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Review Article

Advancing Insights into Progression of Acute Kidney Injury with Sepsis: Early Detection and Management

Tadikonda Rama Rao *, Rayapudi Vasavi Sai Saraswati, Arthika Chauhan Laudia, Saniya Mehrin

Department of Pharm. D, CMR College of Pharmacy, Hyderabad, INDIA

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*Address for Correspondence:

Dr. Tadikonda Rama Rao, Department of Pharm. D, CMR College of Pharmacy, Hyderabad, INDIA

Abstract

Acute kidney injury (AKI) associated with sepsis is a major contributor to morbidity and mortality in critically ill patients. The progression of sepsis-induced AKI (S-AKI) is complex and involves a dysregulated immune response, including systemic inflammation, endothelial dysfunction, and microvascular injury. These mechanisms compromise renal function, leading to significant challenges in management. Early detection and timely intervention are crucial to improving outcomes, yet effective treatment strategies remain elusive.

Advances in understanding the pathophysiology of S-AKI have provided critical insights into the underlying mechanisms of kidney damage during sepsis. These insights have led to the identification of potential biomarkers that can aid in early diagnosis, predict disease progression, and guide therapeutic decisions. Current management of S-AKI includes fluid resuscitation, broad-spectrum antibiotics, and renal replacement therapy (RRT), aimed at stabilizing the patient and supporting renal function. Emerging therapies, such as novel pharmacological agents and approaches to modulate the immune response, are under investigation, offering promise for improving clinical outcomes. However, more research is needed to validate these treatments and ensure their safety and efficacy.

The advancing insights into the pathophysiology of S-AKI, coupled with the development of innovative diagnostic tools and therapeutic strategies is critical for improving the management of sepsis-induced kidney injury. Future research should focus on bridging the gap between basic science, clinical practice, and large-scale clinical trials to optimize care and outcomes for patients suffering from S-AKI.

Keywords: Sepsis, Acute kidney injury, Immune response, Systemic inflammation, Endothelial dysfunction, Microvascular injury.

INTRODUCTION

Sepsis is a leading global cause of mortality, originating from the intricate, dysregulated systemic response to a wide variety of infectious pathogens. This life-threatening condition ensues when infection induces widespread tissue and organ damage, triggering a cascade of inflammatory responses that result in severe immune suppression. Sepsis is strongly associated with a variety of debilitating comorbidities, precipitating dysfunction across critical organ systems, including the cardiovascular, renal, hepatic, and central nervous systems[1]. Acute kidney injury (AKI) encompasses a range of conditions marked by alterations in urine output and serum creatinine levels[2]. Sepsis-associated acute kidney injury (S-AKI) is a prevalent complication among hospitalized and critically ill patients, significantly elevating the risk of chronic comorbidities and contributing to markedly high mortality rates and was associated with a greater risk of in-hospital death and prolonged hospitalization compared to AKI from alternative etiological factors[3]. It significantly increases in-hospital mortality by six to eight times and elevates the risk of progression to chronic kidney disease (CKD) by threefold. Moreover, a significant proportion of patients with S-AKI may require renal replacement therapy (RRT).

The risk of developing acute kidney injury (AKI) after sepsis is elevated in patients who are older, male, have a higher severity of illness, demonstrate reduced urinary output, exhibit increased central venous pressure, require vasopressor support, and have prior use of ACE inhibitors or angiotensin II receptor blockers (ACEI/ARB). Moreover, elevated serum creatinine at the time of presentation and a pH level below 7.3 has also been identified as significant predictors of AKI in patients with sepsis[4]. Sepsis-induced acute kidney injury (SI-AKI) is characterized by a complex and distinctive pathophysiological process, primarily driven by an amplified immune reaction. This response is associated with systemic endothelial dysfunction and alterations in renal resident cells, which may facilitate the progression of kidney damage[5]. Early recognition and effective management of patients at risk for sepsis-

associated acute kidney injury (AKI) could potentially reduce related morbidity and mortality.

