

# Micro RNAs in septic acute kidney injury: pathophysiology, biomarkers and therapeutic targets

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## Abstract

**Introduction:** Septic acute kidney injury (S-AKI) is a life-threatening complication of sepsis with high mortality and limited treatment options. Emerging evidence highlights the role of microRNAs (miRNAs) as critical regulators of the key pathogenic pathways involved in S-AKI, including inflammation, apoptosis, oxidative stress, and microvascular dysfunction.

**Aim:** To provide a comprehensive overview of the current knowledge of miRNA involvement in the pathophysiology, diagnosis, and potential treatment of S-AKI.

**Materials and methods:** A structured literature review was conducted using recent experimental and clinical studies published in peer-reviewed journals from 2018 to 2025. Key miRNAs implicated in S-AKI were identified and analyzed for their diagnostic and therapeutic relevance.

**Results:** Several miRNAs, such as miR-155, miR-146a/b, miR-21, miR-210, and miR-22-3p, modulate essential signaling cascades in S-AKI, either promoting or attenuating kidney injury depending on context. Circulating and urinary miRNAs demonstrate high sensitivity and specificity as early biomarkers, often outperforming traditional markers like serum creatinine. Furthermore, experimental models show that targeting specific miRNAs using mimics or antagonists can significantly mitigate renal damage in sepsis.

**Conclusion:** miRNAs offer a promising dual application in S-AKI—as sensitive noninvasive biomarkers and as novel therapeutic targets. Future research should focus on validating their clinical utility and overcoming challenges related to targeted delivery and off-target effects. miRNA-based interventions may become integral components of personalized therapy in sepsis-related kidney injury.

## Keywords

acute kidney injury, biomarker, inflammation, microRNA, sepsis, therapy

## Introduction

Sepsis is a severe systemic inflammatory response to infection that can lead to multiple organ failure. When acute kidney injury occurs in the setting of sepsis, the condition

is referred to as septic acute kidney injury (S-AKI). S-AKI occurs in 50–60% of patients with sepsis and is associated with high mortality (up to 50–70%).<sup>[1]</sup> The pathophysiological mechanisms of S-AKI are not completely understood. However, it is thought that dysregulation of the inflamma-

tory response, microvascular disturbances, and metabolic reprogramming of cells play key roles.

In recent years, there has been a growing interest in small non-coding RNA molecules known as microRNAs (miRNAs) and their role in sepsis and acute kidney injury. MicroRNAs are ~22-nucleotide single-stranded RNAs that regulate gene expression at the post-transcriptional level. They typically do so by binding to the 3' untranslated regions (UTRs) of target mRNAs and suppressing their translation or inducing mRNA degradation. Each miRNA can modulate hundreds of genes, controlling a wide array of biological processes such as immune responses, cell death, proliferation, etc. It has been shown that the expression profile of numerous miRNAs changes during sepsis and AKI, which hints at a crucial role for these molecules in pathogenesis. Furthermore, microRNAs are stable in bodily fluids and easily measurable, making them attractive candidates as biomarkers and therapeutic targets in S-AKI.<sup>[2-4]</sup>

This review presents the main pathological mechanisms in septic kidney injury—including inflammation, apoptosis, oxidative stress, and microvascular dysfunction—and reviews contemporary data on the involvement of microRNAs in these processes. We discuss both clinical and experimental evidence for the role of microRNAs as early biomarkers of S-AKI, as well as studies exploring their potential as therapeutic targets (via inhibition or replacement of specific miRNAs). **Table 1** summarizes the major microRNAs associated with S-AKI, along with their effects and potential diagnostic or therapeutic value.

## Pathogenetic mechanisms of S-AKI

### Inflammation and immune dysfunction

Systemic inflammation underlies septic pathophysiology and plays a central role in kidney injury. Sepsis is characterized by an excessive cytokine response (the so-called “cytokine storm”), activation of the innate immune system, and tissue infiltration by neutrophils and mononuclear cells. In the kidneys, this leads to endothelial damage and injury to tubular epithelial cells, disruption of the barrier function, and inflammatory edema.

