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Progress in the treatment of sepsis-associated acute kidney injury

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Abstract: Sepsis-associated acute kidney injury (SA-AKI) is a common critical illness in hospitalized patients, characterized by high incidence, high mortality. The pathogenesis of SA-AKI is complex, with both direct mechanisms related to infection and indirect mechanisms driven by adverse treatment outcomes in sepsis. Once a diagnosis of SA-AKI is made, it is crucial to initiate appropriate support measures in time to limit further damage to the kidney, such as anti - infective therapy, fluid resuscitation, vasopressor therapy, and renal replacement therapy. There are many scholars committed to exploring the best treatment plan. Promising strategies, including new therapeutic drugs, targeted therapy and Chinese medicine therapy, hold significant potential for mitigating both the short- and long-term consequences of SA-AKI. This article provides a review on the progress in SA-AKI treatment.

Keywords: Sepsis; Acute kidney injury; Fluid resuscitation; Renal replacement therapy; Exosome; Treatment; Critical illness

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Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1] and often leads to acute kidney injury (AKI). International data indicate that sepsis accounts for approximately 45%-70% of all AKI cases in the intensive care unit (ICU) and is a leading cause of death among ICU patients [2]. Data from China show that sepsis is a primary cause (32%-35%) of hospital-acquired AKI, with sepsis-induced AKI comprising over half of all AKI cases in the ICU [3]. A recent consensus from the Acute Disease Quality Initiative (ADQI) workgroup defines sepsis-associated acute kidney injury (SA-AKI) as AKI occurring within 7 days after the diagnosis of sepsis (according to Sepsis-3.0 criteria), based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [2]. SA-AKI is a heterogeneous disease driven by the host's response to infection or direct mechanisms related to the infection, as well as indirect mechanisms resulting from adverse outcomes of sepsis treatment. These include systemic and renal inflammation, complement activation, dysregulation of the renin-angiotensin-aldosterone system (RAAS), mitochondrial dysfunction, metabolic reprogramming, microcirculatory and macro-circulatory abnormalities, exposure to nephrotoxic drugs, abdominal compartment syndrome, among others [2]. Current evidences suggest that compared to other types of AKI, SA-AKI is associated with higher mortality and lower chances of renal recovery [4]. This article reviews the treatment of SA-AKI, aiming to provide new insights and directions for future specific therapies for SA-AKI.

1 Anti-infective Therapy

The innate immune response in sepsis is triggered by exposure to damage-associated molecular patterns (endogenous molecules released by damaged cells) and pathogen-associated molecular patterns (such as lipopolysaccharide and double-stranded RNA). These molecular patterns act as ligands for receptors located on cell surfaces (e.g., Toll-like receptors) or within the cytoplasm (e.g., NOD-like receptors). Activation of these receptors initiates the transcription and release of type I interferons and pro-inflammatory cytokines [such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and IL-6] [5]. In sepsis, the dysregulated host innate immune response to pathogens is characterized by increased systemic and renal inflammation, including elevated expression of inflammatory markers and increased oxidative stress, ultimately leading to inflammation-induced apoptosis and aggravated kidney injury.

Early administration of appropriate antimicrobial agents is crucial in sepsis treatment. The choice of antibiotics must consider both efficacy and safety, as the agents themselves can cause adverse effects (e.g., nephrotoxicity) potentially accelerating or worsening the progression of SA-AKI. If sepsis is suspected, antibiotics should ideally be administered within 1 hour of recognition. The Surviving Sepsis Campaign (SSC) guidelines also recommend empiric use of antibiotics covering methicillin-resistant *Staphylococcus aureus* (MRSA) for adult sepsis/septic shock patients at high risk for MRSA infection. However, unnecessary use of MRSA coverage in patients without MRSA risk can be harmful. For patients at high risk for multiple drug resistance (MDR) organism infection, combination therapy with two antibiotics covering Gram-negative bacteria is recommended for empiric treatment to increase the likelihood of adequate coverage. For patients at low risk for MDR infection, monotherapy is suggested to reduce antibiotic-related adverse effects such as direct toxicity, *Clostridium difficile* infection, and antibiotic resistance. Once the pathogen and its susceptibility are identified, combination therapy with two Gram-negative agents should be discontinued, unless highly resistant pathogens are involved [6].

Two commonly used antibiotics for empiric sepsis treatment are the β-lactam agents—piperacillin-tazobactam combined with cefepime. Both possess broad in vitro activity against Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa*. They are often combined with vancomycin to enhance anti-MRSA coverage [7]. Previous studies found that the combination of piperacillin-tazobactam and vancomycin increased the risk of AKI [8-10], leading the US Food and Drug Administration (FDA) to issue a warning regarding this combination. However, these studies relied solely on serum creatinine values to define AKI; the observed increase in serum creatinine might be due solely to inhibition of tubular creatinine secretion without underlying kidney injury. A randomized clinical trial by Qian *et al.* [11] in adults with suspected infection provided the highest-quality evidence to date, demonstrating that piperacillin-tazobactam in combination with vancomycin did not increase the incidence of AKI or mortality compared to cefepime combined with vancomycin. Pevzner *et al.* [12] conducted a prospective analysis finding that treatment with ampicillin combined with clavulanate, gentamicin, or metronidazole could reduce blood urea nitrogen concentrations in children with sepsis, However, treatment of newborns with netilmicin, cefepime, linezolid, or imipenem in combination with cilastatin worsened kidney function in these patients. Validation experiments found that gentamicin significantly improved renal function in septic rats, identifying antibiotics that should be prioritized or used cautiously in neonatal sepsis.

The selection of antimicrobial agents should consider the patient's history and comorbidities, suspected site of infection, potential immunodeficiencies, presence of invasive devices, and local prevalence and resistance patterns. Controlling or eliminating the source of infection to achieve source control and restore optimal bodily function remains the cornerstone of sepsis treatment [5].