PATHOPHYSIOLOGY

Sepsis-related acute kidney injury (AKI) is a critical and complex condition with a high mortality risk. It is characterized by a rapid loss of kidney function, indicated by increased levels of blood urea nitrogen (BUN) and creatinine, along with a reduced glomerular filtration rate (GFR) and decreased urine production. However, the exact mechanisms underlying sepsis-induced AKI have yet to be fully clarified[6]. The new concept suggests that the mechanism is not solely reliant on hypoperfusion but instead involves multiple contributing factors. These include inflammation of the nephrons, glomerular dysfunction caused by ischemia-reperfusion injury, stress induced by hypoxia and oxidative processes, tubular damage driven by cytokines and chemokines, as well as apoptosis in tubular and mesenchymal cells. The main factors contributing to the occurrence of sepsis-associated AKI are altered renal microvascular oxygenation during sepsis, an irregular immune response, and dysfunction at the cellular level as shown in figure 1[7].

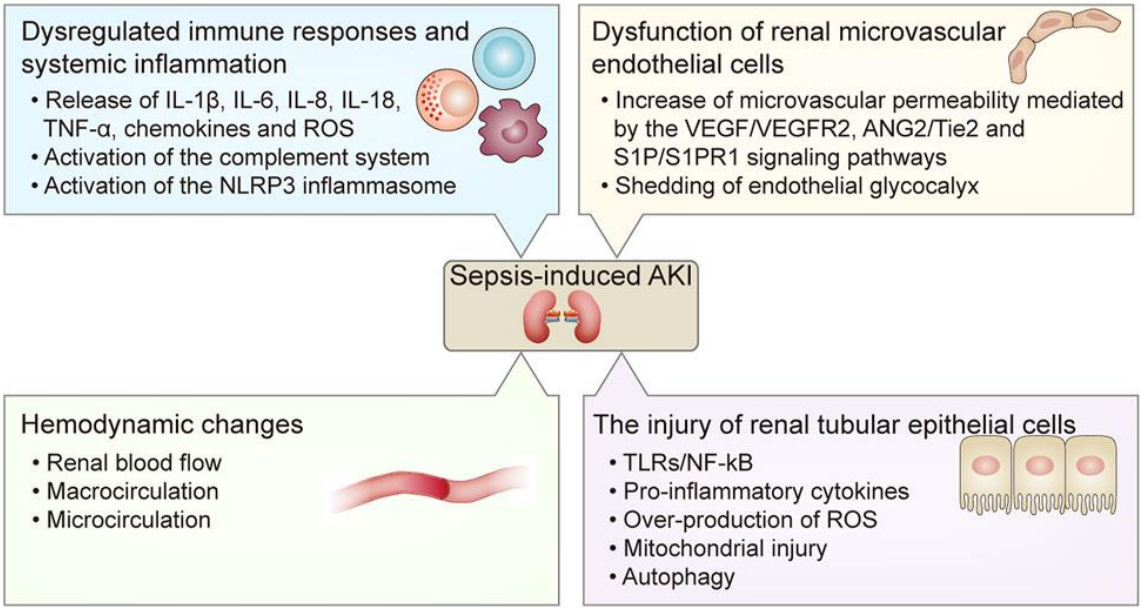

Figure 1: Pathophysiology of Sepsis induced AKI [6]

Cytokine Signalling Cascade

During sepsis, inflammatory mediators like pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) bind to Toll-like receptors (TLRs) on immune cells, triggering a signaling cascade that releases pro-inflammatory cytokines. Similarly, TLR-2 and TLR-4 on renal tubular epithelial cells activate comparable pathways when PAMPs or DAMPs pass through the glomerulus, resulting in oxidative stress, reactive oxygen species (ROS) production, and mitochondrial damage[8].

Dysregulated Microcirculation and Pericyte Depletion

Sepsis-associated AKI was traditionally attributed to macrocirculatory disturbances, such as hypotension and decreased renal blood flow (RBF), leading to acute tubular necrosis. However, recent studies reveal that RBF is often preserved or even elevated in humans during sepsis, directing focus to microcirculatory dysfunction. Despite adequate RBF, impaired microvascular flow contributes to tissue hypoxia and disrupted cellular energy metabolism. Advanced imaging has demonstrated reductions in peritubular capillary oxygen saturation and ATP levels, driven by endothelial injury, leukocyte infiltration, and oxidative stress[9].

Pericytes, essential for maintaining capillary integrity and regulating blood flow, have emerged as crucial contributors to sepsis-associated AKI. Their detachment from endothelial cells leads to vascular congestion, capillary loss, and tubular epithelial damage. Pericyte depletion worsens AKI by promoting lipid accumulation, cell apoptosis, and fibrosis. Key molecular mechanisms, such as NF-κB activation, TLR4 signaling, and sirtuin 3 pathways, regulate vascular permeability and pericyte function, influencing microcirculatory stability as shown in figure 3[10].