It has been found that S-AKI involves an overproduction of pro-inflammatory cytokines (IL-6, IL-8, TNF- $\alpha$ , etc.), which contributes to damage of the nephrons. At the same time, sepsis also causes immune dysregulation—the initial hyperinflammatory phase can transition into immunoparalysis, which predisposes patients to secondary infections. In the context of the kidneys, an imbalance between pro- and anti-inflammatory signals disrupts homeostasis and triggers a cascade of injurious processes.

### Apoptosis

Apoptotic cell death of renal cells is a key mechanism of acute kidney injury in sepsis. The combination of ischemia (due to hypotension and reduced renal blood flow), inflammatory mediators, and the toxic effects of bacterial products (e.g., endotoxin) induces apoptosis of tubular epithelial cells. The early phase of S-AKI is associated with activation of apoptotic pathways through both the intrinsic (mitochondrial) and extrinsic (death receptor-mediated) routes. The overproduction of calcium ions, inflammatory cascades, and the release of reactive oxygen species during sepsis can directly trigger apoptosis in renal cells.

Apoptosis results in the loss of functional nephrons, damage to tubules and glomeruli, and further deterioration of kidney function. Histological studies in sepsis models show apoptotic changes in the proximal tubules along with inflammatory infiltrates, confirming the significance of this mechanism.

### Oxidative stress

Sepsis leads to abundant generation of reactive oxygen species (ROS) and reactive nitrogen species, resulting in oxidative stress in tissues. In the kidneys, activated neutrophils, macrophages, and dysfunctional mitochondria release large amounts of superoxide, peroxide, and other ROS. Excess free radicals directly damage cell membranes, proteins, and DNA, leading to lipid peroxidation, enzyme inactivation, and cell death.

Oxidative stress and inflammation reinforce each other—ROS activate pro-inflammatory signaling pathways, while inflammatory cells produce additional ROS, creating a vicious cycle. Consequently, the microvascular endothelium is damaged, and vascular permeability increases, contributing to tissue hypoxia. In septic kidney injury, levels of antioxidant enzymes (e.g., superoxide dismutase [SOD]) are observed to be reduced, whereas levels of malondialdehyde (MDA, a marker of lipid peroxidation) are elevated; these changes correlate with the severity of renal injury. This underscores the significance of the imbalance between pro-oxidant and antioxidant systems in the pathogenesis of S-AKI.

### Microvascular dysfunction

Microvascular disturbances in sepsis critically contribute to ischemic damage to the kidneys. Septic hypotension and vasodilation, despite being systemic, can result in inadequate perfusion of the renal cortex due to redistribution of blood flow and endothelial dysfunction. In the kidney's microvasculature, inflammatory processes cause endothelial injury and trigger coagulation with the formation of microthrombi. These microthrombi, together with the broader disseminated intravascular coagulation (DIC), further reduce perfusion and lead to ischemia of nephrons.

