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Timing of Continuous Renal Replacement Therapy Initiation in Sepsis-Associated Acute Kidney Injury: A Comprehensive Review and Future Directions

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Abstract: This review examines the application of continuous renal replacement therapy (CRRT) in patients with sepsis-associated acute kidney injury (S-AKI), with a particular focus on the timing of CRRT initiation. This review addresses the controversy surrounding initiation timing and proposes future research directions. Through a systematic review of recent literature on CRRT for S-AKI, working principles, therapeutic mechanisms, initiation timing of CRRT, and related meta-analyses were summarized. Current studies indicate that the optimal timing for CRRT initiation in S-AKI patients remains inconclusive, with ongoing debate regarding whether early initiation significantly improves patient survival and renal function. This lack of consensus reflects the heterogeneity of the S-AKI patient population and the limitations of existing research methodologies. Future studies should focus on advancing the application of precision medicine in S-AKI and developing individualized treatment strategies by integrating multidimensional information to optimize CRRT utilization and improve patient outcomes.

Keywords: Sepsis; Sepsis-related acute kidney injury; Continuous renal replacement therapy (CRRT); Timing of initiation

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1. Introduction

Sepsis is a life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection. It is diagnosed when a patient with suspected or confirmed infection exhibits an increase in Sequential Organ Failure Assessment (SOFA) score of ≥ 2 points from baseline [1]. The kidney is among the most frequently affected vital organs in sepsis. Acute kidney injury (AKI) is defined by a sudden decline in renal function, manifested by an increase in serum creatinine and/or a decrease in urine output [2]. Sepsis-associated acute kidney injury (S-AKI) is diagnosed when a patient meets the diagnostic criteria for both sepsis and AKI [3]. Epidemiological studies indicate that sepsis accounts for 45%–70% of all AKI cases [4], while

approximately 60% of sepsis patients develop AKI [5]. Moreover, S-AKI significantly increases the risk of in-hospital mortality and long-term chronic kidney disease, with a poorer prognosis compared to non-septic AKI [6-8].

Among available therapies, continuous renal replacement therapy (CRRT) has emerged as a crucial treatment modality for S-AKI patients due to its ability to continuously remove toxins and regulate electrolyte and acid-base balance. However, considerable debate persists regarding the optimal timing of CRRT initiation in S-AKI patients without absolute indications. This article aims to summarize the working principles of CRRT, its therapeutic mechanisms in S-AKI, the controversy surrounding initiation timing, and future research directions, thereby providing a reference for the clinical management of S-AKI.

2. Working principle of CRRT

CRRT is an extracorporeal blood purification technique that operates uninterruptedly for 24 hours or more, mimicking the kidney's purification function by gently correcting fluid overload and removing excess toxins [9,10]. Compared to conventional intermittent dialysis, CRRT offers more precise volume control, improved hemodynamic stability, and superior correction of acid-base balance and electrolyte disturbances [11]. These advantages have established CRRT as the preferred renal replacement therapy for critically ill patients. A 2015 multinational cross-sectional study of AKI patients in intensive care units (ICUs) revealed that CRRT was utilized in 75.2% of cases, compared to only 24.1% for intermittent dialysis [12].

CRRT employs three primary mechanisms for solute removal: diffusion, convection, and adsorption. Diffusion is a passive transport process driven by concentration gradients, primarily used for removing small molecular solutes. Convection involves the simultaneous movement of solutes and solvents driven by pressure gradients [13]. Adsorption, while not the primary removal mechanism, contributes to the elimination of certain macromolecules through direct binding to semipermeable membrane materials [14].

Based on different combinations of these clearance mechanisms, CRRT can be classified into four main modalities: continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemodiafiltration (CVVHDF), and slow continuous ultrafiltration (SCUF). Each modality has distinct characteristics and is suited to specific clinical situations (**Table 1**).

Table 1. Comparison of different CRRT modalities

Characteristics	SCUF	CVVH	CVVHD	CVVHDF
Clearance method	Convection	Convection	Diffusion	Convection + Diffusion
Small molecule clearance efficiency	+	++	+++	+++
Medium molecule clearance efficiency	+	+++	+	+++
Large molecule clearance efficiency	+	+++	+	+++
Replacement fluid	No	Yes	No	Yes
Dialysate	No	No	Yes	Yes

Clearance efficiency: + Low, ++ Medium, +++ High.