Furthermore, the transition of pericytes to myofibroblasts, triggered by factors like LPS-binding proteins, exacerbates microvascular dysfunction and local tissue damage. While progress has been made in understanding these mechanisms, further research is needed to fully elucidate the role of pericytes in regulating microcirculation and glomerular filtration during sepsis, advancing our knowledge of sepsis-associated AKI[11].

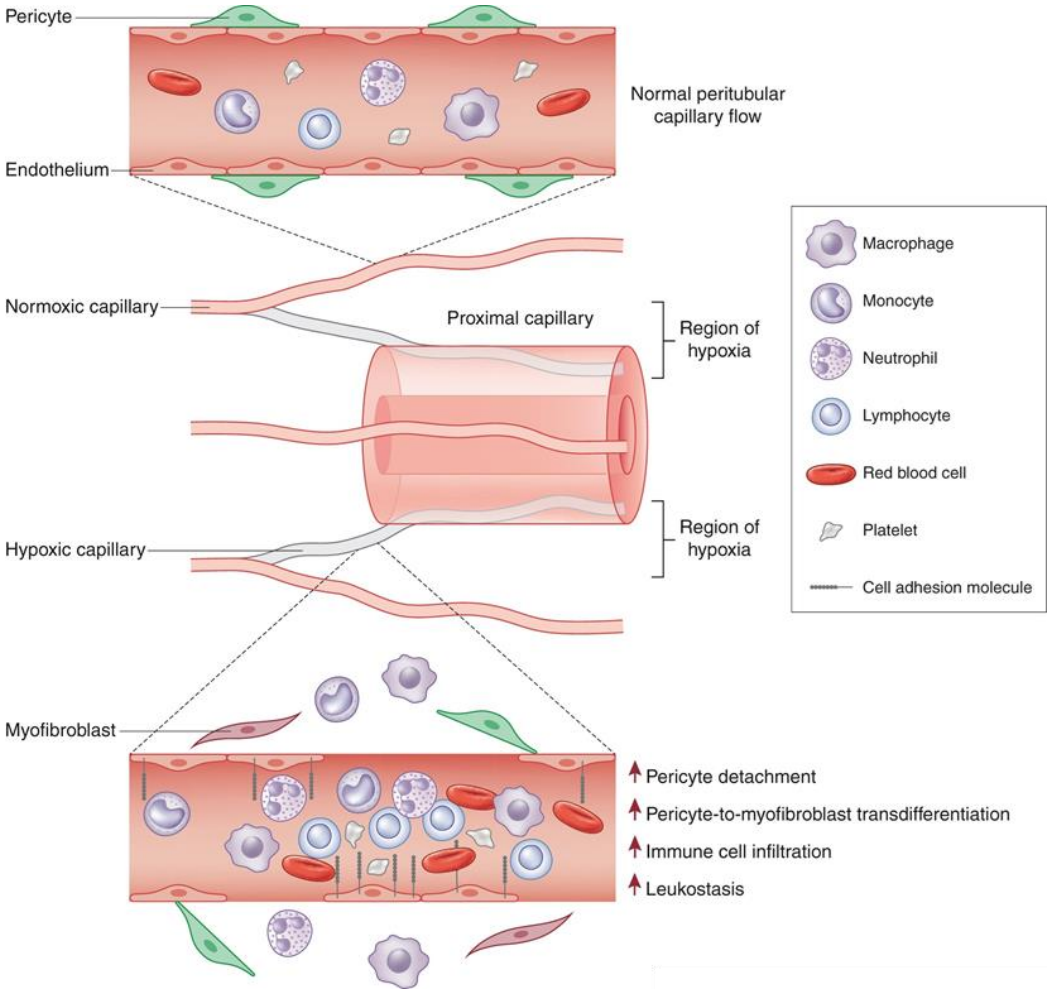

Figure 2: Microcirculation Dysregulation and Pericyte Loss[11]

Dysfunction in the RAAS Signaling Cascade

The renin-angiotensin-aldosterone system (RAAS) is essential for controlling vascular resistance, maintaining fluid and electrolyte balance, and regulating glomerular filtration rate (GFR). Among critically ill patients, increased renin levels are associated with higher mortality rates, a greater incidence of adverse renal events, and an increased need for renal replacement therapy (RRT). Additionally, patients with persistent vasodilatory shock often exhibit elevated renin levels. Notably, inflammatory processes can disrupt angiotensin-converting enzyme activity, leading to a reduction in angiotensin II production[12-13].