**Table 1.** Key microRNAs associated with septic acute kidney injury (S-AKI), their effects, and potential value

microRNA	Effect on S-AKI	Potential Value
miR-21	Promotes cell survival, suppresses apoptosis. Upregulated in S-AKI; modulates apoptosis and inflammation in a context-dependent manner and can intensify tubular injury via PTEN/FOXO1-mediated cell-cycle arrest or protect via AKT activation and NF-κB suppression.	Diagnostic and therapeutic biomarker. Early biomarker- serum levels correlate with kidney injury; Potential therapeutic target - enhancing miR-21 (e.g., by preconditioning) protects the kidney, whereas inhibiting it may be beneficial when its expression is pathologically high.
miR-146a	Negative regulator of NF-κB-mediated inflammation. Often reduced in severe sepsis; targets IRAK1 and TRAF6, thereby tempering TLR4/NF-κB signaling and cytokine production.	Early biomarker and potential therapeutic target for S-AKI. Acts as an anti-inflammatory agent - upregulation via miR mimic or drugs like dexmedetomidine reduces inflammation and improves kidney function in S-AKI. Being explored as a therapy (e.g., MSC-derived exosomes enriched in miR-146b improved survival in septic models).
miR-155	Potentiates inflammation via TLR4/NF-κB pathway. Strongly upregulated in sepsis with AKI; pro-inflammatory – suppresses SOCS1 and other negative regulators, leading to NF-κB hyperactivation and elevated IL-6 and TNF-α. Also promotes tubular cell apoptosis (targets Bcl-2, SIRT1).	Indicator of inflammation severity. Diagnostic marker - plasma miR-155-5p correlates with NGAL and creatinine in septic patients. Therapeutic target – miR-155 inhibition alleviates kidney injury in sepsis (reduces cytokines, increases SOCS1); nanocarriers are in development for targeted anti-miR-155 delivery to the kidney.
miR-210	Associated with hypoxia and mitochondrial dysfunction. Upregulated in S-AKI (hypoxia-induced); shifts cellular metabolism toward anaerobic pathways and may aid hypoxia adaptation. High levels reflect tissue hypoxia and injury severity.	Indicator of hypoxic injury. Prognostic biomarker – plasma miR-210 is an independent predictor of outcome in AKI; combined with other markers, it improves mortality risk stratification. Potential target for modulating hypoxia responses; theoretically, reducing miR-210 could limit maladaptive hypoxic responses.
miR-494	Supports renal regeneration, inhibits apoptosis.	Therapeutic target for regeneration.
miR-192	Associated with tubular injury and inflammation.	Early diagnostic biomarker.
miR-23a-3p	Modulates oxidative stress and inflammation. Downregulated in S-AKI; normally anti-inflammatory – lowers NF-κB activity (targets FKBP5) and reduces apoptosis (targets Wnt5a/Egr1). Loss of miR-23a-3p in sepsis contributes to uncontrolled inflammation.	Diagnostic marker (in combination panels); Therapeutic target – restoring miR-23a-3p in sepsis models reduces renal injury. Could also prevent progression to chronic damage/fibrosis by modulating Wnt signaling. Its serum reduction helps differentiate sepsis patients with vs without AKI.
miR-10a-5p	Role in S-AKI under investigation. Implicated in sepsis pathophysiology. Supports endothelial protection and angiogenesis	Prognostic biomarker. Combined with miR-29a, it strongly predicts 28-day survival, outperforming individual markers. Vascular endothelium protection – potential therapeutic target
miR-22-3p	Anti-inflammatory, cytoprotective microRNA. Downregulated in S-AKI; targets HMGB1 and PTEN to limit NF-κB signaling and apoptosis. Its deficiency leads to excessive inflammation and cell death.	Early warning and prognostic biomarker (low levels signal higher AKI risk and worse survival). Therapeutic target- miR-22-3p mimics in septic models suppress inflammation and apoptosis, making it a candidate for nephroprotective therapy. Vascular endothelium protection – potential therapeutic target.
miR-106a	Pro-inflammatory and pro-apoptotic (elevated in sepsis). Targets thrombospondin-2 (THBS2) and possibly other genes, contributing to endothelial dysfunction and tubular injury. Inhibition in vitro reduces LPS-induced IL-6, TNF-α and apoptosis.	Therapeutic target (endothelial protection). Anti-miR-106a treatment in septic models protects the kidney from injury. Also proposed as a diagnostic marker – serum miR-106a is higher in sepsis patients with AKI compared to those without.

Note: miR-146a and miR-146b have similar functions and are combined here for clarity. The effects and values listed are derived from experimental and clinical studies (see references).