3. Mechanisms of CRRT for S-AKI

Sepsis is the primary cause of AKI; however, the pathophysiological mechanisms of S-AKI remain incompletely understood. This knowledge gap is primarily attributed to three factors: limitations in the timeliness of existing AKI diagnostic methods, difficulties in obtaining renal tissue biopsy samples from critically ill patients, and

the fact that most patients have already progressed to S-AKI upon seeking medical attention, complicating the establishment of a temporal sequence between sepsis onset and AKI development [6,15]. Nevertheless, insights from animal experiments and clinical studies have deepened the understanding of S-AKI. Currently, the main pathophysiological mechanisms of S-AKI can be summarized in four interrelated aspects: dysregulation of the immune response, altered hemodynamics, renal tubular epithelial cell injury, and disruption of systemic regulatory mechanisms.

Immune response dysregulation is primarily characterized by a cytokine storm and complement system activation, leading to increased systemic and local renal inflammatory responses [16]. Hemodynamic alterations include abnormal renal blood flow, reduced renal perfusion, and microcirculatory dysfunction, which interact to form a vicious cycle exacerbating local hypoxia and tissue damage [17]. Renal tubular epithelial cell injury involves oxidative stress, mitochondrial dysfunction, and cellular metabolic reprogramming, directly affecting renal function. Additionally, disturbances in autophagic processes may delay renal function recovery [16-18]. Disruptions in systemic regulatory mechanisms, such as abnormal function of the renin-angiotensin-aldosterone system, further exacerbate renal injury. Notably, host susceptibility factors (e.g., diabetes mellitus, advanced age) and certain therapeutic measures (e.g., use of nephrotoxic antibiotics) may increase the risk of or exacerbate S-AKI [15,18,19]. These mechanisms interact to form a complex pathophysiological network that collectively leads to the development and progression of S-AKI (**Figure 1**).