BIOMARKERS

Biomarkers are vital for managing AKI in sepsis, providing early identification, risk evaluation, and insights into the underlying mechanisms of the condition. They assist in assessing the risk of AKI, identifying septic AKI from other types, and monitoring progression or treatment effectiveness, enhancing diagnostic accuracy and patient outcomes[14]. Emerging biomarkers enable earlier and more accurate detection of AKI in sepsis, representing various underlying pathophysiological processes.

Proenkephalin

Proenkephalin (PENK) is an emerging biomarker for assessing kidney function and injury. It acts as a reliable surrogate marker for endogenous opioids called enkephalins. A precursor of the enkephalin family, preproenkephalin A is a 267-amino acid peptide that is encoded by the PENK gene. The smaller peptides met-enkephalin, leu-enkephalin, and PENK are produced by the cleavage of this precursor. As natural opioids, enkephalins mostly bind to delta opioid receptors, which are found in the central nervous system and, followed by kidneys[15].

PenKid has been identified as a reliable predictor of various conditions associated with higher morbidity and mortality, such as chronic kidney disease, worsening renal function, the need for renal replacement therapy, and AKI, particularly in cardiac surgery and heart failure. In ICU studies on septic patients, PenKid has proven to be a highly specific marker of renal function, distinguishing itself from other AKI biomarkers by remaining unaffected by systemic inflammation when renal function is intact[16].

Neutrophil gelatinase-associated lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL) belongs to the family of lipocalin proteins. In humans, NGAL exists in various forms: a 25 kDa monomer, a 45 kDa dimer, and a 135 kDa heterodimer, which is covalently linked to gelatinase[17]. Neutrophil gelatinase-associated lipocalin (NGAL) is a key biomarker for detecting and predicting acute kidney injury (AKI), particularly in cases of sepsis. It is secreted by

neutrophils and renal tubular cells in response to damage or stress, with its levels in blood and urine rising significantly earlier than traditional markers like serum creatinine[18]. In septic AKI, NGAL expression increases due to a combination of systemic inflammation and direct tubular injury, emphasizing its dual role in signaling both kidney damage and repair mechanisms.

Cystatin C

Serum cystatin C has emerged in recent years as a promising biomarker for the early diagnosis of acute kidney injury (AKI). This 13-kDa, nonglycosylated protein belongs to the cystatin superfamily, known for inhibiting cysteine proteases. It is consistently produced by all nucleated cells, freely filtered by the glomerulus, and predominantly reabsorbed in the proximal tubules through megalin-mediated endocytosis, where it is subsequently metabolized[19]. Cystatin C has gained recognition as a reliable predictor of AKI in critically ill patients. Unlike serum creatinine, its levels are minimally influenced by factors such as age, gender, race, or muscle mass, making it a more consistent and accurate indicator for renal function assessment across diverse patient populations[20]. This property makes it a more reliable indicator of kidney function, especially in populations where serum creatinine may be unreliable, such as elderly patients or those with altered muscle mass.

Cell free DNA

Serum cell-free DNA (cfDNA) refers to extracellular DNA fragments found circulating in the bloodstream. These fragments are generated through various cellular processes, including necrosis, apoptosis, pyroptosis, and NETosis, a mechanism associated with the formation of neutrophil extracellular traps. Additionally, cfDNA can originate from actively secreted DNA or external sources. This biomarker has gained recognition as a noninvasive diagnostic tool for a range of medical conditions, such as sepsis, autoimmune rheumatic disorders, physical trauma, malignancies, and cardiovascular or cerebrovascular diseases[21].In healthy individuals, cfDNA levels naturally increase after physical exertion. However, in patients with certain medical conditions, such as sepsis, the intensified inflammatory response leads to a marked increase in various biomarkers, including cfDNA concentrations. Patients with sepsis exhibit elevated levels of cfDNA, with particularly high concentrations observed in those suffering from sepsis-associated acute kidney injury (S-AKI). In critically ill individuals, including those in intensive care units (ICU), cfDNA serves as a valuable prognostic indicator[14].