2. Fluid Resuscitation and Vasopressor

Normally, people believe that AKI occurs due to reduced renal perfusion during sepsis, where an increase in nitric oxide synthesis induced by cytokines leads to systemic arterial dilation and reduced vascular resistance, increasing the risk of impaired organ perfusion under conditions of increased metabolic demand. However, evidences show that not all SA-AKI patients experience a decrease in renal blood flow, with the theory of local renal microcirculation imbalance taking a more prominent role. Inflammation and oxidative mediators cause endothelial damage, loss of the glycocalyx, and activation of the coagulation cascade, all of which lead to microcirculatory disturbances. In SA-AKI, the heterogeneity of renal microcirculation blood flow distribution increases, and capillaries with insufficient blood flow are more prevalent. Moreover, during AKI, renal blood flow redistributes, with blood flow shifting from the renal medulla to the renal cortex, indicating that mechanisms other than ischemia may be involved in SA-AKI.

2.1 Fluid Resuscitation

2.1.1 Management of Resuscitation Volume

Fluid resuscitation can enhance large vessel perfusion (e.g., stroke volume and cardiac output) and microvascular perfusion (e.g., capillary blood flow). Restoring vascular volume via fluid redistribution is a key goal in treating sepsis. The ADQI workgroup recommends that the fluid regimen consider the severity and progression speed of AKI [2]. Fluid overload (FO) can significantly reduce the renal recovery rate, prolong mechanical ventilation time, increase hospital stay, and mortality. The SSC guideline recommend administering at least 30 mL/kg of fluid within 3 hours, although the evidence for this recommendation is of lower quality [6]. One study has shown that critically ill patients have a high probability of developing AKI either before ICU admission or within the first 24 hours [15], with sepsis being a common cause. Close monitoring of renal function is recommended, and treatment goals for critically ill patients at risk of or with progressing AKI should aim for balanced or negative fluid balance. AKI patients are more prone to FO, which decreases renal blood flow and accelerates AKI progression due to increased venous pressure. A retrospective analysis found an association between early FO and mortality, suggesting that fluid resuscitation management should be implemented early in critically ill AKI patients [16].

However, some studies have reached opposing conclusions. A secondary analysis of the CLOVERS trial (Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis) found that a 2L difference in fluid volume between SA-AKI patients was insufficient to affect clinical outcomes [17]. More high-quality clinical trials are needed to provide further evidence.

2.1.2 Choice of Resuscitation Fluid Type

There is significant controversy surrounding the type of fluid used for resuscitation. Crystalloid fluids include balanced and non-balanced solutions, while colloid fluids include albumin, hydroxyethyl starch, and succinylated gelatin. Some trials have found that the use of balanced crystalloids for fluid resuscitation in children with septic shock within the first 7 days of hospitalization significantly reduces the risk of new or progressive AKI compared to 0.9% saline, possibly due to the lower chloride content [18]. However, the BaSICS trial (Balanced Solution Versus Saline in Intensive Care Study) found no statistically significant difference in short-term AKI incidence between balanced crystalloids and 0.9% saline in critically ill patients [19]. Subgroup analysis based on the presence of sepsis at the time of enrollment or the stage of AKI did not show benefits of balanced fluids either. A secondary analysis of the trial suggested that balanced fluids might be more beneficial in sepsis patients, with a possible dose-effect relationship [20]. One recent study indicates that 0.9% saline can be safely used without adverse effects, and based on current evidence, using up to 4 L of 0.9% saline appears to be safe [21]. The ADQI workgroup recommends using either balanced crystalloids or 0.9% saline based on the patient's individual biochemical characteristics, with close

monitoring of biochemical effects [2]. For high-risk SA-AKI patients, balanced crystalloids should be the first choice for fluid resuscitation, superior to chloride-rich solutions and synthetic colloids [22].

Theoretically, high-molecular-weight colloids can selectively expand intravascular space. If large amounts of fluid are needed, albumin can be considered, but no high-quality studies have shown significant benefits from albumin-containing regimens. Its use is only recommended for patients receiving large amounts of crystalloid fluid [22]. Critically ill AKI patients are at risk of protein-energy malnutrition, which is a risk factor for poor prognosis. However, some studies show that higher protein doses in critically ill AKI patients on mechanical ventilation are associated with longer hospital stays and higher mortality, possibly due to impaired amino acid utilization in metabolic acidosis. Similar results have been observed in the sepsis subgroup, although without statistical significance. Protein supply in AKI patients should be approached with caution [23]. Another meta-analysis found similar results, recommending close monitoring of protein supply in critically ill AKI patients and cautioning against overfeeding [24].

2.2 Application of Vasopressors

The target for arterial blood pressure control in sepsis patients remains unclear. For hemodynamically unstable patients with AKI who remain responsive to volume after fluid resuscitation, the use of vasopressor agents may be considered to prevent FO. Norepinephrine (NE) is the first-line vasopressor for sepsis and SA-AKI patients [2,22]. The SSC guidelines recommend adding vasopressin rather than increasing the NE dose if the mean arterial pressure is still not met after NE administration [6]. Medullary ischemia and hypoxia may be key pathological features of SA-AKI. Studies using a sheep SA-AKI model found that vasopressin treatment improved renal function, renal medullary perfusion, and oxygen tension maintenance better than NE, and the using vasopressin to achieve higher target blood pressure in sepsis patients may lead to more sustained renal function improvement [25]. Recently, one large study has identified and validated four distinct sepsis phenotypes, which are related to different vasopressor treatments [26]. Based on the interaction between genotype and exposure, SA-AKI has multiple clinical phenotypes and sub-phenotypes. The selective sub-phenotype of SA-AKI may respond better to specific vasopressors (e.g., arginine vasopressin, angiopoietin-2), but further validation is needed [22]. Whether the choice of vasopressor affects the course of SA-AKI remains to be studied.

3 Extracorporeal Blood Purification Therapy

Tissue damage in sepsis results both from direct pathogenic injury and from the dysregulated host response to infection. Renal replacement therapy (RRT) can correct the metabolic, electrolyte, and fluid imbalances caused by severe AKI. Blood purification therapies, including RRT, can influence the molecular and electrolyte composition of the blood and help control immune dysregulation in sepsis by removing endotoxins, cytokines, pathogens, and inflammatory factors [2]. Beyond maintaining homeostasis (renal indications), they can modulate the excessive inflammatory response (non-renal indications) and reduce levels of pathogenic substances, serving as an adjunctive therapy for sepsis.

