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Sepsis-Associated Acute Kidney Injury in Adults: Mechanistic Heterogeneity, Dynamic Risk Stratification, and the Path Toward Precision Care

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Abstract: Sepsis-associated acute kidney injury (SA-AKI) is a common, high-risk, and biologically heterogeneous syndrome in critically ill adults. Building on the 2023 Acute Disease Quality Initiative consensus and major reviews published in 2024 and 2025, this narrative update synthesizes evidence through July 15, 2026 and advances three clinically oriented principles. First, incident SA-AKI should be anchored to sepsis onset, whereas progression, persistence, recovery, and post-AKI acute kidney disease should be anchored to each patient's AKI onset. Second, biomarkers and prediction models should be matched to the clinical question and sampling window rather than ranked by area under the curve alone. Third, prognostic enrichment, which identifies patients at high absolute risk, must be distinguished from predictive enrichment, which identifies differential treatment benefit. Contemporary pathobiology extends beyond systemic hypotension and renal ischemia to include macro-microcirculatory uncoupling, venous congestion, endothelial glycocalyx injury, immunothrombosis, mitochondrial dysfunction, metabolic reprogramming, regulated cell death, and maladaptive repair. Urinary extracellular-vesicle complement receptor 1, multi-omics panels, cell-cycle-arrest and endothelial biomarkers, and explainable machine-learning models are promising, but most remain research tools requiring assay standardization, independent validation, strict temporal separation of predictors and outcomes, and prospective clinical-impact evaluation. Supportive care remains the foundation of management. Fluid amount and composition, perfusion targets, medication safety, and kidney replacement therapy should be individualized according to physiology and kidney trajectory; neither routine restrictive fluid strategies after initial resuscitation nor accelerated kidney replacement therapy without emergency indications has improved survival in unselected populations. Progress toward precision care will require reproducible treatment-response phenotypes, prespecified interaction testing, and risk tools linked to feasible interventions that improve patient-centered outcomes.

Keywords: Acute Kidney Injury; Biomarkers; Precision Medicine; Sepsis.

1. Introduction

Sepsis-associated acute kidney injury (SA-AKI) is a common and clinically consequential complication of sepsis. Reported incidence varies with case mix, baseline-creatinine ascertainment, urine-output availability, and timing definitions, but across cohorts SA-AKI is consistently associated with higher short-term mortality, greater use of kidney replacement therapy (KRT), prolonged critical illness, and increased risk of subsequent acute kidney disease (AKD) and chronic kidney disease (CKD) [2–5]. SA-AKI is not a single pathological entity; it is a syndrome shaped by infection burden, host response, hemodynamic instability, preexisting kidney reserve, drug exposure, and organ-support practices. The 2023 ADQI consensus defined SA-AKI as AKI occurring within 7 days after sepsis onset using Sepsis-3 and KDIGO criteria and distinguished early onset (within 48 hours) from late onset (more than 48 hours to 7 days) without changing the core definition [2]. Major reviews published in 2024 and 2025 subsequently emphasized enrichment, subphenotyping, clinical trials, and the broader mechanistic, diagnostic, therapeutic, and prognostic landscape [1,45].

These prior syntheses establish the foundation for the present review, but several developments reported since their literature searches require focused appraisal. Mechanistic studies now connect endothelial-barrier failure, TREM-1/NLRP3 activation, kidney-derived mitochondrial DNA signaling, spatially heterogeneous mitochondrial injury, and stress-induced senescence. Diagnostic research increasingly targets persistent AKI, recovery, post-AKI AKD, and late outcomes, while urinary extracellular vesicles, multi-omics signatures, and externally validated machine-learning models raise new questions about assay feasibility, target leakage, transportability, and clinical impact. The central challenge is therefore no longer simply to identify another associated marker, but to determine which biological signal is informative at a defined time point, for a defined clinical decision, and with a feasible downstream action.

This adult-focused narrative review therefore makes three specific contributions. First, it applies a dual-time-anchor framework: incident SA-AKI is anchored to sepsis onset, whereas progression, persistence, recovery, and post-AKI AKD are anchored to each patient's AKI onset. Second, it organizes biomarkers and prediction models by intended clinical question and sampling window rather than by discrimination alone. Third, it distinguishes prognostic enrichment from predictive enrichment and specifies the evidence required before a biological or data-driven phenotype can guide treatment. Established supportive care is separated from investigational precision strategies, and mechanistic discovery, prognostic association, external validation, clinical utility, and evidence capable of changing practice are explicitly differentiated.