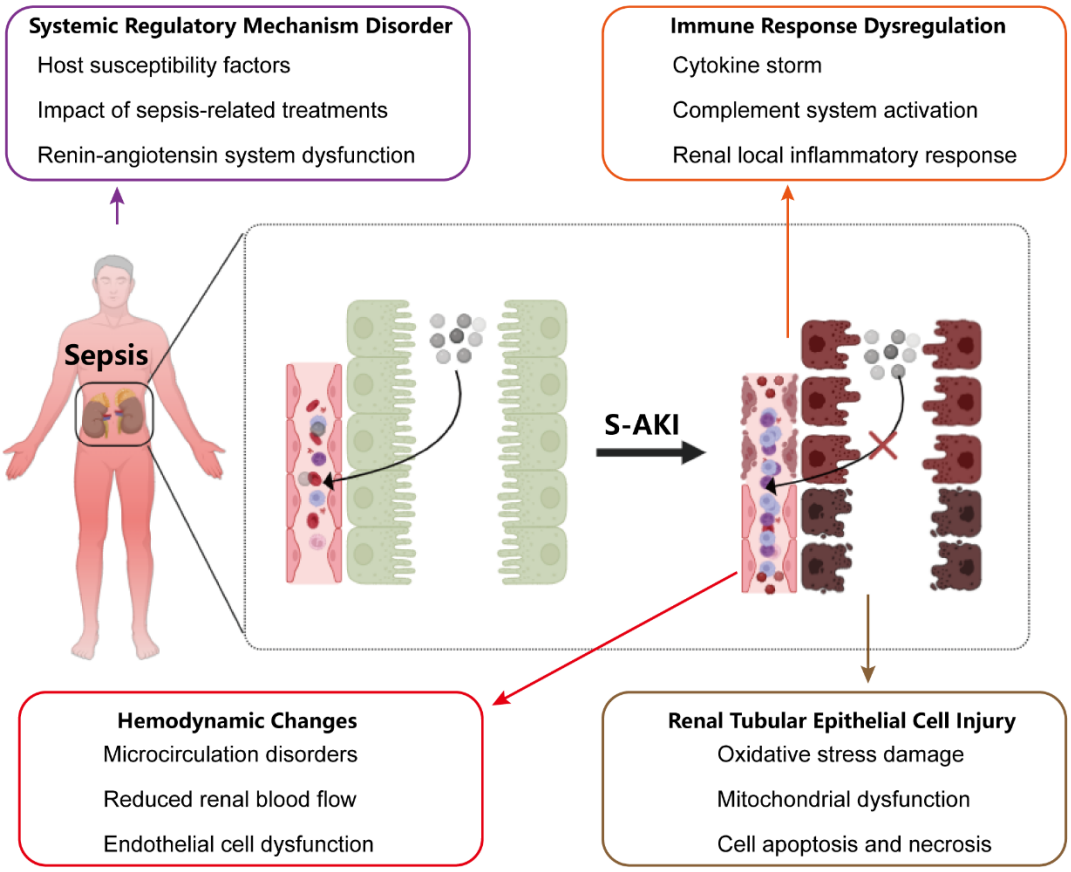

Figure 1. The pathophysiological mechanisms of S-AKI

CRRT, as a key therapeutic modality for S-AKI, effectively intervenes in multiple pathological aspects of S-AKI through various mechanisms, including maintaining hemodynamic stability, modulating inflammatory responses, and improving metabolic status. Hemodynamically, CRRT maintains stability by continuously and gradually removing fluids and solutes. This feature significantly improves renal blood flow abnormalities and microcirculatory dysfunction in S-AKI patients, optimizing renal perfusion. Additionally, CRRT demonstrates significant effects in fluid management, metabolic waste removal, and regulation of water-electrolyte and acid-base balance, helping to prevent further renal injury [20].

Regarding immunomodulation, CRRT modulates the excessive inflammatory response in sepsis by removing inflammatory mediators (e.g., IL-1β, IL-6, TNF-α) [21]. Notably, the removal of macrophage migration inhibitory factors may promote the conversion of macrophages from pro-inflammatory to pro-repairing types, potentially facilitating the renal repair process [22]. Through these mechanisms, CRRT effectively alleviates the systemic inflammatory state and attenuates secondary renal injury.

In terms of metabolism and energy balance, CRRT plays multiple roles. First, it provides additional energy by replacing glucose, citrate, or lactate in the fluid [23]. Second, CRRT reduces intestinal wall edema, facilitating the implementation of early enteral nutrition [24]. Furthermore, by removing inflammatory factors and neutralizing hyperglycemia, CRRT improves insulin sensitivity, promotes metabolic recovery, and alleviates excessive metabolic adaptation [21]. These effects are potentially beneficial in ameliorating the mitochondrial dysfunction and decreased ATP levels commonly observed in S-AKI. However, it is important to note that CRRT may result in the loss of amino acids, L-carnitine, vitamins, and trace elements. Therefore, clinicians using CRRT must weigh its positive effects against potential adverse effects to ensure adequate nutritional support for patients.

Notably, anticoagulants (e.g., citrate or heparin) used in CRRT are not only effective in preventing coagulation in the extracorporeal circulation but also have anti-inflammatory effects [25,26]. This dual effect helps control the pro-inflammatory state in sepsis while reducing the risk of thrombotic complications common in critically ill patients, thus indirectly protecting renal function.

In conclusion, by simultaneously acting on multiple levels of hemodynamics, immunomodulation, and metabolic homeostasis, CRRT not only effectively alleviates AKI symptoms but also potentially promotes the renal repair process. However, the application of CRRT also faces challenges, such as potential nutrient loss, anticoagulant use balance, and complications from invasive procedures. This underscores the need for individualized treatment strategies that weigh the benefits and risks of CRRT in clinical practice.

4. The advantages and disadvantages of early initiation of CRRT

CRRT demonstrates significant potential in the treatment of severe acute kidney injury (S-AKI). As understanding has deepened, CRRT has evolved from a purely renal replacement therapy to an essential modality for organ function support in critical care. Consequently, its indications have expanded to encompass both renal and non-renal conditions. However, as an invasive treatment, CRRT is associated with various complications, including catheter-related bloodstream infections, coagulation dysfunction, and loss of drugs and micronutrients [27]. Therefore, clinicians must conduct a comprehensive assessment of the patient's clinical condition when determining whether and when to initiate CRRT, ensuring that its benefits outweigh the potential risks [28].

The early initiation of CRRT in S-AKI treatment offers multiple advantages, including the maintenance of hemodynamic stability, modulation of inflammatory responses, and improvement of metabolic status,

thereby effectively impeding S-AKI progression. However, early initiation also presents several potential risks. The primary concern is the risk of complications, including bleeding associated with central venous catheter placement, infections, pneumothorax, and anticoagulant-related hemorrhage. Additionally, CRRT may excessively remove micronutrients, trace elements, and therapeutic drugs, potentially compromising treatment efficacy. Furthermore, CRRT significantly increases healthcare costs and resource consumption [29].

Conversely, late initiation of CRRT has its merits, such as reducing the risk of unnecessary invasive procedures and associated complications, as well as optimizing resource utilization, and decreasing overall treatment costs. However, delayed initiation may also lead to adverse effects, including fluid overload and exacerbation of electrolyte imbalances [30].