sTERM-1

In the context of sepsis-associated acute kidney injury (AKI), sTREM-1 has gained recognition as a highly promising biomarker due to its robust diagnostic and prognostic potential. Urinary levels of sTREM-1 remain markedly elevated in sepsis, typically ranging from 30 to 50 pg/ml, in stark contrast to the negligible levels observed in healthy individuals. As sepsis progresses or AKI manifests, urinary sTREM-1 concentrations escalate rapidly, serving as a clear indicator of poor clinical outcomes. Notably, the early rise in sTREM-1 levels—detectable as early as 24 to 48 hours before the onset of AKI—offers a critical window for timely intervention and optimized patient management. The diagnostic efficacy of urinary sTREM-1 for AKI is further underscored by an area under the receiver operating characteristic (ROC) curve ranging between 0.7 and 0.9[22].

Moreover, the dynamic fluctuations in sTREM-1 levels provide profound insights into the likelihood of AKI development and the trajectory of patient outcomes. A sustained upward trend in urinary sTREM-1 levels is strongly indicative of an increased risk of AKI or a potentially unfavorable progression of the underlying condition. These characteristics underscore the utility of sTREM-1 as a reliable, noninvasive biomarker for early detection, risk stratification, and prognostic assessment in septic patients at risk of AKI[23].

NOVEL THERAPEUTIC INNOVATIONS

ANTI INFLAMMATORY AND IMMUNOMODULATORY THERAPIES

Cytokine Modulation

The progression of sepsis induced AKI is known to be significantly influenced by humoral mediators, such as cytokines. Continuous venovenous hemofiltration (CVVH) with dialysis, specifically continuous hemodiafiltration (CHDF) using polymethylmeth-acrylate (PMMA) membrane hemofilter, could eliminate a variety of proinflammatory cytokines[24]. Cytosorb, a haemoadsorption device, integrated with the renal replacement therapy which plays an important role in mitigating the cytokine storm and reduces the organ damage by improving haemodynamics[25].

Immune Checkpoint Modulation

The developing treatment approach for managing sepsis-induced acute kidney damage (AKI) is immune checkpoint modulation, a strategy that targets the immunological dysregulation that is characteristic of sepsis. The programmed cell death protein-1/programmed cell death-ligand 1 (PD-1/PDL1) pathway is one of these immunological checkpoint pathways (12). T-cell function is adversely affected by the receptor PD-1, which is inducibly expressed on T-cells[26]. The levels of serum sPD-L1 were considerably higher in sepsis patients with decreased kidney function[27].

CELL BASED THERAPIES

Mesenchymal Stem Cells

Mesenchymal Stem Cells9 (MSCs) have the ability to alleviate acute kidney injury (AKI) caused by sepsis, crush syndrome, and ischemia/reperfusion injury (IRI). There are two mechanisms that are primarily responsible for their therapeutic effects.

MSCs secrete growth factors and inflammatory regulators through paracrine and endocrine

communication, which prevents vascular endothelial and tubular cells from apoptosis, encourages regeneration, and lowers the infiltration of local inflammatory cells in the kidneys.

Immunomodulatory activities: MSCs promote tissue healing and reduce inflammation by inducing regulatory T cells (Tregs) and transforming pro-inflammatory M1 macrophages into anti-inflammatory M2 macrophages[28].

Exosomes

Exosomes are extracellular vesicles (EVs) that are crucial for cell-to-cell communication of information. The primary source of exosomes is multivesicular bodies (MVBs), which have a diameter of 30 to 100 nm and include lipids, proteins, RNA, and other substances[29]. Exosomes, which are increasingly recognized as promising therapeutic options for a number of conditions, have the potential to be used in the development of novel Acute Kidney Injury [AKI] therapy approaches. Mesenchymal Stem Cell-Exosome have been demonstrated to repair AKI by IncRNA, proteins, miRNA, circRNA and mRNA which promotes tubular proliferation, reducing oxidative and inflammatory stress, inhibiting renal tubular cell death, and promoting vascular regeneration depicted in figure 3[30].