2. Literature Search Strategy

This narrative review was informed by searches of

PubMed/MEDLINE, Embase, Web of Science, the Cochrane Library, ClinicalTrials.gov, and major journal and guideline websites through July 15, 2026. Controlled vocabulary and free-text terms were combined for sepsis-associated acute kidney injury, persistent acute kidney injury, acute kidney disease, kidney recovery, microcirculation, endothelial glycocalyx, pyroptosis, ferroptosis, mitochondrial DNA, metabolic reprogramming, urinary extracellular vesicles, C-C motif chemokine ligand 14, tissue inhibitor of metalloproteinases 2, insulin-like growth factor-binding protein 7, machine learning, subphenotype, kidney replacement therapy, and clinical trial. Reference lists of key consensus reports, reviews, randomized trials, and recent biomarker studies were also examined to identify additional eligible reports. Priority was given to consensus reports, guidelines, randomized trials, multicenter cohorts, externally validated prediction studies, systematic reviews, and pivotal mechanistic studies published from 2019 to 2026. The scope focused primarily on adult critically ill populations; pediatric studies were not systematically reviewed. Conference abstracts, trial registries, and public-review drafts were used only to describe ongoing research and were not treated as confirmatory evidence. Because the review was not preregistered and did not include duplicate independent screening or formal risk-of-bias assessment, it should not be interpreted as a systematic review or meta-analysis.

3. Evolving Concept of Sepsis-Associated Acute Kidney Injury

The conventional explanation of SA-AKI centered on systemic vasodilation, reduced effective circulating volume, renal hypoperfusion, and ischemia. Experimental and clinical observations now show that kidney injury may occur even when total renal blood flow is preserved or increased. Regional flow heterogeneity, capillary intermittency, impaired oxygen extraction, and cellular metabolic suppression may therefore be more important than global oxygen delivery in a substantial subgroup [3–5]. Restoring blood pressure remains necessary in shock, but it does not guarantee restoration of the renal microcirculation or cellular energetics.

Heterogeneity is also evident at the bedside. Urinary proteomic profiling published in 2024 identified distinct immunological patterns corresponding to clinically defined SA-AKI subphenotypes, including profiles enriched for repair and regeneration versus immune activation [6]. Previously described AKI subphenotypes differ in inflammatory signatures, kidney recovery, mortality, and apparent response to vasopressin [7–9]. These findings support noninvasive molecular phenotyping as a potential bridge between pathobiology and clinical stratification, although reproducibility and prospective treatment-interaction testing remain essential.

4. Updated Pathobiology

4.1. Uncoupling Between the Macrocirculation and Renal Microcirculation, and Venous Congestion

Early hypotension can reduce renal perfusion pressure, but mean arterial pressure, cardiac output, and renal microvascular flow are not linearly related. The cortex and medulla differ in oxygen supply, energy demand, and vascular regulation. Capillary no-flow, shunting, abnormal red-cell transit, and impaired oxygen utilization can produce regional hypoxia despite apparently adequate systemic hemodynamics. Concurrently, elevated renal venous pressure, right ventricular dysfunction, and intra-abdominal hypertension may reduce effective filtration pressure and increase interstitial pressure [3–5]. This combination helps explain persistent oliguria or rising creatinine after systemic blood pressure has normalized and argues against routinely escalating vasopressors solely to achieve a higher pressure target.

4.2. Endothelial Glycocalyx Injury and Immunothrombosis

The endothelial glycocalyx maintains barrier integrity, limits leukocyte adhesion, restrains coagulation, and transduces shear stress. During sepsis, matrix metalloproteinases, hyaluronidases, reactive oxygen species, and inflammatory cytokines promote glycocalyx shedding. The resulting endothelial hyperpermeability causes albumin leakage and interstitial edema, while exposed adhesion molecules, von Willebrand factor release, and platelet activation facilitate intrarenal immunothrombosis.

