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Literature Review

THE DIFFERENTIATING OF SEPSIS-ASSOCIATED AND SEPSIS-INDUCED ACUTE KIDNEY INJURY IN INTENSIVE CARE UNIT PATIENTS

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ABSTRACT

Introduction: Acute kidney injury (AKI) is a severe and common complication in Intensive Care Unit (ICU) patients, commonly resulting from sepsis. It is associated with elevated mortality, chronic renal failure, and other long-term consequences. Sepsis-associated AKI (SA-AKI) and Sepsis-induced AKI (SI-AKI), a specific sub-phenotype, differ in their underlying pathophysiology. **Objective:** To examine the distinctions between SA-AKI and SI-AKI, focusing on their pathophysiology, biomarkers for detection, and associated prognoses in critically ill patients. This literature review examines the findings of randomized control trials (RCTs) or meta-analysis studies that learn about biochemical mediators and biomarkers for SA-AKI and SI-AKI, including NGAL, Kim-1, and others, as well as the prognostic impact of these conditions. The literature was gathered from Google Scholar and PubMed using the keywords Sepsis-Associated Acute Kidney Injury, Sepsis-Induced Acute Kidney Injury, Intensive Care Unit, and Sepsis and published within the last ten years (2018–2023). Articles unavailable in the full text were excluded. **Review:** SA-AKI and SI-AKI are distinct entities within the broader spectrum of sepsis and AKI. SI-AKI involves sepsis-induced direct kidney damage, which differentiates it from other forms of SA-AKI. Various biomarkers such as NGAL, Kim-1, and others are crucial for early detection and differentiation between these conditions. Patients with SA-AKI and SI-AKI usually have a bad outlook. They are more likely to die, be disabled for a long time, and need longer stays in the ICU and hospital than patients with sepsis or AKI alone. Figuring out the underlying pathophysiology and using the right biomarkers can help with early diagnosis and could lead to better outcomes for patients through targeted therapies. **Summary:** SA-AKI and SI-AKI represent critical complications in ICU patients with sepsis, leading to high mortality and long-term adverse outcomes. Differentiating between these conditions using biomarkers is essential for early detection and management. These patients have a worse prognosis than those with sepsis or AKI alone. This shows how important it is to keep researching and finding better ways to treat these serious complications in critically ill patients.

Keywords: Acute Kidney Injury; Intensive Therapy; SA-AKI; SI-AKI; Sepsis

ABSTRAK

Pendahuluan: Cedera Ginjal Akut (Acute Kidney Injury/AKI) adalah komplikasi yang umum dan parah pada pasien ICU, yang sering kali disebabkan oleh sepsis. Hal ini dikaitkan dengan angka kematian yang tinggi, gagal ginjal kronis, dan konsekuensi jangka panjang lainnya. AKI terkait sepsis (SA-AKI) dan AKI yang diinduksi sepsis (SI-AKI), sebuah subfenotipe spesifik, berbeda dalam patofisiologi yang mendasarinya. **Tujuan:** Untuk membedakan antara SA-AKI dan SI-AKI, dengan fokus pada patofisiologi, biomarker untuk deteksi, dan prognosis terkait pada pasien yang sakit kritis. Tinjauan pustaka ini merupakan tinjauan naratif yang mengkaji hasil uji coba terkontrol acak (RCT) atau studi metaanalisis yang mempelajari mediator biokimia dan biomarker untuk SA-AKI dan SI-AKI, termasuk NGAL, Kim-1, dan lainnya, serta dampak prognostik dari kondisi ini. Literatur dikumpulkan melalui Google Scholar dan PubMed dengan menggunakan kata kunci Sepsis-Associated Acute Kidney Injury, Sepsis-Induced Acute Kidney Injury, Intensive Care Unit, dan Sepsis dan diterbitkan dalam sepuluh tahun terakhir (2018–2023). Peneliti mengecualikan artikel yang tidak tersedia secara lengkap. **Review:** SA-AKI dan SI-AKI adalah entitas yang berbeda dalam spektrum sepsis dan AKI yang lebih luas. SI-AKI melibatkan kerusakan ginjal langsung yang diinduksi sepsis, yang membedakannya dengan bentuk SA-AKI lainnya. Berbagai biomarker seperti NGAL, Kim-1, dan lainnya sangat penting untuk deteksi dini dan diferensiasi antara kondisi-kondisi ini. Prognosis pasien dengan SA-AKI dan SI-AKI umumnya buruk, dengan kemungkinan kematian

