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Editorial

Contemporary Issues in Kidney Disease: Addressing Acute Kidney Injury and Inflammation

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Acute Kidney Injury

Acute kidney injury (AKI) is marked by a rapid decrease in kidney function, typically occurring over a few hours to several days. This leads to the retention of metabolic waste products and the disruption in electrolyte, fluid, and acid-base homeostasis.[1] It is a multifaceted syndrome characterized by high rates of morbidity and mortality, precipitating short-term adverse outcomes and posing a significant risk for cardiovascular events, kidney cancer, and chronic kidney disease (CKD), among survivors. Furthermore, the incidence of COVID-19-related AKI has been notably high, as reported by Reslina et al., mirroring the global pandemic.[2] In addition to the rising number of COVID-19-related acute kidney injuries (AKI), wasp stings (Fauziyah et al.) and snake bites are also becoming increasingly common causes worldwide.[3] Consequently, AKI profoundly impacts the quality of life for survivors and imposes substantial burdens on healthcare system.[2]

At present, diagnosing AKI remains challenging. Firstly, in its early stages, AKI can be asymptomatic because clinical signs are largely dependent on the degree of renal impairment. Secondly, the glomerular filtration rate (GFR) is a key indicator for evaluating renal function; however, no tools are available for real-time monitoring of GFR. In clinical practice, urine volume and serum creatinine levels are employed to assess changes in GFR, but they are neither sensitive nor specific.[2]

Managing AKI clinically is also challenging because of its complex pathophysiological mechanisms, influenced by various comorbidities and etiologies. The primary goal of managing AKI is to address the underlying causes of the condition and prevent further kidney damage. However, identifying these causes can be complex and may not be recognized by clinicians until it is too late, resulting in potential kidney damage. Unfortunately, no specific pharmacological approach is available at this time. Additionally, patients with AKI may experience various complications, including imbalances in electrolyte, fluid, and acid-base levels. Consequently, the primary clinical strategies employed in managing AKI are symptomatic and supportive therapies. Fluid management plays a crucial role in both preventing and treating AKI.[4] In cases of severe AKI, renal replacement therapy

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(RRT) becomes necessary and can be life-saving. The most accurate indicators for initiating RRT include volume overload, metabolic acidosis, refractory hyperkalemia, or signs of uremia. However, there is considerable debate over the best timing to initiate RRT in patients who do not have severe complications.[5] Additionally, ongoing discussions center around whether continuous or intermittent RRT is preferable and the appropriate timing for discontinuing RRT.[6, 7]

From a therapeutic standpoint, RRT with extracorporeal hemoadsorption can remove inflammatory mediators, expanding its role beyond just maintaining fluid and electrolyte balance. While the pathogenesis of acute kidney injury (AKI) remains not fully understood, immune response dysregulation is believed to be one of the pathological mechanisms underlying sepsis and COVID-19-associated AKI. In theory, early removal of inflammatory mediators can help restore immune balance, alleviating the severe systemic effects of infection.[8] Additionally, decreased renal perfusion is widely recognized as a leading mechanism in most cases of AKI. This leads to renal ischemia and hypoxia, increasing reactive oxygen species (ROS). Substantial evidence revealed that AKI is associated with increased ROS and decreased antioxidants.[9] Therefore, targeting excessive ROS may represent a new and specific approach to treating AKI.

Inflammation

This AKI can lead to the development of CKD in many patients. Numerous studies show that AKI is a significant risk factor for progressing to CKD and end-stage renal disease (ESRD).[10-12] AKI presents a wide range of clinical scenarios, from mild to severe injury, with the potential to lead to permanent and complete loss of renal function.[13] Patient with AKI should be closely monitored for the development of new CKD or progression of underlying CKD.[11] Mechanism of progression from AKI to CKD include subclinical inflammation leading to persistent structural and functional changes within the kidneys, impaired renal regenerative capacity resulting in maladaptive repair, and vascular and tubular injury causing reduced blood flow and impaired kidney function.[10] Progression of CKD can result in ESRD, which necessitates definitive treatment options such as dialysis or kidney transplantation to sustain life. Hemodialysis is one of the most prevalent kidney replacement therapies worldwide, as it allows for removing waste products, excess fluids, and electrolyte imbalances that accumulate in patients with kidney failure.[14] Outcome of maintenance hemodialysis patients remains poor with high morbidity and mortality. Patients on dialysis have a significantly reduced life expectancy compared to the general population of the same age and sex.[13] One of the most important factors for survival on dialysis is the presence of cardiovascular comorbidities with an underlying high inflammation state.[15]

Inflammation in hemodialysis patients likely stems from uremia and the dialysis procedure. Oxidative stress, accumulation of uremic toxins, and bioincompatibility of dialysis membranes all contribute to the inflammatory state. Several inflammation markers, like C-reactive protein, Interleukin-6, and Tumor Necrosis Factor-alpha, are often elevated in dialysis patients. While there are many inflammatory markers associated with negative outcomes in hemodialysis patients, such as C-reactive protein, Interleukin-6, and Tumor Necrosis Factor-alpha, research suggests that high-sensitivity C-reactive protein (hs-CRP) is a strong predictor of mortality and other complications in these patients.[16] It is essential to highlight that while hs-CRP serves as a strong predictor, it is not the sole determinant of patient outcomes. Other factors, including the patient's overall health status, comorbidities, and treatment adherence, also play significant roles. Another important consideration is the role of asymmetric dimethylarginine (ADMA) in hemodialysis patients. ADMA is an endogenous inhibitor of nitric oxide synthase, and elevated levels of ADMA are associated with higher cardiovascular risk and increased mortality in this population.[17]

ADMA is an important factor linked to increased inflammation and poorer outcomes in hemodialysis patients. Studies have demonstrated that ADMA levels are significantly higher in hemodialysis patients compared to healthy individuals. The increase in ADMA is thought to be due to decreased renal clearance and increased oxidative stress and inflammation associated with the hemodialysis procedure. This increase causes impairment of nitric oxide production, which can lead to endothelial dysfunction, increased vascular resistance, and, ultimately, cardiovascular complications.[18]

Many studies have linked ADMA with other factors. One of the factors is vitamin D deficiency in hemodialysis patients, which is associated with increased inflammation and higher mortality.[17, 19] Prevalence vitamin D deficiency is very high in the CKD and dialysis population. A prevalence rate of 80-90% has been reported. The mechanism by which vitamin D deficiency can lead to heightened inflammation involves its role in regulating the immune system. Vitamin D has anti-inflammatory properties and its deficiency is associated with increased inflammatory cytokine production.[20] Lusito et al. study found a correlation of vitamin D deficiency with ADMA in hemodialysis patients.

Kidney disease is a multifaceted and complex condition that poses significant challenges in modern healthcare. Addressing AKI and inflammation stands out as particularly critical among the various contemporary issues in kidney disease. AKI, a sudden loss of kidney function that can arise from a multitude of causes, demands prompt and effective management to prevent long-term damage. Additionally, inflammation, a key driver of CKD progression, necessitates targeted therapeutic strategies to mitigate its harmful effects. These interconnected issues underscore the need for innovative solutions and comprehensive care approaches to improve patients' lives with kidney disease.

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