A 2026 translational study integrating kidney transcriptomics, human glomerular endothelial cells, and a cecal ligation and puncture model implicated the TLR4-NF-κB-TNF-α-MMP axis in glycocalyx and intercellular-junction injury [10]. Dexamethasone suppressed this pathway and improved microcirculatory perfusion in experimental systems. These findings strengthen the endothelial-barrier mechanism but do not establish dexamethasone as a kidney-specific treatment for patients with SA-AKI. Clinical biomarker data provide complementary evidence: a 2025 study reported that a panel combining urinary [TIMP-2]·[IGFBP7], angiopoietin-2, and procalcitonin discriminated SA-AKI more effectively than a conventional clinical model [11]. However, the small, single-center cohort and internal validation limit the reproducibility of proposed thresholds across settings.

4.3. Immune Dysregulation, Pyroptosis, Autophagy, and Neutrophil Extracellular Traps

Pathogen-associated and damage-associated molecular patterns activate toll-like receptors, triggering receptor expressed on myeloid cells 1 (TREM-1), and the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome. Caspase-1 activation cleaves gasdermin D and promotes interleukin-1β and interleukin-18 release. Pyroptotic cells then release additional intracellular danger signals, amplifying inflammation.

A 2026 study showed that genetic deletion of TREM-1 reduced experimental kidney injury, inflammasome activation, gasdermin D cleavage, and circulating cytokines; pharmacological modulation further supported a TREM-1-NLRP3 inflammasome axis [12]. These findings support a mechanistic link between TREM-1 activation and NLRP3-mediated pyroptosis. Inflammasome activation is also coupled to mitochondrial injury, autophagic flux, and metabolic state. Moderate early mitophagy may remove damaged mitochondria and reduce danger-signal release, whereas lysosomal dysfunction and blocked autophagic flux during prolonged sepsis may aggravate injury. Current evidence remains preclinical, and no validated companion

biomarker or kidney-specific treatment has been established.

Neutrophil extracellular traps (NETs) provide another link between innate immunity and microvascular obstruction. Their DNA, histones, and granule proteins can injure the endothelium and tubules, whereas interactions with platelets promote immunothrombosis. Deoxyribonuclease, peptidyl arginine deiminase 4 inhibition, and anti-histone strategies remain largely preclinical. Because these pathways also contribute to pathogen containment, successful translation will require careful selection of infection stage, immune phenotype, and treatment timing [1,5].

4.4. Mitochondrial Injury and Metabolic Reprogramming

Tubular epithelial cells depend heavily on oxidative phosphorylation and fatty-acid oxidation. Sepsis can disrupt the electron-transport chain, reduce mitochondrial membrane potential, increase mitochondrial fission, suppress peroxisome proliferator-activated receptor-α and related metabolic programs, and decrease ATP generation. Cells may shift toward less efficient glycolysis while accumulating toxic lipid intermediates.

Spatial proteomics published in 2025 showed that mitochondrial injury is not uniform along the nephron. Different tubular segments displayed distinct abnormalities in oxidative phosphorylation, mitochondrial quality control, and related pathways [14]. This spatial heterogeneity helps explain why whole-kidney average expression may obscure clinically relevant cell populations. Damaged mitochondria also release mitochondrial DNA (mtDNA). A 2025 study linked kidney-derived mtDNA to systemic interleukin-6 release and found elevated circulating mtDNA in patients with SA-AKI [13]. The study connects local kidney injury with systemic inflammation, although tissue-of-origin specificity and assay standardization remain unresolved.

4.5. Ferroptosis and Interacting Forms of Regulated Cell Death

Ferroptosis is driven by iron-dependent lipid peroxidation and involves phospholipid remodeling, glutathione depletion, and inadequate glutathione peroxidase 4 (GPX4) activity. Numerous animal studies report protection through nuclear factor erythroid 2-related factor 2, heme oxygenase-1, GPX4, iron-homeostasis, or lipid-peroxidation pathways. However, many experiments use high-dose lipopolysaccharide or natural compounds with uncertain pharmacology. Pyroptosis, apoptosis, necroptosis, and ferroptosis may coexist in different cells and phases of the same illness. A single cell-death inhibitor may therefore be ineffective when the dominant pathway or therapeutic window is mismatched [1,5].

4.6. Sublethal Injury, Cellular Senescence, and the Acute Kidney Injury-to-Chronic Kidney Disease Transition

Not all injured tubular cells die. Some lose polarity and transport function, undergo cell-cycle arrest, and develop a senescence-associated secretory phenotype (SASP). Temporary arrest may permit DNA repair, whereas persistent arrest promotes interleukin-6, transforming growth factor-β, capillary rarefaction, myofibroblast activation, and fibrosis.