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yang lebih tinggi, kecacatan jangka panjang, dan rawat inap di ICU dan rumah sakit yang lebih lama dibandingkan dengan pasien dengan sepsis atau AKI saja. Memahami patofisiologi yang mendasari dan menggunakan biomarker yang tepat dapat membantu diagnosis dini dan berpotensi meningkatkan hasil akhir pasien melalui terapi yang ditargetkan. **Rangkuman:** SA-AKI dan SI-AKI merupakan komplikasi kritis pada pasien ICU dengan sepsis, yang mengarah pada kematian yang tinggi dan hasil jangka panjang yang merugikan. Membedakan antara kondisi ini dengan menggunakan biomarker sangat penting untuk deteksi dini dan manajemen. Prognosis untuk pasien-pasien ini lebih buruk dibandingkan dengan pasien dengan sepsis atau AKI saja, menggarisbawahi perlunya penelitian lanjutan dan strategi terapi yang lebih baik untuk mengurangi komplikasi parah pada pasien yang sakit kritis.

Kata kunci: Cedera Ginjal Akut; Terapi Intensif; SA-AKI; SI-AKI; Sepsis

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INTRODUCTION

Over half of the patients in intensive care units (ICUs) around the world experience Acute Kidney Injury (AKI), with sepsis being the most common underlying cause. Epidemiological studies indicate that AKI is associated not only with acute severe effects but also with significant long-term consequences. Although patients may recover from AKI, they remain at risk of developing recurrent kidney injuries (1,2).

Sepsis-associated AKI can manifest in a variety of phenotypes and prognoses (3). Patients with AKI and those meeting the consensus criteria for sepsis are considered to have Sepsis-Associated Acute Kidney Injury (SA-AKI). Meanwhile, Sepsis-Induced Acute Kidney Injury (SI-AKI) can be seen as a sub-phenotype of SA-AKI, where mechanisms induced by sepsis produce direct kidney damage (1). The prognosis for SA-AKI and SI-AKI events is worse compared to sepsis and AKI separately (4). There are still a lot of questions that need to be answered about definitions, epidemiology, pathophysiology, how to diagnose, how to treat, and how extracorporeal and new therapies affect patients (5).

SA-AKI is defined as AKI occurring within seven days of a sepsis diagnosis. It is further categorized into early SA-AKI, which develops within 48 hours of sepsis diagnosis, and late SA-AKI, which arises between 48 hours and seven days. The proposed seven-day window is based on the observation that AKI typically develops within a few days following the onset of sepsis. Beyond this period, AKI is generally considered less likely to be directly related to the initial sepsis event. The difference between early and late SA-AKI is important because late-stage AKI progression has worse clinical outcomes and a higher death rate than early-stage AKI. Phenotyping for focused assessment and management can be improved by distinguishing between the early and late phases of SA-AKI. Untreated or early sepsis patients are at a higher risk of experiencing SI-AKI, whereas those who get sepsis-related treatments are more prone to developing SA-AKI. Additional variables may also contribute to the development of AKI (1).

REVIEW

Pathogenesis

Sepsis is marked by an overproduction of many pro-inflammatory cytokines and is linked to malfunction in multiple organs. SI-AKI is distinguished by a fast rapid loss of kidney function, as indicated by elevated creatinine and Blood Urea Nitrogen (BUN) levels, as well as reduced Glomerular Filtration Rate (GFR) and urine production. Multiple factors can

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contribute to SI-AKI, such as systemic inflammation and immune system dysregulation, hemodynamic change, activation of the complement system, dysregulation of the renin-angiotensin-aldosterone system (RAAS), dysfunction of mitochondria, metabolic reprogramming, and dysfunction of the microcirculatory system. Various factors can indirectly contribute to SA-AKI, such as nephrotoxic drugs, hyperchloremia, and abdominal compartment syndrome (1,6).

Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) are released following the invasion of a pathogen. These patterns attach to groups of receptors known as pattern recognition receptors, with one example being Toll-Like Receptors (TLRs).

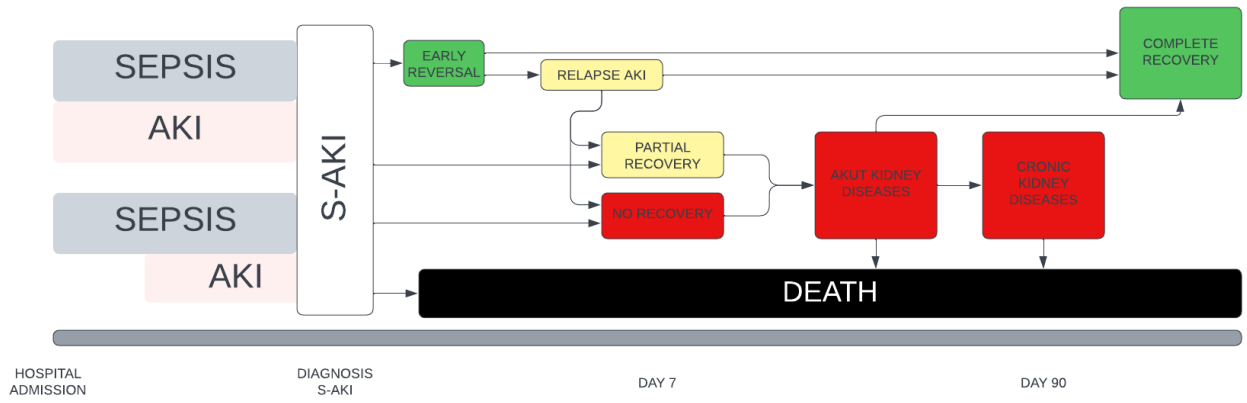

Figure 1. The Clinical Progression and Outcome of Sepsis-Associated Acute Kidney Injury (SA-AKI) (The exact timing of renal injury onset in sepsis is unclear. Patients who come with sepsis probably have AKI, and conversely, patients who come with AKI also definitely have sepsis. AKI may coexist with sepsis at the time of hospital admission; (a) or develop during treatment; (b). S-AKI may improve early in the first week after diagnosis and is linked to a favorable prognosis. AKI can develop within the first 7 days, leading to permanent damage and progressing to SA-AKI. During this period, patients may achieve full or partial recovery, but some may suffer ongoing injury without improvement. In the long term, this lack of recovery can lead to chronic kidney disease (CKD))

Toll-like receptors (TLRs) are present on the plasma membrane of immune cells, endothelial cells, and tubular epithelial cells (TEC). The binding process results in the overproduction of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-18, TNF-α, chemokines, and Reactive Oxygen Species (ROS), while also activating the complement system. Uncontrolled immune response and extensive inflammation play a crucial role in the development of septic AKI (6,7).

The Renal Blood Flow (RBF) is the sum of cardiac output and the effective circulatory volume. During the onset of sepsis, there is an initial rise in cardiac output, followed by a progressive decline as a result of septic damage. Multiple studies have discovered that RBF remains stable or may even be elevated during the early stages of septic AKI (8). These findings suggest that renal hypoperfusion is not necessary for septic AKI to occur. Vasodilation is caused by endothelial dysfunction in the

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kidney blood vessels and the release of vasoactive substances like nitric oxide (6,8–10). Multiple studies have shown that sepsis can present with microcirculatory changes even without macrocirculatory alterations (11). These findings suggest that changes in microvascular hemodynamics may contribute to the development of SI-AKI.

The renal blood vessels consist of renal arteries, glomerular microvasculature, and peritubular capillaries. Endothelial cells primarily regulate the homeostasis of RBF and microvascular permeability. Alterations in the interaction among endothelial cells result in heightened capillary permeability and leukocyte secretion. Prior research has shown that endothelial nitric oxide synthase (eNOS) levels drop in a septic model induced by Cecal Ligation and Puncture (CLP), and this enzyme plays a crucial role in vasodilation (12).