Endothelial cells during sepsis express elevated levels of adhesion molecules, which facilitates the attachment of neutrophils and platelets to the vessel wall. The combination of reduced renal blood flow, microthrombosis, and increased vascular permeability leads to tissue edema and severe microcirculatory disturbances, exacerbating renal ischemia and injury. Microvascular dysfunction is closely intertwined with the other pathological mechanisms— inflammation and oxidative stress damage the endotheli-

um, and ischemia-reperfusion events generate additional inflammatory and oxidative injuries.

In summary, S-AKI is a multifactorial condition: inflammatory hyperstimulation, cell apoptosis, oxidative stress, and microvascular disturbances act synergistically to damage the kidney tissue. The following sections examine how microRNAs influence these key pathogenetic factors, as well as their potential for diagnosis and therapy.

## Role of microRNAs in the pathogenesis of S-AKI

MicroRNAs have a wide array of target genes and therefore can modulate numerous pathogenetic pathways in septic kidney injury, including inflammatory signaling, apoptosis, oxidative stress, endothelial function, etc. Depending on which genes they regulate, a given miRNA can exert either injurious (pro-pathogenic) or protective effects in S-AKI. Below we discuss some of the most studied microRNAs and their influence on key mechanisms.

### miR-155

MicroRNA-155 is one of the most important pro-inflammatory microRNAs. During sepsis and S-AKI, miR-155 expression rises significantly, and high miR-155 levels are associated with more severe kidney injury. miR-155 suppresses negative regulators of inflammatory signaling (such as SOCS1), thereby promoting NF- $\kappa$ B activation and excessive cytokine production. It also exacerbates tubular cell apoptosis by targeting anti-apoptotic genes like Bcl-2 and SIRT1. In a mouse sepsis model, inhibiting miR-155 (via an antagomir) led to reduced TNF- $\alpha$  and IL-6 levels, increased SOCS1 expression, and significantly alleviated kidney injury. These findings indicate that miR-155 amplifies inflammation and apoptosis in S-AKI and that its suppression may be protective.<sup>[5]</sup>

### miR-146a/miR-146b

These miRNAs (from the same family) are induced as part of the negative feedback regulation of the TLR4/NF- $\kappa$ B pathway. They target key adaptor molecules like IRAK1 and TRAF6, thereby suppressing excessive inflammatory responses. In the context of septic kidney injury, high levels of miR-146 generally correlate with dampened inflammation. For instance, in kidney epithelial cells (HK-2), a miR-146b mimic suppresses NF- $\kappa$ B activation and reduces the production of inflammatory cytokines. In animal models, up-regulating miR-146a has shown protective effects: in a septic kidney injury model, treatment with dexmedetomidine increased miR-146a expression, which in turn decreased oxidative stress and inflammation and improved renal function. Similarly, mesenchymal stem cell-derived exosomes enriched with miR-146b suppressed IRAK1 expression and significantly improved the survival of septic mice while protecting the kidneys. These findings underscore the anti-inflammatory, protective role of miR-146 in S-AKI.<sup>[6]</sup>

### miR-21

This is one of the most studied microRNAs in kidney injury, but it shows contradictory effects in sepsis. On one hand, some studies indicate that overexpression of miR-21 during sepsis prolongs kidney dysfunction and exacerbates tubular cell apoptosis. Elevated kidney miR-21-3p caused

cell cycle arrest (affecting the AKT/CDK2/FOXO1 pathway) and apoptosis progression in mice with LPS-induced AKI. On the other hand, several studies report a protective effect of miR-21: it has been shown that miR-21 can reduce apoptosis and inflammation by targeting PTEN (thus activating the AKT survival pathway) and PDCD4 (thereby suppressing NF- $\kappa$ B). For example, delivering an miR-21 mimic in a septic model resulted in lower levels of inflammatory cytokines and less structural damage to the kidney. Conversely, the absence of miR-21 has been linked to more severe injury in sepsis. These conflicting results suggest that the effect of miR-21 is context-dependent—different signaling pathways, cell types, or stages of injury might alter its function. Further research is needed to determine whether miR-21 exerts a net protective or harmful role in S-AKI.<sup>[7,8]</sup>