A 2025 study implicated immediate early response 3 (IER3) in the transition from SA-AKI to CKD. IER3 suppressed mitochondrial translocation of peroxiredoxin 5, increased oxidative mitochondrial injury and stress-induced senescence, and aggravated chronic remodeling in experimental systems [15]. This work supports assessment of the quality and durability of kidney recovery rather than reliance on a single decline in serum creatinine; however, confirmation in human tissue and prospective cohorts is still required. Taken together, these findings support an interacting rather than linear model of SA-AKI: macro-microcirculatory uncoupling and venous congestion promote endothelial-barrier failure and immunothrombosis; immune activation, mitochondrial dysfunction, metabolic reprogramming, and regulated cell death then amplify tubular injury. Surviving cells may recover, remain arrested, or enter maladaptive repair, producing branching and non-mutually exclusive trajectories that include persistent AKI, post-AKI AKD, CKD, KRT, or death [1,3–5,10,12–15].

5. Diagnosis and Dynamic Risk Stratification

5.1. Functional Criteria and the Biomarker Framework

Serum creatinine and urine output remain the foundation of AKI diagnosis, staging, and treatment decisions [16]. A representative stable outpatient creatinine is preferable for baseline assessment; the admission value may already reflect AKI, whereas back-calculation from an assumed glomerular filtration rate can misclassify patients with CKD. Positive fluid balance may dilute serum creatinine, and creatinine trajectories become difficult to interpret after KRT. Urine output is influenced by diuretics, catheter management, hemodynamics, and KRT. ADQI therefore recommends integrating functional change with injury or stress biomarkers to identify subclinical injury and biologically distinct risk within the same clinical stage [17]. A large analysis showed that biomarker-positive, creatinine-negative subclinical injury carries clinically meaningful risk and supports biomarker-informed staging [18]. A KDIGO 2026 AKI/AKD document is currently available only as a public-review draft; its recommendations remain provisional and it should not be cited or described as a finalized guideline [19].

5.2. Competing Causes and Bedside Evaluation

SA-AKI should remain a syndromic diagnosis rather than a default explanation for every increase in creatinine during sepsis. Evaluation should consider urinary obstruction, drug-associated tubular or interstitial injury, glomerular disease, rhabdomyolysis, venous congestion or cardiorenal physiology, hepatorenal physiology, intra-abdominal hypertension, thrombotic microangiopathy, and other context-specific causes. Urinalysis and sediment examination, quantification of proteinuria or hematuria, creatine kinase and hemolysis testing when indicated, renal ultrasonography, and focused cardiac or venous-congestion assessment can identify alternative or coexisting processes and may change management [2,3,5,19].

5.3. Biomarkers Answer Different Clinical Questions

Neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18, and liver-type fatty-acid-binding protein (L-FABP) mainly reflect tubular injury. Cystatin C and proenkephalin more closely reflect filtration function. Urinary [TIMP-2]·[IGFBP7] reflects

tubular stress and cell-cycle arrest and is most relevant to short-term risk or subclinical injury in selected high-risk settings, whereas urinary C-C motif chemokine ligand 14 (CCL14) has been evaluated mainly for persistence among patients with established moderate-to-severe AKI.

Proenkephalin changed early in septic AKI in the Kidney in Sepsis and Septic Shock study [20]. Serial urinary [TIMP-2]·[IGFBP7] measurements were associated with progression to death, dialysis, or severe AKI in septic shock [21]. Urinary CCL14 has been externally validated for persistent severe AKI in heterogeneous critically ill populations with established KDIGO stage 2–3 AKI, not in a purely SA-AKI cohort [22]. Its performance and decision thresholds specifically within SA-AKI therefore require further confirmation. These biomarkers should not be ranked solely by area under the curve (AUC) without considering intended use. Early stress detection, etiologic discrimination, persistence prediction, KRT risk, and long-term prognosis are different tasks with different optimal sampling windows. A high-risk biomarker result does not itself establish that a biomarker-triggered treatment will improve outcomes. For clinical interpretation, incident SA-AKI should be anchored to sepsis onset: early cases occur within 0–48 hours and late cases first occur after 48 hours through day 7. After each patient's AKI onset, the first 48 hours are used to assess reversal or progression; persistence beyond 48 hours through day 7 indicates persistent AKI, whereas kidney abnormalities beyond day 7 through day 90 constitute the post-AKI AKD phase. Biomarkers and prediction tools should therefore be matched to the intended task and sampling window rather than ranked by AUC alone [2,16–28,42–44].