3.1 Timing of RRT Initiation

The SSC guideline suggestes using either continuous or intermittent RRT for adult SA-AKI patients requiring RRT [6]. The indications for initiating RRT in SA-AKI patients are consistent with those for AKI from other causes [2]. The KDIGO clinical practice guideline recommends initiating RRT emergently when life-threatening complications related to AKI (such as fluid overload, electrolyte, or acid-base disturbances) are present, or for conditions modifiable by RRT [27]. Recently, a joint expert opinion from the Italian Society of Anesthesia and Intensive Care and the Italian Society of Nephrology suggested adhering to a "personalized medicine" approach, where RRT initiation in specific SA-AKI patients should be neither too early nor too late [28]. A meta-analysis found that early RRT reduced 28-day mortality in SA-AKI patients with a Sequential Organ Failure Assessment (SOFA) score ≤ 12 or KDIGO AKI stage 2 [29], but this finding requires validation. A multicenter randomized controlled trial published in found no statistically significant difference in 90-day mortality between an early and a delayed RRT strategy in patients with severe AKI in the initial phase of septic shock; furthermore, initiating RRT too early might unnecessarily expose patients whose renal function could have recovered spontaneously to the risks of RRT [30]. The Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial also found no benefit for an accelerated RRT strategy, suggesting that unnecessary RRT might impair kidney repair and the recovery of endogenous renal function [31]. The timing of RRT initiation should be based on individual patient characteristics.

3.2 Choice of Treatment Modality

RRT modalities include intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and combined blood purification therapies such as hemoperfusion, endotoxin adsorption, plasma exchange, and combinations with extracorporeal membrane oxygenation (ECMO), among others. The main CRRT modalities are continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). Compared to CRRT, IHD has lower treatment costs and allows for rapid removal of fluid and solutes, but it can affect hemodynamics and carries a risk of exacerbating cerebral edema. Compared to IHD, CRRT offers advantages in hemodynamically unstable patients and may increase the clearance of inflammatory factors, potentially

benefiting SA-AKI patients. Koyner *et al.* [32], in a large, real-world, multicenter study comparing the long-term impact of different initial RRT modalities on renal function in critically ill adult AKI survivors, found that patients treated with CRRT had lower RRT dependence than those treated with IHD. Although hemofiltration is superior to hemodialysis in clearing medium and large molecular toxins, there is currently a lack of clinical studies comparing different solute clearance modes with clinical outcomes [3]. It is noteworthy that different CRRT modes and treatment doses affect antimicrobial clearance; for patients with severe infections, therapeutic drug monitoring is the best method for adjusting antimicrobial dosing [33].

Endotoxin is a major component of the outer membrane of Gram-negative bacteria. Endotoxemia activates various cells and blood mediators, causing organ damage and a cascading inflammatory response. Endotoxin levels are directly correlated with increased mortality in patients with septic shock. Polymyxin B hemoperfusion (PMX-HP) can reduce circulating endotoxin levels in septic patients. A meta-analysis found that septic/septic shock patients with mixed infections or those aged <70 years had significantly reduced 28-day mortality after receiving PMX-HP [34]. An Italian consensus stated that septic shock patients with a Multiple Organ Dysfunction Syndrome (MODS) score >9 and an endotoxin activity assay level between 0.6 and 0.9 are more likely to benefit from PMX-HP [28]. Another network meta-analysis showed that PMX-HP and plasma exchange might have potential survival benefits; the use of plasma exchange and hemoperfusion, with or without CVVH, might be associated with fewer ICU days or ventilator days [35].

3.3 Choice of Anticoagulation Strategy

The goal of anticoagulation is to maintain the patency of the extracorporeal circuit, ensuring the smooth progress of RRT. The choice and dose of anticoagulant should be determined after assessing the patient's coagulation status and excluding contraindications. The *Chinese Clinical Practice Guideline for Acute Kidney Injury* [3] makes the following recommendations: For patients with hypercoagulability and/or thromboembolic risk or disease, and without contraindications to heparin-based drugs, use unfractionated heparin or low-molecular-weight heparin. For patients with a history of or concurrent heparin-induced thrombocytopenia, and without contraindications to citrate or argatroban, choose regional citrate or argatroban anticoagulation; fondaparinux is not recommended. For patients with active bleeding or high bleeding risk, and without citrate contraindications, regional citrate anticoagulation is the first choice. For patients with citrate contraindications, and without argatroban contraindications, argatroban is recommended. Monitor coagulation status both within the extracorporeal circuit and systemically during and after anticoagulation therapy to individualize the anticoagulant dose. Furthermore, adverse events should be closely observed and managed during anticoagulation therapy.

4 Future Treatment Options

4.1 New Therapeutic Drug

Alkaline phosphatase, a novel therapeutic drug, plays an important role in host defense and innate immunity. To improve treatment efficacy, researchers have developed recombinant human alkaline phosphatase, which has a broad detoxification effect by dephosphorylating and improving the systemic inflammatory response of sepsis (especially in the kidneys). An international, double-blind, phase 3 trial—the REVIVAL trial—aimed to investigate the effects of this drug on SA-AKI patients. Recently published results showed that it did not reduce the 28-day all-cause mortality in patients but had potential benefits in reducing 90-day kidney adverse events [36]. A post-hoc analysis of the REVIVAL trial identified the clinical phenotypes that may benefit the most from this drug treatment [37]. Currently, no targeted drugs have been approved for the treatment of SA-AKI, but several clinical trials for drugs targeting sepsis or SA-AKI patients are underway in China, with hopes that more drugs will be applied to clinical practice in the near future.