5. Timing of CRRT initiation in S-AKI treatment

The optimal timing for the initiation of CRRT in patients with S-AKI remains a subject of considerable debate. Existing studies yield conflicting results, primarily divided into two perspectives: those supporting early initiation and those questioning its benefits.

Several studies have demonstrated that early CRRT initiation can improve outcomes for S-AKI patients. A retrospective cohort study of 210 patients, divided into early and late groups based on the median interval between vasoactive drug administration and CRRT initiation, found significantly lower 28-day mortality rates in the early group ($P = 0.034$). Multifactorial analysis confirmed that early CRRT was independently associated with reduced mortality ($P = 0.032$) [31].

Another retrospective study, using a 24-hour post-S-AKI diagnosis threshold to define early and late groups, found no statistically significant difference in 90-day survival. However, the early group demonstrated significantly better Sequential Organ Failure Assessment (SOFA) scores and renal function improvement, suggesting that early CRRT may contribute to systemic organ function restoration in S-AKI patients [32].

An *et al.* conducted a randomized study with 156 S-AKI patients, dividing them into early (CRRT immediately after S-AKI diagnosis) and late (CRRT upon progression to acute indication or KDIGO stage 3) groups. The early group showed more significant improvements in renal function (urea nitrogen, creatinine) and inflammatory markers (C-reactive protein, TNF-α, IL-6). Moreover, the 60-day survival rate was significantly higher in the early group (76.92% vs. 57.69%), indicating that early CRRT can effectively improve renal function and inflammatory status, thereby reducing morbidity and mortality [33].

A single-center randomized controlled study by Zarbock *et al.* included 231 patients with severe AKI, divided into early treatment (within 8 hours of KDIGO stage 2 diagnosis, $n = 112$) and delayed treatment (within 12 hours of KDIGO stage 3 or not initiated, $n = 119$) groups. Results showed that early initiation of renal replacement therapy significantly reduced 90-day mortality (39.3% vs. 54.7%), increased renal function recovery rates, and shortened treatment duration and hospitalization [34].

Conversely, several studies have found that early CRRT did not significantly improve patient outcomes. A multicenter randomized controlled trial conducted by Barbar *et al.* assigned S-AKI patients to either an early group (CRRT initiated within 12 hours after diagnosis of acute kidney injury in the failure stage) or a delayed group (CRRT initiated if renal function had not been restored after 48 hours). The results revealed 90-day mortality rates of 58% and 54% in the early and delayed strategy groups, respectively, with no statistically significant difference ($P = 0.38$) [35].

Another multicenter trial by Gaudry *et al.* included patients with KDIGO stage 3 AKI who required mechanical ventilation, vasoactive drugs, or both, and who did not have potentially fatal complications directly

related to renal failure. The early group initiated CRRT immediately after randomization, while the delayed group started CRRT upon the onset of serious complications or after more than 72 hours of anuria post-randomization. The results showed no significant difference in 60-day survival rates between the two groups (48.5% in the early versus 49.7% in the delayed group). Notably, the rate of catheter-related bloodstream infections was higher in the early group compared to the delayed group (10% vs 5%), and renal function recovery was faster in the delayed group. This study suggests that a delayed strategy may avoid unnecessary renal replacement therapy in some patients [36].

Given the inconsistency of individual study results, researchers have attempted to draw more reliable conclusions through meta-analyses. However, these meta-analyses still present divergent findings. A meta-analysis by Gaudry *et al*., encompassing 10 studies (2,083 patients), found no significant difference in mortality between early and late initiation groups (43% vs 44%) [37]. Similarly, Li *et al*.'s meta-analysis did not identify a survival benefit associated with early initiation of renal replacement therapy. They further suggested that early CRRT initiation might lead to unnecessary treatment exposure in some patients, resulting in healthcare resource wastage and increased incidence of adverse events. The team proposed that early CRRT initiation may be beneficial only for critically ill patients with clear and urgent indications (e.g., severe acidosis, pulmonary edema, and hyperkalemia) [38].

Conversely, a meta-analysis by Xia *et al*., including 3914 patients, found that when initiation timing was based on disease severity rather than time alone, early CRRT patients showed advantages in 28- or 30-day survival and time to renal function recovery. However, no significant difference was observed in 60- or 90-day mortality [39]. Another systematic review indicated that while early RRT initiation was not significantly different from standard initiation overall, it may provide benefits in specific subgroups (e.g., surgical ICU patients and patients treated with CRRT) [40].

