview of hyperkalemia management specifically focusing on newer agents for managing both acute and chronic hyperkalemia. Hyperkalemia is associated with higher morbidity and mortality, especially in those with CKD and chronic heart failure.[3] Decreased renal excretion, abnormal potassium body distribution, and cellular release, and pseudohyperkalemia will commonly lead to elevated serum potassium.[3] Lopes *et al.* review data on potassium binder use in hyperkalemic patients taking renin–angiotensin–aldosterone system inhibitors (RAASi).[8] Patiromer is a nonabsorbed polymer binder that exchanges calcium for potassium in the gastrointestinal tract, leading to increased potassium excretion. Zirconium cyclosilicate is similar but exchanges sodium for potassium. Even though limited data exists, the use of these new potassium binders might help to continue renin–angiotensin system blockers even among those with mild hyperkalemia and offer long-term benefits. Long-term studies are warranted to address the long-term benefits and safety of these agents[8] in those with and without CKD.

Hutchison and colleagues addressed progress made in the area of hyperphosphatemia. Despite the availability of multiple agents to treat hyperphosphatemia, medication compliance continues to remain as a critical barrier. In their article, authors reviewed both newer agents to treat high-serum phosphorus levels and based on some recent studies, the possibility of treating hyperphosphatemia to a specific target in the CKD population.[9] Seethapathy and Nigwekar[10] summarized the pathogenesis and management aspects of calciphylaxis, previously called calcific

uremic arteriopathy. Calciphylaxis is a rare but devastating disease leading to painful ischemic skin ulcers from microvascular calcification and thrombosis. Vitamin K deficiency may lead to the development of calciphylaxis as vitamin K is integral to inhibiting calcification. Inflammation (common in CKD) and thrombophilia can also potentiate the disease formation. Early diagnosis is vital, and a skin biopsy is often warranted before instituting therapy. The authors notably highlight the utility of old and new management therapies, including calcimimetics, parathyroidectomy, sodium thiosulfate, vitamin K, apixaban, calcification inhibitor SNF 472, wound care, and pain control.[10]

Chen and Abramowitz reviewed the clinical benefits of treating chronic metabolic acidosis in CKD patients.[11] Metabolic acidosis occurs because of a decrease in urine acid secretion from reduced functional nephrons in CKD. Left untreated, there is a higher risk of osteopenia, muscle mass loss, worsening secondary hyperparathyroidism, hypotension, heart failure, insulin resistance, kidney disease progression, and mortality.[12] These authors reviewed recent trials studying the effects of sodium bicarbonate on muscle mass and endothelial dysfunction.[10] Recently, clinical trials have demonstrated veverimer, a hydrochloric acid binder, as a therapeutic option for managing metabolic acidosis in those with CKD.[13] Although exciting, the results of ongoing larger clinical trials on this subject would offer more supportive evidence on the role of this new agent in CKD. In summary, this series of articles illustrates noteworthy current and upcoming treatment options for complex electrolyte disorders, helping advance our knowledge in this growing field of nephrology.

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