4.2 Novel Treatment Methods

4.2.1 Exosome Therapy

Exosomes are nano-sized extracellular vesicles, and exosome transport serves as a new pathway for intercellular communication during sepsis. This can prevent excessive inflammation, thereby reducing morbidity and mortality. Various types of cells can secrete exosomes. Mesenchymal stem cells (MSCs) have various sources, including bone marrow, adipose tissue, umbilical cord, and human placenta. Jin *et al.* [38] revealed the potential protective effect of exosomes derived from bone marrow mesenchymal stem cells on sepsis-induced AKI in rats. Exosomes derived from human amniotic epithelial cells may improve the survival rate, kidney function, and reduce kidney injury in SA-AKI mice by preventing early endothelial dysfunction in sepsis [39]. Gao *et al.* [40] created a SA-AKI mouse model through cecal ligation and puncture, finding that exosomes from adipose tissue-derived mesenchymal stem cells (AD-MSCs) significantly reduced serum inflammatory cytokine expression, suppressed kidney inflammation, improved kidney function and tissue morphology, and reduced mortality. The mechanism may involve the silent information regulator 1 (SIRT1) signaling pathway. Exosomes are rich in various bioactive molecules, such as nucleic acids, microRNAs, SIRT1, proteins, and lipids. Studies have found that exosomes derived from AD-MSCs loaded with miR-342-5p can alleviate SA-AKI and explore potential mechanisms [41]. He *et al.* [42] found that exosomes from AD-MSCs can alleviate lipopolysaccharide-induced AKI, providing potential molecular targets for the treatment of SA-AKI. Li *et al.* [43] also found that exosomes from fibroblasts improve kidney function by promoting mitochondrial autophagy and inhibiting NLRP3 inflammasome activation. However, some studies have

found that exosomes from macrophages mediate glomerular endothelial cell dysfunction in SA-AKI, with acidic sphingomyelinase involved in regulating this process, which may be a potential therapeutic target for SA-AKI [44]. All these studies suggest that exosome-based therapy may be a promising alternative for the treatment of SA-AKI.

4.2.2 Targeted Therapy

Drug therapy for AKI often lacks effective targeted drug delivery carriers. Kidney-targeted nanoparticles represent an emerging therapeutic strategy; however, these exogenous nanoparticles are rapidly cleared in the body and fail to achieve the desired targeting effect. One study constructed KTP-modified renal tubular epithelial cell membrane-coated zeolite imidazolate framework-8 nanoparticles loaded with fibroblast growth factor 21 (FGF21) (KMZ@FGF21) for targeted therapy of septic AKI. In a mouse model, KMZ@FGF21 specifically accumulated in the kidneys and effectively alleviated AKI-related kidney damage, indicating that KMZ@FGF21 enhanced the kidney-protective potential of FGF21 [45]. Wei *et al.* [46] designed a series of polyvinylpyrrolidone (PVP)-curcumin nanoparticles (Cur NPs), providing a controlled kidney-targeted delivery nano-system to deliver curcumin with antioxidant and anti-inflammatory properties to treat cisplatin-induced AKI. Cur NPs offer a novel and simple strategy for precise positron emission tomography (PET)-guided kidney drug delivery. These targeted therapies offer new insights into precision drug delivery for kidney diseases.

4.3 Chinese Medicine Therapy

Chinese medicine has unique advantages in treating sepsis. Modern pharmacological studies show that Chinese medicine exhibits "multi-component, multi-target, and multi-pathway" synergistic effects. In recent years, scholars have continuously explored the role of Chinese medicine in treating SA-AKI. Research has found that extracts of *Huanglian* (*Rhizoma Coptidis*) and magnolol can improve kidney function and tissue damage in SA-AKI mice and even reverse AKI in septic mice. The potential mechanism may involve the modulation of heme oxygenase-1 levels [47]. Other studies have confirmed the efficacy of *Tongfu Yiqi* Decoction and *Zhenwu* Decoction in improving kidney function and reducing inflammation in SA-AKI patients. Additionally, research has demonstrated that schisantherin A can alleviate lipopolysaccharide-induced AKI, although it may not completely mimic human SA-AKI [48]. In our preliminary studies, we found that *Qingwen Baidu* Decoction can lower serum creatinine and urea nitrogen levels in SA-AKI mice induced by cecal ligation and puncture, reducing kidney pathological damage. These studies provide valuable references for the application of Chinese medicine in AKI treatment. In conclusion, Chinese medicine is a treasure of ancient Chinese science and deserves further research.

5 Conclusion and Outlook

SA-AKI is a common and critical condition with a complex pathophysiological mechanism, which remains not fully understood. The management of sepsis focuses on early recognition, timely use of antibiotics and fluid resuscitation, as well as the use of vasopressors and organ support therapy when necessary. Previous research by our team found that the missed diagnosis rate of AKI in non-nephrology patients ranged from 49.61% to 60.92%, indicating that some non-nephrology physicians tend to overlook the occurrence of AKI in clinical practice. The mortality rate of patients with missed AKI diagnoses is significantly higher than that of non-missed diagnoses, and the mortality rate of ICU patients with missed AKI diagnoses is notably higher than that of non-ICU patients with missed diagnoses [49-50]. The recently released *Chinese Clinical Practice Guidelines for Acute Kidney Injury* provide localized, authoritative guidance for AKI clinical practice in China. Clinicians should follow guidelines such as avoiding the use of potentially nephrotoxic drugs (e.g., hydroxyethyl starch), optimizing volume status and hemodynamics, and closely monitoring serum creatinine and urine output. The interdisciplinary collaboration has also provided new perspectives for AKI treatment. China has accumulated rich experience in the long-term practice of Chinese medicine, and our team has been dedicated to providing new approaches for the clinical treatment of SA-AKI with Chinese medicine. The future therapeutic potential of Chinese medicine preparations remains promising. With the continuous deepening of our understanding of the pathogenesis of SA-AKI, we look forward to more targeted and rational treatment methods.