### miR-210

Known as a “hypoxic” microRNA, its expression is driven by HIF-1 under low oxygen conditions. Sepsis often causes tissue hypoxia; accordingly, miR-210 is significantly elevated in S-AKI, both in kidney tissue and in the circulation. miR-210 is thought to participate in metabolic reprogramming toward anaerobic metabolism and adaptation to hypoxia. Clinically, plasma miR-210 levels correlate with the severity of acute injury—in a study of critically ill patients, plasma miR-210 was an independent predictor of survival in AKI. In another cohort of septic patients, miR-210 was among the most upregulated miRNAs in those who developed AKI, and the combined measurement of miR-210 with other markers achieved high sensitivity (~81%) and specificity (~81%) for early detection of S-AKI. These findings suggest that miR-210 not only reflects the hypoxia-driven pathophysiology and mitochondrial dysfunction but may also hold prognostic value in septic kidney injury.<sup>[9]</sup>

### miR-22-3p

MicroRNA-22-3p is an anti-inflammatory and cytoprotective microRNA that is decreased in septic AKI. Under normal conditions, miR-22-3p restrains inflammation and apoptosis by targeting factors such as HMGB1 (an alarmin that activates TLR4/NF- $\kappa$ B) and PTEN (a negative regulator of the AKT pathway). In a septic model, reduced miR-22-3p expression leads to hyperactivation of NF- $\kappa$ B inflammatory signaling and increased apoptosis, whereas delivery of a miR-22 mimic has the opposite effect—it inhibits PTEN, enhances pro-survival AKT/mTOR signaling, and lowers cytokine release. Clinical data support its importance: low serum and urinary miR-22-3p levels in septic patients are associated with higher AKI risk and lower 28-day survival. For this reason, miR-22-3p is considered a potential early warning and prognostic biomarker, as well as a possible therapeutic target—boosting its activity might protect the kidneys in sepsis.

### miR-23a-3p

MicroRNA-23a-3p is another protective microRNA, whose expression declines in S-AKI. Normally, miR-23a-3p helps maintain an anti-inflammatory balance: it suppresses the expression of the protein FKBP5 (a cofactor needed for full activation of glucocorticoid receptors and NF- $\kappa$ B), thus limiting the inflammatory response. It also targets Wnt5a, a component of the Wnt/ $\beta$ -catenin pathway associated with kidney injury and fibrosis. In vitro, LPS exposure was shown to reduce miR-23a-3p levels in renal epithelial cells, leading to increased FKBP5 expression, NF- $\kappa$ B activation, and release of IL-6 and IL-8. Overexpression of miR-23a-3p (or inhibition of FKBP5) suppressed this inflammatory response and decreased apoptosis. In a sepsis model, restoring miR-23a-3p reduced kidney damage, confirming that it exerts protective effects through broad anti-inflammatory actions.<sup>[10]</sup>

### miR-16-5p

An example of a microRNA that exacerbates injury through its effects on apoptosis. miR-16-5p is upregulated in septic AKI and contributes to the inflammatory response and cell death by targeting Bcl-2—a key anti-apoptotic protein. By suppressing Bcl-2, miR-16-5p lowers the threshold for apoptosis in tubular cells, leading to more pronounced LPS-induced inflammation and cell death. Blocking miR-16-5p (with an antagonist) produces the opposite effect: it restores Bcl-2 levels and limits inflammation, thereby protecting the cells. Similar outcomes have been observed with inhibition of other pro-apoptotic miRNAs like miR-543 and miR-34b-5p, which also target members of the Bcl-2 family or related molecules.<sup>[11]</sup>