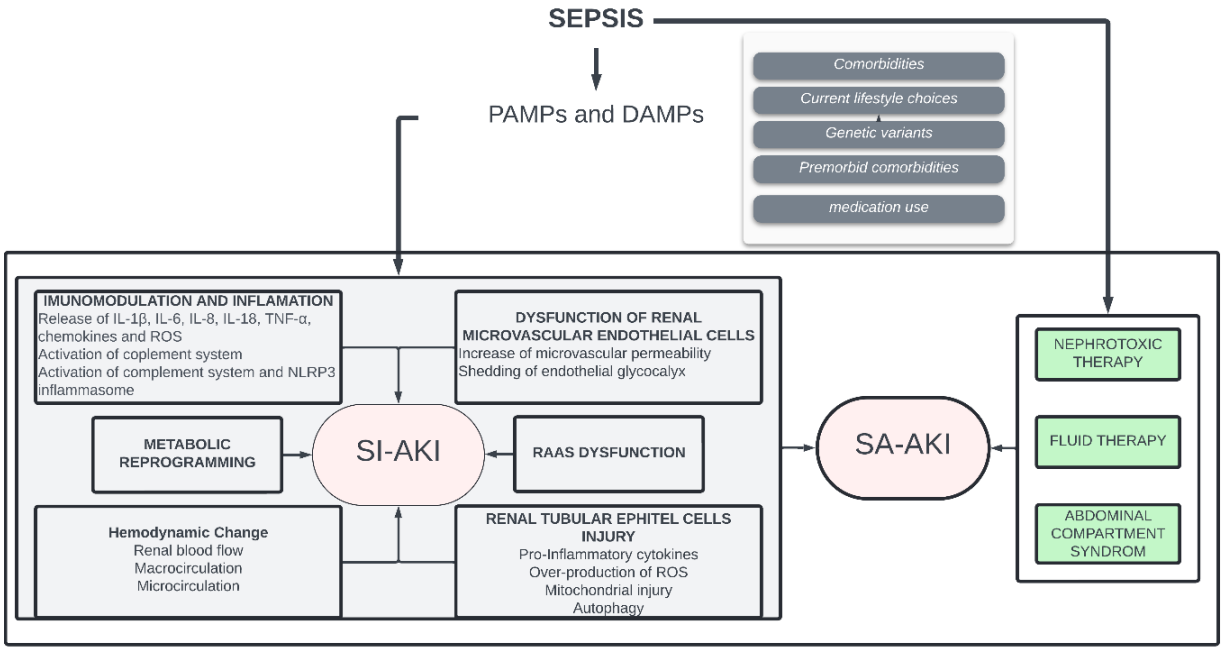

Figure 2. Pathogenesis of Sepsis AKI

(The release of PAMPs, like lipopolysaccharides, and DAMPs from damaged cells and tissues can trigger the activation of a dysfunctional immune response, which is characteristic of sepsis. The underlying susceptibility to tissue and organ damage varies among individuals, influenced by non-modifiable factors such as comorbidities, lifestyle choices (e.g., smoking), genetic variations (e.g., single nucleotide polymorphisms), pre-existing health conditions, and medication use (e.g., renin-angiotensin-aldosterone system inhibitors for blood pressure control). Additionally, modifiable factors, such as the use of vasopressors, mechanical ventilation, or the presence of bacteremia, also play a role. 1) imbalanced immune response and widespread inflammation, including the release of pro-inflammatory cytokines; 2) hemodynamic alterations, including changes in renal blood flow, macrocirculation, and microcirculation; 3) dysfunction of renal microvascular endothelial cells; 4) Renal tubular epithelial cell damage mediated by the TLRs/NF-κB signaling pathway and a decline in autophagy during the later stages of sepsis; 5) RAAS dysfunction and 6) metabolic reprogramming play a role in the occurrence of SI-AKI. Other sepsis-related factors indirectly contribute to AKI. These include the use of nephrotoxic therapies, fluid therapy, and abdominal compartment syndrome)

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Endothelial glycocalyx shedding was observed in all sepsis patients, along with a rise in soluble glycocalyx components in the plasma. The damage to the endothelium and the loss of the glycocalyx cause leukocyte leakage and platelet aggregation, leading to a decrease in blood flow velocity. This can result in the development of microthrombi and subsequent blockage of capillaries (7). Therefore, renal blood vessel endothelial cells are major contributors to SI-AKI development.