Conflict of Interest None

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·研究进展·

脓毒症相关急性肾损伤的治疗进展

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摘要：脓毒症相关急性肾损伤(SA-AKI)是住院患者常见的危重症，具有发病率高、死亡率高的特点。SA-AKI发病机制复杂，有与感染相关的直接机制，也有脓毒症治疗不良结局所驱动的间接机制。一旦诊断为SA-AKI，及时启动适当的支持措施、限制对肾脏的进一步损害至关重要，如抗感染治疗、液体复苏、血管加压药治疗及肾脏替代治疗等。不断有学者致力于探索最佳治疗方案，新型治疗药物、靶向治疗及中药治疗在减少SA-AKI的短期和长期影响方面具有巨大潜力。本文就SA-AKI相关治疗进展作一综述。

关键词：脓毒症；急性肾损伤；液体复苏；肾脏替代治疗；外泌体；治疗；危重症

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Progress in the treatment of sepsis-associated acute kidney injury

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Abstract: Sepsis-associated acute kidney injury (SA-AKI) is a common critical illness in hospitalized patients, characterized by high incidence, high mortality. The pathogenesis of SA-AKI is complex, with both direct mechanisms related to infection and indirect mechanisms driven by adverse treatment outcomes in sepsis. Once a diagnosis of SA-AKI is made, it is crucial to initiate appropriate support measures in time to limit further damage to the kidney, such as anti-infective therapy, fluid resuscitation, vasopressor therapy, and renal replacement therapy. There are many scholars committed to exploring the best treatment plan. Promising strategies, including new therapeutic drugs, targeted therapy and Chinese medicine therapy, hold significant potential for mitigating both the short- and long-term consequences of SA-AKI. This article provides a review on the progress in SA-AKI treatment.

Keywords: Sepsis; Acute kidney injury; Fluid resuscitation; Renal replacement therapy; Exosome; Treatment; Critical illness

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脓毒症是宿主对感染的反应失调所导致的危及生命的器官功能障碍[1]，常导致急性肾损伤(acute kidney injury，AKI)。国际数据显示，脓毒症约占重症监护病房(intensive care unit，ICU)中所有AKI患者的45%~70%，是ICU患者的主要死亡原因[2]。我国数据显示，脓毒症是医院获得性AKI的主要病因(32%~35%)，ICU中脓毒症所致AKI比例达半数以上[3]。急性疾病质量倡议(Acute Disease Quality Initiative，ADQI)工作组最近发布的共识将脓毒症相关AKI(sepsis-associated acute kidney injury，SA-AKI)定义为在诊断脓毒症(Sepsis 3.0诊断标准)后7 d内发生的AKI(改善全球肾脏病预后组织，Kidney Disease Improving Global Outcomes，KDIGO诊断标准)[2]。SA-AKI是一种异质性疾病，由宿主对感染的反应或与感染相关的直接机制，或脓毒症治疗的不良结局驱动的间接机制引起，包括全身和肾脏炎症、补体激活、肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system，RAAS)失调、线粒体功能障碍、代谢重编程、微循环和宏观循环异常、暴露于肾毒性药物、腹腔间隔室综合征等[2]。目前数据表明，与其他类型AKI相比，SA-AKI与更高的死亡率和更低的肾脏恢复机会相关[4]。本文就SA-AKI的治疗作一综述，以期为未来SA-AKI的特异性治疗提供新的思路和方向。

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1 抗感染治疗

脓毒症的固有免疫反应由暴露于损伤相关分子模式(由受损细胞分泌内源性分子)和病原体相关分子模式(如脂多糖和双链RNA等小分子)触发,这些分子模式可作为存在于细胞表面的受体(如Toll样受体)或胞质中的受体(如NOD样受体)的配体。这些受体的激活启动I型干扰素和促炎细胞因子[如肿瘤坏死因子-α(tumor necrosis factor,TNF-α)、白细胞介素(interleukin,IL)-1和IL-6]的转录和释放[5]。在脓毒症中,失调的宿主对病原体的固有免疫反应以全身和肾脏炎症增加为特征,包括炎症标志物的高表达及氧化应激的增加,最终导致炎症诱导的细胞凋亡和肾脏损伤的加重。

早期应用适当的抗菌药物是脓毒症治疗的关键,抗菌药物的选择必须考虑有效性及安全性,其本身会引起不良反应(如肾毒性),可能加速或加重SA-AKI的进展。如果怀疑脓毒症,最好在识别1 h内给予抗菌药物,拯救脓毒症运动(Surviving Sepsis Campaign,SSC)指南同时建议对于耐甲氧西林金黄色葡萄球菌(methicillin-resistant *Staphylococcus aureus*,MRSA)感染风险高的成人脓毒症/脓毒性休克患者,经验性使用覆盖MRSA的抗菌药物。但对无MRSA感染的患者不必要地使用覆盖MRSA的抗菌药物可能有害。对多重耐药(multiple drug resistance,MDR)菌感染高风险的患者,建议使用两种覆盖革兰阴性菌的抗菌药物经验性治疗以增加充分覆盖的可能性;对MDR菌感染低风险的患者,建议单药治疗以减少抗生素相关不良影响,如直接毒性、艰难梭菌感染和抗生素耐药。一旦明确病原体和药敏情况,除非患者有高度耐药病原体,建议停止联合使用两种针对革兰阴性菌的药物[6]。

两种常用的脓毒症经验性治疗的抗生素是β-内酰胺类药物哌拉西林-他唑巴坦和头孢吡肟。两者都具有广泛的抗革兰阳性和革兰阴性细菌的体外活性,包括铜绿假单胞菌。它们通常与万古霉素联合使用,以增强抗MRSA的活性[7]。之前的研究发现,哌拉西林-他唑巴坦联合万古霉素会增加AKI的风险[8-10],基于此,美国食品和药品管理局(Food and Drug Administration,FDA)对这两种药物的联用发出了警告。但这些研究仅靠血肌酐值来判断AKI,血肌酐水平的升高,可能只是由于肾小管肌酐的分泌受到抑制,而没有潜在的肾损伤。近期Qian等[11]在疑似感染的成人患者中进行的一项随机临床试验提供了目前为止质量最高的证据,证明与使用头孢吡肟联合万古霉素相比,哌拉西林-他唑巴坦联合万古霉素并不会增加患者AKI或死亡的发生率。Pevzner等[12]进行了一项前瞻性分析,发现氨苄西林联合克拉维酸、庆大霉素或甲硝唑治疗可降低脓毒症患儿尿素氮浓度,而接受头孢吡肟、利奈唑胺、亚胺培南、西司他汀治疗后患儿血尿素氮水平升高,确定了在新生儿脓毒症中应优先或谨慎使用的抗生素。