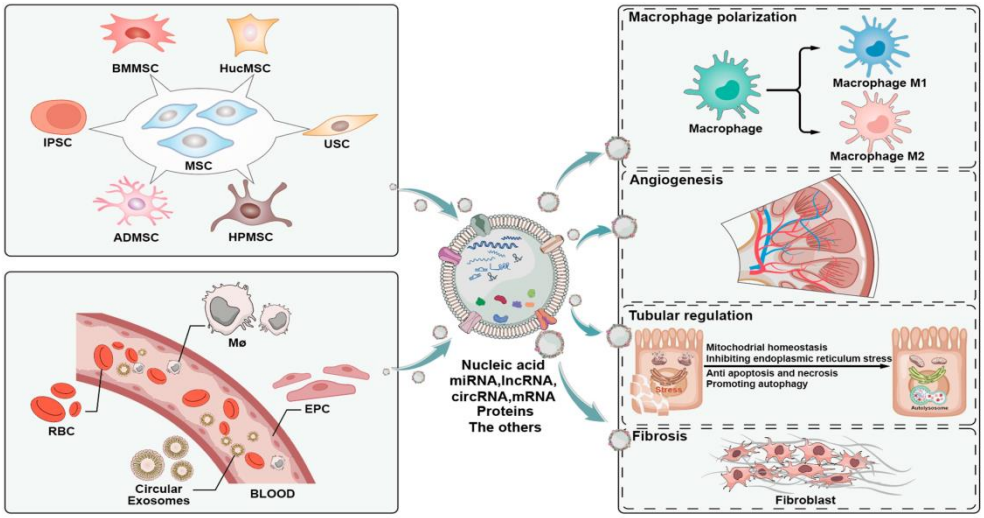

Figure 3: Exosome mediated therapy in AKI with Sepsis [30]

ARTIFICIAL INTELLIGENCE AND MANCHINE LEARNING

Artificial intelligence (AI) and machine learning (ML) are revolutionizing the management of sepsis-associated AKI. By leveraging vast datasets, AI models can accurately forecast the development of AKI in septic patients, facilitating timely preventive measures. Machine learning algorithms enhance treatment precision by optimizing fluid therapy, antibiotic selection, and vasopressor administration, allowing for personalized care tailored to each patient's unique needs. Moreover, AI-driven tools in continuous renal replacement therapy (CRRT) can dynamically adjust treatment settings in real-time, contributing to improved patient outcomes[31].

PHYTOPHARMACEUTICALS

Phytoconstituents, naturally occurring bioactive compounds found in plants, have become a significant focus of research for tackling challenging medical conditions such as sepsis-associated acute kidney injury (AKI). They demonstrate exceptional therapeutic potential, leveraging their potent anti-inflammatory, antioxidant, and immunomodulatory properties. By addressing multiple interconnected pathways driving the development and progression of sepsis-associated AKI, these bioactive compounds offer a comprehensive and targeted approach to treatment. Curcumin is significantly used as the nephroprotective, anti-inflammatory, antioxidant agent which prevents the kidney injury. Quercetin most widely used phytoconstituent which exhibits the renoprotective property by preventing the macrophage activation and reduces the NF-Kb pathway[17].

STANDARD TREATMENT

Antibiotics

In treatment of AKI with sepsis antiobiotics play an significant role in addressing the underlying source of infection in critically ill patients. Based on culture sensitivity test and type of infection antibiotics target Gram positive bacteria and Gram negative bacteria[32]. To improve outcomes, broad-spectrum antibiotics should be initiated within the first hour of sepsis diagnosis. Concurrently, identifying the infection source is crucial to facilitate the administration of targeted antimicrobial therapy. Careful consideration is necessary when using nephrotoxic drugs such as vancomycin, aminoglycosides, and amphotericin B. Delayed antibiotic initiation has been closely associated with a heightened risk of early AKI onset[6].

Fluid Management

Fluid resuscitation plays a key role in treating patients with acute kidney injury (AKI) linked to sepsis. It aims to bring back proper tissue perfusion, boost renal blood flow, and fix hypovolemia, which are vital to stop further kidney damage. In sepsis, patients often lose a lot of fluid due to capillary leak, blood vessel widening, and increased vessel permeability, which calls for aggressive fluid replacement[33]. The fluid choice—be it crystalloids, colloids, or blood products—hinges on the patient's clinical state and underlying issues. Doctors pick crystalloids saline and Ringer's lactate, as the go-to fluids because they work well to expand blood volume. But too much or wrong fluid use can cause problems like fluid overload fluid in the lungs, or worse organ function. So, doctors need to keep a close eye on fluid balance, urine output, and blood flow markers to adjust fluid therapy to what the patient needs and avoid bad outcomes. On top of that fluid resuscitation should go hand in hand with early and right antibiotic use, drugs to boost blood pressure, and ongoing checks to make kidney blood flow as good as possible and slow down AKI in septic patients[34].