Acute TEC injury frequently happens in cases of SI-AKI. TLRs, specifically TLR2 and TLR4, are present in TECs. The apical membrane of TECs contains TLRs that recognize PAMPs and DAMPs. When these molecules bind to the TLRs, it triggers the activation of Nuclear Factor kappa B (NF-κB). This activation leads to the release of an excessive amount of pro-inflammatory cytokines, the generation of ROS, and harm to the mitochondria. Autophagy in proximal tubules was found to be temporarily enhanced largely 3 hours after CLP, as evidenced by the utilization of angiotensin-converting enzyme, a marker specific to proximal tubules. Nevertheless, autophagy was observed to decline between 9 and 18 hours, coinciding with the occurrence of kidney damage both in terms of pathology and function (6,9). Decreased autophagy in the late phases of sepsis may potentially contribute to proximal TEC dysfunction, according to these results.

Early Detection and Diagnosis

The diagnosis of AKI according to KDIGO has certain limitations due to a lack of consensus on determining a baseline blood creatinine level (13,14). Delayed alterations in serum creatinine levels are frequently observed, particularly in cases of sepsis. When there is damage to the kidney parenchyma, it can impact up to 50% of the kidneys without causing a rise in creatinine levels (15,16). Presently, numerous research document early diagnostic indicators for AKI. Distinct biomarkers have unequivocally demonstrated their ability to signal different damage pathways. Integrating injury/stress markers with functional assessments provides a more comprehensive and extensive quantity of information compared to utilizing them individually (7,17). The process cohort study found that the occurrence of positive-biomarker AKI was associated with a worse 30-day survival rate compared to negative-biomarker AKI (18). Table 1 and Table 2 show biomarkers for detecting SA-AKI based on ADQI 28.3.

Table 1. Renal Injury Mechanisms and Biomarkers (8,19)

Mechanism	Biomarkers
Ischemia	NGAL, Kim-1, MCP-1, and cry61
Hypoxia	L-FABP
Cell-cycle arrest	TIMP-2, IGFBP 7

Table 2. Location of Kidney Injury and Biomarkers (8,19)

Location	Biomarkers
Glomerulus	Urin: β2-microglobulin, Albumin, TP (total protein), and α1-microglobulin Blood: creatinine, NGAL, and cystatin C
Proximal tubule	Kim-1, L-FABP, NET-3, NAG, netrin-1, IL-18, HGF, IGFBP 7, and TIMP-2
Distal tubule	NGAL, GST-α/π, cystatin C, Cyr61, and NET-3
Choledochal duct	Calbindin D28

Recent Advances in Biomarkers as Predictors for SI-AKI

The details on the recent advancements in biomarkers used as predictors for SI-AKI are provided in Table 3. By using these biomarkers in a clinical setting, early damage to the parenchymal structure of the kidney can be

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found, without having to wait for signs of renal failure to show up (9,20).

Therapeutic Approaches to S-AKI

The basic principle for treating sepsis patients is typically prompt administration of the right medicines along with source control. Plasma perfusion, renal replacement therapy (RRT) with or without hemoperfusion, nutritional support with protein and calorie supplements, managing fluid balance, keeping acid-base and electrolyte balance, and making sure hemodynamic stability are the main treatments used currently. Carefully used nephrotoxic drugs such as aminoglycosides, amphotericin B, and vancomycin especially when combined with piperacillin-tazobactam can prevent kidney damage (6,7,13,17). The initial therapeutic goals include maintaining a central venous pressure of 8–12 mmHg, a mean arterial pressure (MAP) of 65 mmHg, a urine output of 0.5 ml/kg/hour, and a central venous oxygen saturation of 70% (13,21–23).

Antibiotic Therapy

Within an hour after the diagnosis of sepsis, broad-spectrum antibiotics should be given (6,10,24). In the meantime, the septic source needs to be located to administer the proper antibiotic therapy. Certain medications, including aminoglycosides, amphotericin B, and vancomycin, have nephrotoxic effects and should be used with caution. Early AKI development is linked to delayed antibiotic therapy (6).