抗菌药物的选择应考虑患者病史和合并症、可能的感染部位、潜在的免疫缺陷、侵入性设备的存在及当地患病率和耐药情况。控制或清除感染源以控制源头、恢复机体最佳功能,仍是脓毒症治疗的基石[5]。

2 液体复苏和血管加压药治疗

传统观念认为AKI的发生是由于脓毒症时肾灌注量的减少,细胞因子诱导的一氧化氮合成增加导致全身动脉扩张和血管阻力降低,在代谢需求增加的情况下增加器官灌注受损的风险[5]。但越来越多的研究显示,并非所有SA-AKI均存在肾血流量的下降,肾脏局部微循环失衡学说占据了更重要的地位。炎症和氧化介质导致内皮损伤、糖萼脱落和凝血级联激活均可导致微循环障碍,SA-AKI时肾脏微循环血流分布异质性增加,血流不足的毛细血管增加[13];此外,AKI时肾内血流再分布,即肾血流从肾髓质分流至肾皮质[14],都揭示了SA-AKI期间可能存在除缺血外的机制。

2.1 液体复苏

2.1.1 复苏容量的管理 液体复苏可以提高大血管灌注(如每搏输出量和心输出量)和微血管灌注(如毛细血管血流),通过液体的重新分布来恢复血管内容量是脓毒症的治疗目标。ADQI工作组建议液体方案应考虑AKI严重程度和进展速度[2]。容量过负荷(fluid overload,FO)可显著降低患者肾功能恢复率、延长机械通气时间、增加住院时间和病死率。SSC指南建议在3 h内完成至少30 mL/kg的液体复苏量[6],然而该推荐证据级别较低。有研究显示危重症患者在入ICU之前或最初24 h内发生AKI的概率很高[15],脓毒症是常见的原因之一,建议密切监测肾功能,有AKI或有进展至AKI风险的危重症患者的治疗目标应是平衡或负平衡。AKI患者更容易出现FO,由于静脉压升高导致肾血流量减少,FO会加速AKI的进展。一项回顾性分析发现了更早期FO与死亡率的关联,提出在危重症AKI患者中,即使在初始复苏阶段,也应进行液体复苏管理[16]。

但也有研究得出了相反的结论。对晶体液自由输注与早期血管加压药物治疗脓毒症(Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis,CLOVERS)试验的二次分析显示,在SA-AKI患者中,平均2 L的液体差异不足以影响临床结局[17]。尚需更多的高质量临床试验为临床提供更多的证据。

2.1.2 复苏液类型的选择 用于复苏的液体类型也有许多争议,晶体液包括平衡液和非平衡液,胶体液包括白蛋白、羟乙基淀粉、琥珀酰明胶等。有试验发现,在脓毒症休克患儿住院的最初7天内使用平衡晶体液进行液体复苏,与使用0.9%氯化钠溶液相比,发生新发或进行性AKI的风险显著降低,可能与其氯化物的含量较低有关[18]。然而,重症监护中平衡液与0.9%氯化钠溶液的对比研究(Balanced Solution Versus Saline in Intensive Care Study,BaSICS)试验[19]发现,两种液体治疗的危重患者短期内AKI的发生率无统计学差异。进一步对该人群分别按入组时是否发生脓毒症、及入组时的AKI分期进行了亚组分析,结果也均未显示使用平衡液有益。对该试验的二次分析认为使用平衡液在脓毒症患者中更可能有益,且存在一定程度的剂量-效应关系[20]。最近有研究表明,0.9%氯化钠溶液可以安全使用,且不会产生不良反应[21],鉴于目前的证据,最多使用4 L的0.9%氯化钠溶液似乎是安全的。ADQI工

作组建议根据患者个体的生化特征使用平衡液或0.9%氯化钠溶液进行液体复苏，同时密切监测其生化效果[2]，对SA-AKI高危患者，平衡晶体液是液体复苏的首选，优于富氯化物溶液和合成胶体[22]。

理论上讲，高分子量的胶体可选择性扩张血管内的空间，如需大量补液，可以考虑白蛋白，然而迄今为止尚无高质量研究显示含白蛋白方案的显著益处，只能推荐在接受大量晶体液的患者中使用[22]。发生AKI的危重症患者存在蛋白质-能量营养不良的风险，是不良预后的危险因素之一，但有研究表明，在接受机械通气的危重症AKI患者中，接受较高剂量的蛋白质与较长的住院时间和较高的死亡率有关，可能与患者代谢性酸中毒导致组织氨基酸利用受损有关，在脓毒症亚组中也观察到相同的结果，尽管没有统计学意义，对AKI患者的蛋白质供应也应谨慎[23]。另一项meta分析也发现了类似结果，建议应密切监测危重症AKI患者的蛋白供应，并在临床工作中警惕过度喂养的发生[24]。

2.2 *血管加压药的应用* 目前对脓毒症患者动脉血压控制的目标尚不清楚，对血流动力学不稳定、液体复苏后仍保持较好容量反应性的AKI患者，可考虑使用血管活性药物，避免FO发生。去甲肾上腺素（norepinephrine，NE）是脓毒症和SA-AKI患者的一线血管加压药[2,22]，SSC指南建议若患者应用NE后平均动脉压仍不达标，应加用血管加压素，而不是增加NE剂量[6]。髓质缺血缺氧可能是SA-AKI的关键病理生理特征，有研究建立了绵羊SA-AKI模型，发现血管加压素治疗SA-AKI在肾功能、肾髓质灌注和氧分压维持方面优于NE，在脓毒症患者中使用血管加压素达到较高的目标血压可能会有更持久的肾功能改善[25]。最近的一项大型研究得出并验证了四种独特的脓毒症表型，这些表型与不同的血管活性药治疗有关[26]。根据基因型和暴露之间的相互作用，SA-AKI有多种临床表型和亚表型，SA-AKI的选择性亚表型可能对特定的血管活性药物（如精氨酸加压素、血管生成素-2）有更好的反应，但仍需进一步验证[22]。血管加压药的选择是否会影响SA-AKI的病程仍待研究。