5.4. Urinary Extracellular Vesicles and Multi-Omics

Urinary extracellular vesicles carry membrane proteins, RNA, and metabolites derived from kidney cell populations and may reflect local pathology more directly than plasma biomarkers. A 2025 single-vesicle surface-proteomic study identified complement receptor 1 (CD35) expressed on urinary extracellular vesicles as a candidate biomarker. The reported AUC was 0.89 for SA-AKI in a validation cohort, 0.84 for subclinical injury in a prospective cohort, and 0.77 for persistent injury [23]. Clinical translation is limited by complex isolation methods, variation in urine processing, platform standardization, and weaker performance for mortality and AKD; CD35-positive urinary extracellular-vesicle testing should therefore be regarded as a research assay rather than a routine clinical test.

Multi-omics studies have likewise produced promising but preliminary signatures. A 2025 animal-to-human study developed a three-metabolite panel comprising inosine, creatine, and 3-hydroxybutyrate and reported an AUC of approximately 0.90 in a small clinical validation sample [24]. A 2026 single-center study combined untargeted metabolomics, feature-selection algorithms, machine learning, and in silico analyses to identify five early candidate metabolites [25]. Both studies suggest that metabolic disruption may precede overt creatinine elevation, but small samples, high feature-to-event ratios, and lack of independent external validation create substantial risk of overfitting.

5.5. Inflammatory, Endothelial, and Stress-Biomarker Panels

Combining biomarkers from complementary pathways may outperform single-marker strategies. A 2025 panel integrating tubular stress, endothelial dysfunction, and inflammation achieved an AUC of 0.898 in a cohort of 96 patients [11]. In a 2026 hybrid cohort of 211 patients, early serum S100A8/A9 was independently associated with SA-AKI. Its AUC was 0.721 alone, and addition to the Sequential Organ Failure Assessment (SOFA) score increased the AUC from 0.771 to 0.861; S100A8/A9 was not independently associated with 28-day mortality [26]. This early single-center finding illustrates that a candidate diagnostic or short-term risk marker may not necessarily provide independent prognostic information. Replication, assay standardization, and evaluation against clinically relevant comparators are required before routine use.

5.6. Explainable Machine Learning

Table 1. Clinical-question-oriented interpretation of selected diagnostic and risk-stratification tools in SA-AKI.

Tool	Best-matched question/window	Current clinical position
Creatinine + urine output	Diagnosis, staging, and serial trajectory assessment	Clinical standard; delayed or nonspecific and affected by baseline estimation, fluid balance, diuretics, and KRT.
[TIMP-2]·[IGFBP7]	Short-term tubular stress or subclinical injury, usually before overt functional decline	Adjunct in selected high-risk settings; not an etiologic test or a validated treatment-selection marker.
Urinary CCL14	Persistence after established KDIGO stage 2–3 AKI	Externally validated in heterogeneous ICU AKI; SA-AKI-specific thresholds and treatment benefit remain unproven.
CD35-positive urinary extracellular vesicles / multi-omics	Early molecular injury and biological phenotyping	Research assays; limited by processing, platform standardization, small samples, and overfitting risk.
Explainable machine learning	Dynamic 48-hour, 7-day, or persistence-risk estimation	External validation exists for some models; temporal leakage, calibration, transportability, workflow, and impact must be tested.
Molecular subphenotype	Potential predictive enrichment for fluids, vasopressors, or targeted therapy	Hypothesis-generating; requires a stable classifier and prospectively specified treatment-by-subphenotype interaction testing.

Note: AUC, area under the curve; AKI, acute kidney injury; CCL14, C-C motif chemokine ligand 14; IGFBP7, insulin-like growth factor-binding protein 7; KRT, kidney replacement therapy; TIMP-2, tissue inhibitor of metalloproteinases 2.

A 2025 multicohort study included 46,097 patients from four retrospective cohorts and one prospective cohort to estimate the risk of persistent SA-AKI. The final gradient-boosting model used AKI stage, 24-hour creatinine change, urine output, furosemide dose, body mass index, SOFA score, KRT, mechanical ventilation, lactate, blood urea nitrogen, prothrombin time, and age. Its AUC was 0.852 in the prospective cohort, slightly higher than that of urinary CCL14

(0.821) [27]. Because current AKI stage and KRT were among the predictors, the model is best interpreted as dynamic persistence-risk stratification after kidney injury has been recognized, rather than as pre-AKI prediction.