Fluid Resuscitation

Patients with sepsis or septic shock should begin resuscitation and treatment immediately to prevent damage to the macro and microcirculation, according to the Surviving Sepsis Campaign (SSC) 2021. Within the first three hours after resuscitation, it is suggested to administer crystalloid fluid intravenously at a rate of 30 mL/kg as the initial option. Monitoring is needed to avoid fluid excess during resuscitation (25,26). Isotonic crystalloid fluid is recommended for people who are susceptible to AKI. This is still up for dispute, though. Excessive doses of 0.9% saline have been linked to pro-inflammatory cytokine release, renal vasoconstriction, hyperchloremic metabolic acidosis, and disturbance of natural coagulation pathways (27). This can lead to AKI in patients and worsen the patient's condition (15,27–29). At the same time, the use of hydroxyethyl starch (HES) and gelatin solutions raises the risk of AKI and mortality (7).

Vasoactive Agents

Vasopressors should be started when fluid resuscitation is not sufficient (30). The SSC 2021 recommends norepinephrine as the first-line vasopressor for septic shock (25). Vasopressin and Septic Shock Trial (VASST) showed similar results and no more harmful effects in any of the patients who were tested with norepinephrine or vasopressin. Vasopressin and Septic Shock Trial (VASST) revealed comparable results and no increased adverse effects in any of the patients under investigation using norepinephrine or vasopressin. Additionally, vasopressin has fewer adverse effects on the kidneys than dopamine (1,30–32). The administration of vasopressors, such as terlipressin or vasopressin, appears to increase urine production and creatinine clearance similarly. Less is known, though, about the impact of raising MAP to values over 60–65 mmHg. Urine output was found to be enhanced by raising MAP from 65 to 75 mmHg in certain studies, however, raising MAP to values above 85 mmHg did not yield any further advantages. Several other studies were unable to

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demonstrate the advantages of raising RPP to values above 65 mmHg (11,33,34).

Renal Replacement Therapy (RRT)

Renal Replacement Therapy (RRT) has been used for the management of AKI, and numerous research findings indicate that RRT might be advantageous for some patient populations (35). However, recent research reports that RRT provides limited effects on AKI patient recovery (36). Eighty patients in a French multicenter trial with an initial blood creatinine level of 188 µmol/L were given conservative care or hemofiltration for 96 hours (25 mL/kg/hour) within 24 hours of organ failure owing to sepsis. Early initiation, occasionally in the absence of SA-AKI, had unfavorable effects, such as increasing organ failure. Following this, 620 patients were randomly assigned. Three hundred and eleven patients in the early strategy group and thirty-eight patients in the delayed strategy group died on day sixty. However, Kaplan-Meier estimates of mortality did not show a significant difference between the two groups. In the delayed strategy group, kidney replacement therapy was not administered to 151 patients or 49% of the total. Compared to the delayed strategy group, the early strategy group experienced higher rates of catheter-related bloodstream infections (10% vs. 5%). In the delayed strategy group, diuresis a sign of better kidney function occurred earlier (6,37).

There is controversy regarding when to initiate RRT (35,36,38–42). According to the KDIGO criteria, early initiation of RRT is recommended for stage 3 AKI or if any of the following criteria that shown in table 3 (13,38,39). However, recent studies state that early dialysis initiation based solely on the AKI stage has not proven beneficial in reducing mortality (38). The recommended RRT dose is 20-25 ml/kg/hour (21).