In summary, the optimal timing of CRRT initiation in S-AKI patients remains controversial, largely due to limitations in available studies. Firstly, heterogeneity in patient inclusion criteria and definitions of early and late stages across studies complicates direct result comparisons. Secondly, small sample sizes in some studies may affect result reliability. Additionally, the inclusion of non-S-AKI patients in some studies further increases result uncertainty. Notably, the S-AKI patient population itself is highly heterogeneous, and inter-individual differences may lead to significant variability in treatment response and clinical prognosis.

6. Directions for Future Research

Given the current challenges in CRRT treatment for S-AKI patients, future research should focus on the following areas:

(1) Standardization: Develop uniform diagnostic criteria for S-AKI and standardized definitions for CRRT initiation timing to address inter-study heterogeneity.

(2) Clinical trials: Conduct high-quality, large-sample, multicenter randomized controlled trials to compare the efficacy of early versus late CRRT initiation using standardized definitions.

(3) Precision medicine: Advance precision medicine and individualized therapeutic strategies by integrating multidimensional information to identify specific subgroups that may benefit from early CRRT.

Precision medicine, a prevention and treatment strategy that accounts for individual differences, offers significant opportunities in S-AKI management. It is expected to play a crucial role throughout the S-AKI continuum, from prevention and diagnosis to treatment and long-term follow-up. Researchers have made substantial progress in key areas such as identifying S-AKI subtypes, elucidating S-AKI molecular pathway

mechanisms, and optimizing clinical trial designs [41]. These advancements not only provide a solid foundation for achieving individualized S-AKI treatment but also indicate directions for future research.

Current AKI diagnosis heavily relies on serum creatinine levels and urine output; however, this approach has significant limitations. Validation studies of novel AKI biomarkers have addressed these limitations and identified "subclinical AKI," a state of kidney injury characterized by elevated kidney injury markers without concomitant elevation of serum creatinine or decreased urine output [42]. This finding opens new possibilities for early diagnosis and intervention.

Recent studies have identified several emerging markers with prognostic stratification ability beyond traditional indicators. For instance, urinary DKK3 levels can detect postoperative acute kidney injury, improving overall outcomes [43], while blood and urine NGAL predict the risk of renal replacement therapy (RRT) and in-hospital death [44]. These findings not only enhance early AKI diagnosis capabilities but also provide a new basis for developing individualized treatment strategies.

Leveraging data from electronic health records to identify AKI subphenotypes has emerged as an area of increasing research interest, driven by technological advancements. This approach, which integrates big data analytics with clinical practice, opens new avenues for AKI research. By applying artificial intelligence and K-means clustering to vital signs, laboratory results, and clinical data, researchers have successfully identified three sepsis-associated AKI subphenotypes. These subphenotypes differ significantly in terms of pre-hospital comorbidities and are associated with varying risks of clinical outcomes. This big data-based approach to subtype classification is expected to provide more precise guidance for individualized treatment decisions [45].

Furthermore, integrating these AKI subphenotypes with multi-omics data (genomic, metabolomic, proteomic) and imaging data is anticipated to deepen the molecular-level understanding of AKI and identify potential therapeutic targets. To systematically advance research in this domain, the National Institute of Diabetes and Digestive and Kidney Diseases supports the Kidney Precision Medicine Project. This initiative aims to construct a renal reference atlas, characterizing disease subtypes by molecular mechanisms and associated prognoses. This will enable patient stratification based on these features and facilitate the identification of key cells, pathways, and targets for novel therapies [46]. This project marks a new phase in AKI research and is poised to revolutionize clinical practice.

In conclusion, integrating multidimensional information—including clinical indicators, biomarkers, genomics, and imaging data—along with leveraging emerging artificial intelligence and machine learning technologies, is advancing the precision of AKI management. These efforts are expected to yield more sophisticated and accurate predictive models that not only assess a patient's risk of developing S-AKI but also predict the optimal timing for CRRT initiation and likely treatment response. The ultimate goal is to develop optimal CRRT initiation timing and treatment regimens based on each patient's unique characteristics, thereby individualizing CRRT treatment, improving patient prognosis, and reducing healthcare resource waste.

7. Conclusion

CRRT has shown significant efficacy in managing S-AKI, yet the optimal timing for its initiation remains contentious. This uncertainty is largely due to the heterogeneity of S-AKI patients and the limitations of current research methodologies. Future investigations should prioritize precision medicine approaches, integrating multidimensional data with advanced technologies such as artificial intelligence. This strategy aims to develop more accurate predictive models and personalized treatment protocols, ultimately optimizing CRRT timing and enhancing outcomes for S-AKI patients.

Author contributions

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