A separate model developed using the Medical Information Mart for Intensive Care IV database and externally validated in the eICU Collaborative Research Database and a Chinese hospital cohort estimated the risk of moderate-to-severe AKI at 48 hours and 7 days from data collected during the first 24 hours of intensive care [28]. External performance was lower than internal performance, with 48-hour AUCs of approximately 0.77–0.79, illustrating the importance of transportability across populations and settings. Both studies reported calibration, decision-curve analysis, and explainability. Nevertheless, strict temporal separation between predictors and outcomes is essential: variables measured near or within the outcome window, or variables that are components of the outcome definition, can create target or severity leakage. Clinical-impact trials should therefore test not merely whether an alert predicts deterioration, but whether a prespecified response—such as medication review, reassessment of fluid responsiveness and venous congestion, intensified monitoring, or specialist consultation—improves outcomes. Table 1 summarizes how selected tools should be interpreted according to intended use rather than AUC alone.

6. From Prognostic Risk to Treatment-Response Enrichment

6.1. Prognostic and Predictive Enrichment Are Different Questions

Prognostic enrichment identifies patients with a high absolute risk of an outcome regardless of which treatment they receive. Predictive enrichment identifies patients in whom the relative effect of one treatment differs from that in other patients. This distinction is clinically decisive. A high CCL14 concentration, severe AKI stage, or high model-predicted probability of persistent injury may identify a patient with poor prognosis, but it does not establish that accelerated KRT, blood purification, a particular vasopressor, or a mechanism-targeted drug will provide greater benefit. Similarly, statistical significance within one subgroup and nonsignificance within another do not prove treatment heterogeneity; a formal treatment-by-subphenotype interaction is required [45,46].

6.2. Current Evidence for Treatment-Response Heterogeneity

Earlier AKI subphenotype analyses suggested differential response to vasopressin [7]. A 2025 analysis found that previously identified molecular subphenotypes were detectable across sepsis trial cohorts and appeared to respond differently to fluid-resuscitation strategies [29]. These findings are biologically plausible and clinically important, but they arose from secondary analyses and remain vulnerable to multiplicity, classifier instability, missing biospecimens, and differences in timing relative to treatment. Urinary proteomics, endothelial-barrier studies, TREM-1/NLRP3 signaling, mitochondrial injury, senescence, CD35-positive urinary extracellular vesicles, and metabolite panels strengthen the biological basis for heterogeneity [6,10,12–15,23–25], yet most currently support prognosis or mechanism rather than treatment selection.

6.3. Evidence Required Before a Subphenotype Can Guide Care

A clinically usable treatment-response phenotype requires more than biological separation. The classifier should be reproducible across sites and assay platforms, available within the therapeutic window, and based on variables measured before randomization or treatment escalation. The intervention linked to the phenotype must be specific and modifiable, and the interaction hypothesis should be prespecified with adequate power. Analyses should account for death as a competing event and avoid conditioning on post-randomization variables. Patient-centered outcomes should include time to kidney recovery, KRT-free survival, MAKE90, post-AKI AKD, adverse treatment effects, and quality of life rather than creatinine change alone [45,46].

6.4. From Prediction to an Actionable Pathway

Risk information becomes actionable only when it is connected to a feasible care pathway and when acting on it improves outcomes. A low-risk result might support de-escalation of monitoring, whereas a high-risk result could trigger a standardized medication and nephrotoxin review, reassessment of perfusion and venous congestion, closer urine-output and electrolyte surveillance, or early nephrology input. More invasive or costly interventions, including biomarker-enriched blood purification or phenotype-guided vasopressor and fluid strategies, should remain within prospective trials until benefit and safety are demonstrated. This sequence preserves the distinction between better prediction and better care.