Table 3. Recent Biomarkers Used as Predictors for SI-AKI

Biomarkers	Description
sTREM-1	sTREM-1 refers to the dissolved form of the triggering receptor expressed on myeloid cells 1, which is specifically monocytes and neutrophils. TREM-1 is a receptor belonging to the immunoglobulin superfamily that is involved in infl the occurrence of AKI, the presence of sTREM-1 can be identified in the urine of the patient. However, it is impor sTREM-1 in the urine is not correlated to its concentration in the serum (9,20).
NGAL	Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein that belongs to the lipid-binding protein superfamily. It is found on the surface of neutrophils. NGAL expression in the kidney is tightly controlled within 3 hours of an ischemic injury. Between 24 and 48 hours after the injury, the level of NGAL mRNA expression peaks, rising by over 1000 times (9,20).
Cell-Cycle Arrest Protein	Tissue inhibitor metalloproteinase-2 (TIMP-2) is a 21-kDa protein that is non-glycosylated. It is composed of 194 amino acid residues and has a role in controlling cell proliferation and programmed cell death. Urinary insulin-like growth factor-binding protein 7 (IGFBP7) is a 29-kilodalton glycoprotein that belongs to the IGFBP superfamily. AKI patients have higher levels of TIMP-2 and IGFBP7 in kidney tubular cells. This stops the G1 cell cycle by turning on p27KIP1 and p21. Testing the levels of TIMP-2 or IGFBP7 in urine can predict the onset of acute kidney injury (AKI) at an early stage (9,20).
KIM-1	Kidney Injury Molecule-1 is a type 1 transmembrane glycoprotein. In ischemia and nephrotoxic AKI, KIM-1 expression is controlled in the kidney's proximal tubular cells. Using immunological techniques, the extracellular portion of KIM-1 may be isolated from proximal tubular cells and identified. Urinary KIM-1 has a sensitivity of 74.0% and specificity of 86.0% for AKI prediction (9,20).
Netrin-1	Netrin-1's original description states that it can affect axonal migration and the development of the central nervous system during neurogenesis processes. Netrin-1 is mostly found in the kidneys, and finding netrin-1 early in the urine has been linked to renal tubule ischemia-reperfusion injury. Urinary netrin-1 increased 2 hours after cardiopulmonary bypass (CPB), peaked at 6 hours, and continued to grow up to 48 hours after CPB, while creatinine increased only after 48 hours. This information was reported in a study on AKI associated with CPB (9,20).

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Emerging Therapeutic Approaches

Studies have demonstrated that implementing early goal-directed therapy can enhance the chances of survival in patients with sepsis. However, death rates for SI-AKI continue to be elevated. Autophagy activation in proximal tubular epithelial cells (TEC) decreases during the later stages of sepsis. Various drugs have been identified as beneficial in treating S-AKI by promoting autophagy. Additionally, several phytochemicals, known for their anti-inflammatory and antioxidant properties, are considered promising complementary treatments for sepsis-induced acute kidney injury (SI-AKI). Various natural plants contain bioactive compounds that have been found to exhibit anti-tumor, anti-infective, anti-inflammatory, immunomodulatory, and neuroprotective properties. Resveratrol, moringa isothiocyanate-1, rhizoma Coptidis extracts, curcumin, zingerone, and glycyrrhizic acid are some of the substances that can lower oxidative stress and stop inflammation. These substances also decrease the production of IL-1β, IL-6, and TNF-α (6). Additionally, angiotensin II, a potent vasoactive agent, may be beneficial for SA-AKI patients (41).

Angiotensin II

Angiotensin II induces a substantial elevation in MAP within the initial three hours. In the angiotensin II group, 69.9% of patients experienced an increase in MAP, while only 23.4% of patients in the placebo group showed an increase. There was no discernible disparity in the rates of mortality that occurred while patients were still in the hospital. A study of a small group of patients who received RRT showed that those who were given angiotensin II needed less RRT and had a higher chance of living until day 28. If these findings are confirmed in a broader group of individuals, angiotensin II could potentially serve as a novel therapy for SA-AKI (17).

Alkaline phosphatase

Alkaline phosphatase is a naturally occurring enzyme in the body that detoxifies by removing phosphate groups from various molecules (43). Giving systemic alkaline phosphatase has been shown to protect against SA-AKI in both preclinical and small clinical studies (44,45). Administering alkaline phosphatase intravenously enhances the natural process of clearing creatinine from the body and is linked to reduced levels of kidney tubular damage markers. Importantly, this treatment does not lead to a decrease in the need for RRT (46). A 2020 meta-analysis found that alkaline phosphatase shows a relatively slow protective effect by increasing Endogenous Creatinine Clearance (ECC) on days 7, 14, and 28. ECC improved when patients were given 0.212 mg/kg alkaline phosphatase. Mortality was higher at days 28 and 90 in patients who were administered 1.6 mg/kg of alkaline phosphatase (47). Further research is needed on the positive effects of using alkaline phosphatase in SA-AKI patients.