### miR-26a-5p

This is an interesting case of a microRNA that is induced by the inflammatory process itself and acts as an endogenous protective mechanism. In an in vivo sepsis model, miR-26a-5p levels rose in the kidneys in an NF- $\kappa$ B-dependent manner, and this miRNA targeted and suppressed IL-6 expression, thereby easing inflammation. miR-26a-5p also targets CHAC1 (a pro-oxidative factor) and reduces oxidative stress in damaged cells. Blocking exosome release (which retains more miR-26a-5p within cells) further enhanced this protective effect, resulting in lower inflammation and less fibrosis in a proteinuria model. Due to its multiple protective actions (anti-IL-6, anti-oxidative, anti-fibrotic), miR-26a-5p is a potential therapeutic target for bolstering endogenous defense mechanisms in S-AKI.

### Other microRNAs

The pathogenesis of S-AKI involves a complex network of gene regulators, and many additional miRNAs are implicated in various aspects. For example, miR-106a (which is

elevated in sepsis) promotes inflammation and apoptosis by targeting the anti-angiogenic factor THBS2 and likely contributes to endothelial dysfunction. miR-150-5p and miR-181a are involved in JAK/STAT signaling, and their downregulation in S-AKI is associated with increased oxidative stress. miR-128-3p has a dual effect—some studies identify it as pro-inflammatory (stimulating NF- $\kappa$ B and cytokine production), while others find it to be anti-inflammatory (when overexpressed, it suppresses the LPS response via TGF $\beta$ R2). miR-132-3p protects against LPS-induced AKI in mice by reducing the expression of KIM-1 (HAVCR1), a marker of tubular injury. miR-21-5p (when secreted by endothelial progenitor cells in exosomes) improves the condition of the renal endothelium during sepsis by targeting the transcription factor RUNX1, thereby protecting the microcirculation and reducing capillary damage. This wide array of microRNAs and their targets (inflammatory mediators, pro- and anti-apoptotic proteins, antioxidant factors, signaling kinases, etc.) highlights the complexity of gene regulation in S-AKI. MicroRNAs form a regulatory network that largely determines whether certain pathological processes (such as inflammation or apoptosis) are amplified or suppressed. Understanding this network opens up opportunities for new diagnostic approaches (by monitoring miRNA profiles) and for therapeutic interventions (by targeting key microRNAs, as discussed below).

## MicroRNAs as biomarkers for S-AKI

Early diagnosis of acute kidney injury in sepsis is crucial, as timely treatment can improve outcomes. Traditional indicators—serum creatinine and urine output—are late and insufficiently sensitive markers. In the search for more reliable early biomarkers, researchers have turned their attention to circulating microRNAs. miRNAs are ideal candidates for noninvasive biomarkers because they are detectable as stable molecules in low quantities in blood, urine, and other fluids and can be measured with highly sensitive methods (PCR-based techniques).

Accumulating clinical data suggest that certain microRNAs can aid in the early detection of S-AKI and even in outcome prediction. For example, one study in children with sepsis showed that serum miR-21-3p was significantly elevated in those who developed AKI, and measuring it in combination with creatinine, cystatin C, and KIM-1 allowed prediction of AKI with 97% sensitivity and 91% specificity. Another study found that in septic patients, urinary miR-452 increases very early, even before the onset of kidney dysfunction or tissue damage. Urinary miR-452 levels distinguished patients with S-AKI from those without AKI with ~87% sensitivity, outperforming the traditional composite cell-cycle arrest marker [TIMP-2]\*[IGFBP7]. Thus, miR-452 appears to be an early urinary biomarker for septic kidney injury.