7. Therapeutic Strategies

7.1. Infection Control, Medication Safety, and Supportive Care

As of July 2026, no kidney-specific pharmacological therapy has been shown in a high-quality phase 3 trial to reduce mortality or the need for KRT in SA-AKI. Management therefore remains based on prompt antimicrobial therapy and source control, adequate oxygenation and perfusion, avoidance of unnecessary nephrotoxins, adjustment of medication doses to changing kidney function, and correction of life-threatening electrolyte, acid-base, and volume abnormalities [30]. Medication safety requires repeated reassessment rather than a single dose adjustment because serum creatinine lags behind changes in filtration, kidney function may recover rapidly, and KRT alters drug clearance. Antimicrobial underexposure is also harmful; dose reduction should therefore be balanced against infection severity, drug pharmacokinetics, residual kidney function, and the KRT modality. A kidney-protection bundle should specify actionable components, including cumulative nephrotoxin review, hemodynamic reassessment, medication-dose adjustment, therapeutic drug monitoring when available, and serial monitoring of kidney trajectory.

7.2. Fluid Management

Intravenous fluid may restore effective circulating volume but can also aggravate endothelial leakage, tissue edema, and venous congestion. Fluid management involves both amount and composition. Crystalloids remain first-line for resuscitation; current sepsis guidance suggests balanced crystalloids rather than 0.9% saline and recommends avoiding

hydroxyethyl starch [30]. In the SMART trial, balanced crystalloids modestly reduced major adverse kidney events in critically ill adults, and a prespecified sepsis analysis reported lower 30-day in-hospital mortality than with saline [47,48]. These findings support balanced crystalloids as a reasonable default, but they do not prove a kidney-specific treatment effect in established SA-AKI, and the choice of solution cannot compensate for excessive volume administration.

After initial resuscitation, the CLASSIC trial found that restriction of additional intravenous fluid in patients with septic shock did not reduce 90-day mortality [31]. In CLOVERS, an early restrictive strategy prioritizing vasopressors and a liberal-fluid strategy did not differ significantly in death before discharge home by day 90 [32]. These neutral population-level findings should not be interpreted as evidence that early resuscitation fluid is unnecessary. A more individualized approach distinguishes resuscitation, optimization, stabilization, and deresuscitation and integrates dynamic measures of fluid responsiveness, capillary refill, lactate trends, bedside ultrasonography, cumulative balance, and venous-congestion assessment. The ANDROMEDA-SHOCK trial demonstrated the feasibility of a peripheral-perfusion-targeted strategy, although capillary refill cannot replace comprehensive hemodynamic assessment [33]. Molecular heterogeneity in fluid response is a plausible target for future precision trials, but available secondary analyses remain hypothesis-generating [29].

7.3. Vasopressors and Individualized Perfusion Pressure

Norepinephrine remains the standard first-line vasopressor. A higher mean arterial pressure may be appropriate for selected patients with chronic hypertension, but it also increases catecholamine exposure and arrhythmia risk. The SEPSISPAM trial did not support a universally higher pressure target [34]. The VANISH trial did not show a significant overall increase in kidney-failure-free days with early vasopressin compared with norepinephrine [35]. Secondary molecular analyses suggest that treatment response may differ by AKI subphenotype [7], providing a rationale for prospectively stratified vasopressor trials.

7.4. Timing of Kidney Replacement Therapy

KRT should be initiated promptly for refractory hyperkalemia, medically refractory severe acidemia, pulmonary edema, uremic complications, or otherwise uncontrollable metabolic and volume demands. In patients with severe AKI but no emergency indication, AKIKI, IDEAL-ICU, and STARRT-AKI did not support routine accelerated initiation [36–38]. A delayed or standard strategy allowed many patients to avoid KRT, whereas accelerated initiation increased catheter exposure and, in some analyses, KRT dependence at 90 days among survivors. These trials were not restricted to SA-AKI, but sepsis was common; collectively, the findings support decisions based on complications, capacity-demand imbalance, and clinical trajectory rather than a single creatinine value or AKI stage.

In selected euvolemic and hemodynamically stable patients with early AKI, a standardized furosemide stress test may provide information about tubular functional reserve and the risk of progression [49]. It should not be used in patients with unresolved hypovolemia or urinary obstruction and should not serve as a stand-alone trigger for KRT. Persistent-injury models and urinary CCL14 may likewise identify patients more likely to require KRT, but CCL14 validation derives from heterogeneous critically ill cohorts with established stage 2–3 AKI rather than a purely SA-AKI population [22]. Prediction of KRT requirement is not equivalent to prediction of benefit from earlier KRT. A biomarker- or stress-test-guided timing strategy must improve patient-centered outcomes in a randomized trial before changing routine practice.