3 体外血液净化治疗

脓毒症的组织损伤，既是直接致病性损伤的结果，也是宿主对感染的反应失调的结果。肾脏替代治疗（renal replacement therapy，RRT）可以纠正由严重AKI引起的代谢、电解质及液体失衡。血液净化治疗，包括RRT，可以影响血液的分子和电解质组成，通过清除内毒素、细胞因子、病原体和炎症因子来帮助控制脓毒症中的免疫失调[2]，除了维持体内平衡（肾脏适应证），还可以调节过度炎症反应（非肾脏适应证），降低致病性物质的水平，是脓毒症的辅助治疗方式。

3.1 *RRT启动时间* SSC指南建议对于需要RRT的成人SA-AKI患者，使用连续或间断的RRT[6]。SA-AKI患者开始RRT的适应证与其他原因所致AKI一致[2]。KDIGO临床实践指南建议，存在与AKI相关的危及生命的并发症（如液体超负荷、电解质或酸碱失衡），或可通过RRT改变的疾病，应及早开始RRT[27]。最近，意大利麻醉和重症监护协会及意大利肾脏病学会联合发布的专家意见指出应遵循“个性化医疗”，对特定SA-AKI患者RRT的启动既不应太早，也不应太晚[28]。一项meta分析发现，在序贯器官衰竭评估（Sequential Organ Failure Assessment，SOFA）评分≤12分或KDIGO AKI 2期的SA-AKI患者中，早期RRT降低28 d死亡率[29]，但这一发现仍需验证。2018年发表的一项多中心、随机对照试验发现，在脓毒症休克初始阶段的严重AKI患者中，早期和延迟RRT策略组90 d死亡率差异无统计学意义，且过早开始RRT可能会使肾功能本可以自发恢复的患者不必要地暴露于RRT的风险中[30]。急性肾损伤中肾替代治疗的标准与加速启动（Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury，STARRT-AKI）试验也发现加速启动RRT策略没有益处，过度接受RRT可能会损害肾脏修复和内源性肾功能的恢复[31]。RRT的开始时间应基于患者的具体特征。

3.2 *治疗模式的选择* RRT模式包括间歇性血液透析（intermittent hemodialysis，IHD）、连续性肾脏替代治疗（continuous renal replacement therapy，CRRT）、组合血液净化治疗如血液灌流、内毒素吸附、血浆置换、并联体外膜肺氧合（extracorporeal membrane oxygenation，ECMO）等。CRRT主要治疗模式包括持续静脉-静脉血液滤过（continuous venovenous hemofiltration，CVVH）、持续静脉-静脉血液透析（continuous venovenous hemodialysis，CVVHD）和持续静脉-静脉血液透析滤过（continuous venovenous hemodiafiltration，CVVHDF）。与CRRT相比，IHD治疗成本低，可快速清除水分和溶质，但可影响血流动力学，有加重脑水肿的风险；与IHD相比，CRRT在血流动力学不稳定的患者中更具优势，且可增加炎症因子清除，可能使SA-AKI患者获益。Koyner等[32]基于真实世界的大型、多中心研究比较了不同初始RRT模式对危重成年AKI幸存者肾功能的长期影响，发现接受CRRT治疗的患者比接受IHD者有更低的RRT依赖性。尽管血液滤过对中大分子毒素清除优于血液透析，但目前尚缺少比较不同溶质清除模式与临床结局相关的临床研究[3]。值得注意的是，CRRT不同模式及治疗剂量影响抗菌药物的清除，对重症感染的患者，血药浓度监测是最佳的抗菌药物剂量调整手段[33]。

内毒素是革兰阴性菌外膜的主要成分，内毒素血症会激活多种细胞和血液介质，引起器官损伤和级联炎症反应，内毒素水平和脓毒性休克患者死亡率增加直接相关。多黏菌素B血液灌流（polymyxin B hemoperfusion，PMX-HP）可降低脓毒症患者循环中的内毒素水平。有meta分析发现混合感染或年龄<70岁的脓毒症/脓毒性休克患者接受PMX-HP治疗后28 d死亡率显著降低[34]。来自意大利的共识指出多器官功能障碍综合征（multiple organ dysfunction syndrome，MODS）评分>9分且内毒素活性测定在0.6~0.9的脓毒性休克患者更可能受益于PMX-HP[28]。另有网络荟萃分析显示，PMX-HP和血浆置换可能有潜在的生存益处；使用血浆置换和血液灌流，伴或不伴CVVH，可能与更少的ICU住院天数或机械通气天数有关[35]。

3.3 *抗凝策略的选择* 抗凝的目的是维持体外循环回路的

通畅，最大程度保证RRT顺利进行。抗凝药物的选择及剂量应在评估患者凝血状态并排除药物禁忌后进行。《中国急性肾损伤临床实践指南》[3]建议合并凝血活性亢进和(或)血栓栓塞风险或疾病、排除肝素类药物禁忌的患者，使用普通肝素或低分子肝素；既往或合并肝素诱导的血小板减少症患者，排除枸橼酸盐或阿加曲班禁忌后，选择局部枸橼酸盐或阿加曲班抗凝，不建议使用磺达肝癸钠；伴有活动性出血或高危出血风险、排除枸橼酸盐禁忌的患者，首选局部枸橼酸盐抗凝；存在枸橼酸盐禁忌的患者，在排除阿加曲班禁忌后，建议选择阿加曲班。抗凝治疗过程中及结束后分别监测体外及体内凝血状态以个体化选择抗凝药物剂量。此外，抗凝治疗应严密观察并处理不良事件。