Several microRNAs have also been proposed as prognostic markers. As mentioned, low levels of miR-22-3p in serum or urine correlate with worse 28-day survival in patients with sepsis and AKI. Conversely, increased levels of some microRNAs may reflect compensatory mechanisms or the severity of injury; for example, miR-210 and miR-494 have been identified as two of the most strongly upregulated miRNAs in the plasma of patients with S-AKI, and their concentrations show good diagnostic performance (sensitivity ~81% for miR-210) and also correlate with disease outcome. On the other hand, miR-205, which is decreased in S-AKI, has demonstrated high specificity (~90%) for distinguishing patients with and without AKI. This multi-marker approach using a panel of several miRNAs improves accuracy; for instance, combined measurement of miR-29a and miR-10a-5p has greater prognostic value than measuring either alone or than conventional markers (Cys-C, creatinine, KIM-1) for predicting 28-day survival.

In addition to blood, urinary microRNAs are also being investigated as a noninvasive “liquid biopsy” of the kidney. MiR-376b is a sensitive urinary indicator that has been shown to correlate inversely with serum creatinine and urea, with levels sharply declining in patients with septic AKI. Although its sensitivity (~65%) is moderate, miR-376b outperforms some established biomarkers and provides additional information. Similarly, miR-574-5p is decreased in the plasma of septic patients who subsequently develop AKI, making it a candidate for early warning.

Overall, over 15 different microRNAs have been proposed as biomarkers for septic kidney injury. Some of them are summarized in **Table 1**. Despite the promising results, it should be noted that these biomarkers still need validation in larger and more heterogeneous patient cohorts before they can enter clinical practice. Standardization of pre-analytical handling and normalization is needed (since miRNA levels can vary with sample collection and analysis methods). Nonetheless, current data indicate that microRNAs offer a new class of sensitive and specific indicators for early diagnosis and prognosis of S-AKI, potentially enabling earlier intervention and personalized monitoring of patients.

## MicroRNAs as therapeutic targets in S-AKI

The lack of a specific therapy to prevent the progression of S-AKI remains a serious challenge. Standard approaches, such as infection control (antibiotics), hemodynamic stabilization (fluids, vasopressors), and supportive dialysis, are supportive measures and do not always prevent severe kidney damage. In this context, microRNAs have emerged as promising new therapeutic targets, since modulating them directly or indirectly can affect the key pathogenetic mechanisms. The idea is that by inhibiting “harmful” miRNAs (e.g., with antagonist oligonucleotides) or introducing missing/protective miRNAs (via miR mimics), the balance can be tilted toward tissue protection.

Initial direct evidence for the therapeutic value of this approach comes from studies in animal models of sepsis. For example, in mouse models of S-AKI, suppression (via antagonists) of several pro-injury miRs—miR-155, miR-106a, miR-30b, and miR-214-5p—led to substantial improvements in kidney function and histology compared to untreated controls. Inhibiting these miRNAs reduced inflammatory infiltrates, apoptosis, and tubular necrosis, demonstrating that they are key mediators of injury. Conversely, raising the levels of certain protective microRNAs also showed a beneficial effect: it has been shown that pre-activation of specific miRNA pathways renders the kidneys more resistant to sepsis. For instance, pre-treating animals with dexmedetomidine, as mentioned earlier, works in part by inducing miR-146a, which is a component of the protective mechanism against inflammation and oxidative stress. Another study showed that ginkgolide A—a natural product with anti-inflammatory properties—protects the kidney in sepsis partly by modulating the expression of specific microRNAs related to the NF- $\kappa$ B pathway. Propofol (an anesthetic) has also demonstrated a renoprotective effect in sepsis, which is mediated by changes in the expression profile of several miRNAs. Interestingly, some experimental strategies to prevent injury, such as remote ischemic preconditioning (e.g., periodic limb ischemia via a tourniquet) or xenon administration, protect the kidneys during sepsis specifically by upregulating endogenous protective microRNAs like miR-21. This suggests that even without directly delivering synthetic miRNAs, several therapeutic approaches exert their effects via regulating miRNA levels in the body.