Renal Replacement Therapy

Acute renal replacement therapy (RRT) serves as a vital supportive measure for patients with severe acute kidney injury (AKI) complicated by multiorgan failure (MOF). In the intensive care unit (ICU), continuous renal replacement therapy (CRRT) is particularly favored for managing hemodynamically unstable patients, as it provides gradual and controlled solute and fluid removal, ensuring greater stability compared to intermittent methods[35]. Renal Replacement Therapy (RRT) is a critical treatment for severe Acute Kidney Injury (AKI) in the context of sepsis, particularly for patients facing severe complications such as refractory hyperkalemia, profound metabolic acidosis, significant fluid overload, or uremic manifestations like encephalopathy and pericarditis. Continuous RRT (CRRT) is commonly preferred for hemodynamically unstable patients due to its ability to gradually remove solutes and fluids, reducing the likelihood of hypotension and ensuring hemodynamic stability. For patients who are more stable, intermittent hemodialysis (IHD) can be used, although its rapid shifts in fluid and solute levels carry a higher risk of hemodynamic instability[36]. Determining the optimal timing for initiating RRT in critically ill patients with AKI, particularly when absolute indications are not present, remains a complex and challenging decision[37].

Pharmacological Inhibitors of Signalling Pathway

Latest advancements in pharmacological therapies for sepsis-induced acute kidney injury (AKI) have emphasized the inhibition of key signaling pathways involved in the disease's progression. Researchers have highlighted pathways linked to inflammation, oxidative stress, and apoptosis as crucial therapeutic targets[6].

Dexmedetomidine

Dexmedetomidine is a sedative medication with a distinctive mechanism of action, functioning as a selective agonist of α2-adrenergic receptors[38]. In addition to enhancing sedation, dexmedetomidine may help reduce inflammatory responses and offer protective effects against organ dysfunction, including acute kidney injury and liver impairment. Dexmedetomidine reduced the expression of sepsis-induced inflammatory factors, such as tumor necrosis factor-alpha and interleukin-6, and lessened tubular apoptosis in mice. It was also found to lower blood norepinephrine levels, leading to improved renal blood flow and increased urinary output. The studies suggest that dexmedetomidine may alleviate sepsis-induced acute kidney injury (AKI) by diminishing the excessive inflammatory response or sympathetic nervous system activity[39].

Alkaline Phosphate

Alkaline phosphatase (ALP) is a naturally occurring enzyme that helps with detoxification, playing a key role in the body's defense system and innate immunity, especially functioning as an internal anti-inflammatory agent. Additionally, ALP dephosphorylates extracellular adenosine triphosphate (ATP), which is pro-inflammatory, leading to the production of adenosine. Adenosine, in turn, has anti-inflammatory and tissue-protective effects. Specifically, high levels of ATP negatively impact the kidney, while adenosine offers reno-protective benefits. Therefore, the dephosphorylation process helps reduce the inflammatory response and provides tissue protection[40].

CONCLUSION

Sepsis-associated acute kidney injury (S-AKI) results from a dysregulated immune response to infection, presenting a complex and multifactorial challenge for clinicians. While some patients may experience renal recovery with improved outcomes, the clinical trajectory of S-AKI varies widely. A clear understanding of its progression is crucial for enhancing both short-term interventions and long-term patient care.

Biomarkers have proven valuable in complementing clinical judgment, functional assessments, and diagnostic criteria, aiding in early detection, guiding therapeutic decisions, and monitoring recovery. Despite significant advances in understanding the pathophysiological mechanisms of S-AKI, effective, targeted interventions for prevention and treatment are still lacking.

Future research should prioritize a deeper exploration of the mechanisms underlying S-AKI, translating laboratory findings, big data insights, and clinical trial outcomes into practical therapeutic strategies. Bridging these knowledge gaps will be pivotal in developing innovative treatments and improving outcomes for patients suffering from this critical condition.

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