4 未来治疗方案

4.1 *新型治疗药物* 碱性磷酸酶，在宿主防御和先天免疫中发挥重要作用，为了提高治疗效果，研究人员开发了重组人碱性磷酸酶，其通过去磷酸化和改善脓毒症的全身炎症反应(尤其在肾脏)而具有广泛的解毒作用。一项国际、双盲、3期试验REVIVAL试验旨在探究该药对SA-AKI患者的作用，最近发布的结果显示其并未降低患者28 d全因死亡率，但在减少90 d肾脏不良事件方面有潜在益处[36]。对REVIVAL试验的事后分析确定了可能从该药治疗中获益最多的临床表型[37]。目前尚无针对性药物被批准用于治疗SA-AKI，国内有多项针对脓毒症或SA-AKI患者的药物临床试验正在进行中，期待有更多药物能早日应用于临床。

4.2 *新型治疗手段*

4.2.1 外泌体治疗 外泌体是纳米级的细胞外囊泡，外泌体转运是脓毒症期间细胞间通信的新途径，可防止过度炎症的发生，降低发病率和死亡率。多种类型的细胞均可分泌外泌体。间充质干细胞来源广泛，包括骨髓、脂肪组织、脐带、人胎盘等。Jin等[38]的研究揭示了骨髓间充质干细胞来源外泌体对脓毒症AKI大鼠的潜在保护作用。人羊毛膜上皮细胞来源的外泌体可能通过预防小鼠脓毒症早期的内皮功能障碍提高SA-AKI小鼠的存活率，改善肾功能并减轻肾损伤[39]。Gao等[40]通过盲肠结扎穿刺制备SA-AKI小鼠模型，发现脂肪组织间充质干细胞(adipose tissue-derived mesenchymal stem cells，AD-MSCs)来源的外泌体可显著降低血清炎症细胞因子表达，抑制肾脏炎症，改善肾脏功能和组织形态，降低小鼠死亡率，其机制可能与沉默信息调节因子1(silent information regulator 1，SIRT1)信号通路有关。外泌体富含核酸、microRNA、SIRT1、蛋白质和脂质等多种生物活性分子，有研究发现AD-MSCs来源外泌体负载的miR-342-5p可缓解SA-AKI，并探讨了可能的机制[41]。He等[42]发现来自AD-MSCs的外泌体可缓解脂多糖诱导的AKI，为治疗SA-AKI提供了潜在的分子靶点。Li等[43]的研究也发现成纤维细胞网状细胞来源的外泌体通过促进线粒体自噬，阻碍NLRP3炎症小体活化，从而改善肾功能。但也有研究发现巨噬细胞来源的外泌体介导SA-AKI中的肾小球内皮细胞功能障碍，酸性鞘磷脂酶参与调节这一过程，可能是SA-AKI的治疗靶点[44]。以上研究均显示基于外泌体的治疗可能是治疗SA-AKI的一种有希望的替代方案。

4.2.2 靶向治疗 AKI的药物治疗往往缺乏有效的靶向药递送载体，肾脏靶向纳米颗粒是一种新兴的治疗策略，然而这些外源性纳米颗粒在体内会被迅速清除而不能达到预期的靶向效果。一项研究构建了靶向肾脏的肽修饰肾小管上皮细胞膜包裹咪唑酯分子筛骨架-8(zeolitic imidazolate framework-8，ZIF-8)的纳米颗粒，用来递送成纤维细胞生长因子21(fibroblast growth factor 21，FGF21)(KMZ@FGF21)治疗AKI，并在小鼠模型中发现KMZ@FGF21在肾脏中特异性积聚，且有效减轻了AKI相关肾脏损害，表明KMZ@FGF21提高了FGF21的肾保护潜能[45]。Wei等[46]设计了一系列聚乙烯吡咯烷酮(polyvinylpyrrolidone，PVP)-姜黄素纳米颗粒(curcumin nanoformulations，Cur NPs)，提供了一种可控的靶向肾脏递送纳米系统，用于输送有抗氧化和抗炎特性的姜黄素来治疗顺铂诱导的AKI，Cur NPs为精准正电子发射断层扫描引导下肾脏药物递送提供了一种新颖而简单的策略。上述靶向治疗为肾脏病的精确给药治疗提供了新思路。

4.3 *中药治疗* 中医药治疗脓毒症有独特优势，现代药理研究结果显示，中药具有“多成分、多靶点、多途径”协同作用的特点，近年来，不断有学者研究中药治疗SA-AKI的作用。研究发现黄连提取物和和厚朴酚在改善SA-AKI小鼠肾功能和组织损伤中的作用，甚至逆转脓毒症小鼠的AKI，潜在机制可能与影响血红素加氧酶-1水平有关[47]。还有研究证实了通腑益气汤、真武汤对改善SA-AKI患者肾功能损伤及炎症反应的疗效。此外，有研究证明五味子素A可以缓解脂多糖诱导的AKI，但其可能不能完全模拟人类SA-AKI[48]。本课题组前期研究发现，清瘟败毒饮可以降低盲肠结扎穿刺导致的SA-AKI小鼠的血肌酐、尿素氮水平，减轻肾脏的病理损伤。这些研究为中药在AKI治疗中的应用提供了一定的参考。总之，中医药是中国古代科学的瑰宝，值得进一步研究。

5 小结与展望

SA-AKI是一种常见的危重症，具有复杂的病理生理机制，但目前仍不完全清楚。对脓毒症的管理侧重于早期识别、及时使用抗生素和液体复苏，及必要时血管活性药物的使用和器官支持治疗。本课题组前期研究发现非肾科患者AKI漏诊率为49.61%~60.92%，显示部分非肾科医师在临床工作中易忽视AKI的发生，漏诊患者病死率明显高于非漏诊患者[49-50]。最近推出的《中国急性肾损伤临床实践指南》，为我国AKI临床实践提供了本土化权威指导。避免使用潜在的肾毒性药物(如羟乙基淀粉)、优化容量状态和血流动力学、密切监测血清肌酐和尿量，是临床医生应当遵循的准则。多学科碰撞也为AKI治疗提供了新思路。我国在中医药的长期实践中积累了丰富的经验，本课题组长期致力于为中医药临床治疗SA-AKI提供新的思路，未来中医药制剂的治疗潜力仍值得期待。随着对SA-AKI发病机制理解的不断加深，期待能有更具针对性、更合理的治疗方法。

利益冲突 无

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(上接第1638页)

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