One of the main obstacles to the clinical application of miRNA-based therapies is the specific delivery of the therapeutic molecules to target cells in the kidney, with minimal side effects. Progress is being made in this area—nano-capsules and vectors are being developed to deliver anti-miR oligonucleotides or miR mimics directly to kidney tissue. For example, nanoparticles have been created that release miR-155 inhibitors into inflamed kidneys in a controlled (pH-sensitive) manner. Another approach involves bioengineered exosomes targeted to renal epithelium, loaded with a given therapeutic microRNA. These technologies are still in preclinical stages, but they outline a new platform for targeted treatment of S-AKI through precise gene regulation.

In summary, targeting microRNAs offers a dual therapeutic potential: (1) limiting damaging processes (inflammation, apoptosis, oxidative stress) by inhibiting pro-injury miRNAs; and (2) enhancing natural defense mechanisms by delivering beneficial miRNAs. Early evidence from animal experiments is encouraging – correcting even a single microRNA can significantly improve septic outcomes at the kidney level. However, these approaches still need to be investigated thoroughly for safety (potential off-target effects, vector immunogenicity) and efficacy in humans. Combining miRNA-based therapies with conventional measures (antibiotics, anti-inflammatory agents) will likely yield the best results. **Table 1** above briefly lists several key microR-

NAs in S-AKI, along with their main effects and prospects for clinical application.

## Conclusion

Sepsis-associated acute kidney injury is a serious complication of sepsis that significantly worsens patient outcomes. Recent advances in molecular biology have revealed that microRNAs play a central role in regulating gene expression in S-AKI and can explain some of the observed pathological phenomena. MicroRNAs act as fine “switches” of inflammatory and cellular signaling pathways, and their dysregulation contributes to inflammation, apoptosis, oxidative stress, and microvascular disturbances in the injured kidneys. At the same time, the profile of circulating miRNAs reflects the extent of injury, making them valuable biomarkers for early diagnosis and prognosis.

Accumulated experimental data suggest that therapeutic modulation of microRNAs could be a novel approach to prevent or treat S-AKI—either by suppressing key pro-injury miRNAs or by administering protective ones. The challenges to clinical application include ensuring specific delivery to the kidneys, avoiding side effects, and confirming efficacy in humans. In the near future, larger clinical studies are expected to validate the diagnostic value of candidate miRNAs and to evaluate the safety of miRNA-targeted therapies. With the development of nanotechnology and gene therapy, the emergence of new drugs that selectively correct the disturbed miRNA network in sepsis is becoming a realistic prospect.

The outlook for this approach is promising—miRNA-based interventions could complement standard therapies, providing more precise control over pathogenetic mechanisms. Thus, in the future it may be possible not only to recognize S-AKI at the earliest stage through its microRNA “signature,” but also to intervene therapeutically at the molecular level to improve outcomes for patients. Additional research is required to realize this potential, including larger in vivo trials, optimization of dosages and delivery methods, and a deeper understanding of the complex interactions among different miRNAs. In conclusion, microRNAs stand out as an innovative diagnostic and therapeutic lever in septic kidney injury, whose full application remains to be realized in the coming years.

## Conflict of interest

The authors declare that they have no conflict of interest.

## Ethical statements

- The authors declared that no clinical trials were used in the present study.
- The authors declared that no experiments on humans or

human tissues were performed for the present study.

- The authors declared that no informed consent was obtained from the humans, donors or donors’ representatives participating in the study – **not applicable**.
- The authors declared that no experiments on animals were performed for the present study.
- The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

## Use of AI

Not applicable.

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## Author contributions

GDN: conceptualization, literature review, writing—original draft, data interpretation, final approval of the manuscript; DGN: clinical input, critical revision of the manuscript, final approval; MN: molecular biology and physiology consultation, review and editing, final approval; ChS: anesthesiology and critical care perspective, scientific supervision, final approval.

## Data availability

Not applicable

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