Thiamine

Thiamine (B1 vitamin) levels can be reduced by increased metabolic demand, parenteral or enteral feeding, diuretics, as well as hemodialysis and hemofiltration. About 20 – 70% of patients with septic shock had thiamine deficiency (48). A possible cause of kidney injury in sepsis could be mitochondrial dysfunction, which refers to the inability of cells to effectively extract and utilize oxygen for aerobic metabolism, even when there is sufficient oxygen supply. In the absence of thiamine, pyruvate is unable to participate in the Krebs cycle, resulting in the conversion of pyruvate into lactate instead of acetyl-

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coenzyme A. Consequently, a lack of thiamine causes a change in the body's metabolic process towards the anaerobic pathway, leading to elevated levels of lactate in the blood, cell death, organ damage (including renal failure), and the possibility of death (48–51). A secondary analysis was done on a randomized controlled trial (RCT) with 70 people who had septic shock. These people were randomly assigned to receive either 200 mg of thiamine through an IV twice a day for 7 days or a placebo. The analysis revealed that the patients who got thiamine had lower levels of serum creatinine and a decreased likelihood of developing RRT (52). Another study stated that thiamine did not show a benefit in-hospital mortality. However, this drug may be considered for use in patients with kidney dysfunction (48). It is not possible to draw definitive conclusions, highlighting the need for further research, particularly in patients with thiamine deficiency (43).

SUMMARY

Acute Kidney Injury (AKI) is prevalent among ICU patients, with sepsis being a common cause. Sepsis-associated AKI (SA-AKI) and its subset, Sepsis-Induced AKI (SI-AKI), pose significant challenges, carrying worse prognoses than sepsis or AKI alone. The differentiation between early (within 48 hours) and late (48 hours to 7 days) SA-AKI is crucial for understanding outcomes, as later stages are linked to higher mortality. SI-AKI happens when systemic inflammation, immune system dysregulation, microvascular dysfunction, and injury to renal tubular epithelial cells (TEC) all work together in a complicated way. Pro-inflammatory cytokines and Reactive Oxygen Species (ROS) play significant roles. Kidney damage is caused by things like endothelial dysfunction and changes in the microcirculation. These changes affect both the large and small blood vessels in the kidneys. Pathogen recognition receptors, such as Toll-Like Receptors (TLRs), have a direct effect on TECs. This causes the NF-κB pathway to be activated and autophagy to slow down, which makes kidney damage worse. Traditional diagnostic criteria for AKI, such as serum creatinine, have limitations, especially in sepsis. Emerging biomarkers (e.g., NGAL, KIM-1, TIMP-2/IGFBP7) offer earlier detection and better prognostic insights. The combination of injury markers with functional assessments provides a more comprehensive understanding of AKI severity. Prompt administration of broad-spectrum antibiotics is crucial within an hour of sepsis diagnosis. Crystalloid fluids are recommended, with careful monitoring to avoid fluid overload. Hyperchloremic fluids like saline are linked to adverse outcomes, while hydroxyethyl starch (HES) and gelatin are associated with increased AKI risk. Norepinephrine is the first-line vasopressor, with vasopressin as an adjunct. Raising the MAP to 65–75 mmHg can improve outcomes, but higher pressures may not offer additional benefits. While RRT is standard in managing AKI, the timing of initiation remains controversial. Early initiation does not consistently reduce mortality, and delayed strategies may prevent unnecessary RRT. Research into therapies like autophagy activation, phytochemicals, angiotensin II, and alkaline phosphatase is ongoing. These approaches show promise in reducing inflammation, oxidative stress, and kidney damage, offering potential new treatments for SA-AKI. However, further validation in larger clinical trials is necessary.

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Conflict of Interest

The authors affirm that there are no conflicts of interest pertaining to this study.

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Authors' Contribution

Nusi Andreas Hotabilardus contributed to the conceptualization, data collection, data analysis, and interpretation, as well as manuscript preparation; **Novita Anggraeni** was responsible for supervision, critical review, and final approval of the manuscript.

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