7.5. Targeted Therapies and Enrichment Designs

Recombinant human alkaline phosphatase dephosphorylates endotoxin and extracellular ATP. A phase 2 trial did not meet its primary 7-day endogenous creatinine-clearance endpoint but generated exploratory longer-term kidney and mortality signals [39]. The phase 3 REVIVAL trial enrolled approximately 650 patients. Twenty-eight-day mortality was 27.9% in both the ilofotase alfa and placebo groups, and the trial was stopped for futility with respect to the primary endpoint [40]. Exploratory signals in 90-day major adverse kidney events cannot supersede the neutral primary result.

The REVIVAL experience illustrates why biological plausibility and early-phase signals are insufficient. Enrollment may occur after the therapeutic window, biological subtypes may be mismatched, and mortality may compete with kidney endpoints. A randomized protocol published in 2025 uses urinary CCL14 to identify patients at high risk of persistent severe AKI before testing hybrid blood purification [41]. This represents an important enrichment strategy, but a protocol does not provide evidence of efficacy. Similar caution is required for experimental inhibition of inflammasomes, ferroptosis, NETs, and mitochondrial injury. A clinically defensible pathway is therefore sequential: confirm the temporal relationship to sepsis and assess competing causes; treat infection and correct hypoperfusion, venous congestion, and medication-related risks; monitor creatinine, urine output, and kidney trajectory; initiate KRT for accepted emergency indications; and reserve biomarker-enriched blood purification, molecularly guided fluid or vasopressor selection, and mechanism-targeted therapies for clinical trials.

8. Acute Kidney Disease Trajectories and Long-Term Outcomes

Acute kidney disease (AKD) encompasses acute or subacute functional or structural kidney abnormalities lasting less than 3 months and includes AKI within this broader duration-based framework. In patients with preceding AKI, persistent kidney dysfunction beyond day 7 and through day 90 is commonly described as the post-AKI AKD phase [42]. Patients may demonstrate rapid recovery, recovery followed by relapse, persistent dysfunction, or fluctuating recovery. A single serum creatinine measurement at discharge is therefore insufficient to characterize long-term kidney risk.

A 2025 cohort of 24,038 patients with sepsis characterized the incidence, trajectories, and outcomes of sepsis-associated AKD. Relapsing and persistent trajectories were associated with higher risks of 1-year mortality, KRT, and incident CKD than the recovery trajectory [43]. Earlier work likewise showed that early recovery after AKI is associated with better long-term outcomes, whereas incomplete or delayed recovery identifies a higher-risk population [44]. These trajectory

studies should be interpreted with caution because survivor bias, unequal creatinine-sampling frequency, and incomplete postdischarge data can influence trajectory assignment and outcome estimates.

Postdischarge care should be individualized according to AKI severity, preexisting CKD, recovery at discharge, albuminuria, KRT exposure, and ongoing medication risk. Follow-up should include serum creatinine or estimated glomerular filtration rate, urine albumin-to-creatinine ratio or protein assessment, blood pressure, volume status, and medication reconciliation. Patients with KDIGO stage 3 AKI, KRT exposure, persistent dysfunction, substantial proteinuria or hematuria, advanced preexisting CKD, recurrent AKI, or diagnostic uncertainty should be prioritized for early nephrology review. Risk-adapted reassessment of kidney function and markers of kidney damage by approximately 3 months is consistent with the ADQI AKD framework [42]. The KDIGO 2026 public-review draft also emphasizes post-AKI follow-up, but its recommendations remain provisional pending final publication [19]. Randomized evidence defining the optimal follow-up interval and the benefit of dedicated post-AKI clinics remains limited.

9. Discussion

9.1. Key Advances and Their Clinical Significance

This review advances three linked propositions. First, temporal definitions must be explicit: incident SA-AKI is anchored to sepsis onset, whereas persistence, recovery, and post-AKI AKD are anchored to AKI onset. Second, the value of a biomarker or model depends on the clinical question, index time, sampling window, calibration, transportability, and downstream action—not on AUC alone. Third, prognostic and predictive enrichment are not interchangeable. These principles explain why incident SA-AKI, persistent AKI, post-AKI AKD, and treatment-response phenotypes should not be collapsed into a single outcome and why a marker that predicts deterioration may still fail to improve care.

Most developments reported in 2025 and 2026 remain preclinical or at an early validation stage. High discrimination in a small case-control or single-center sample does not establish clinical utility, especially when feature selection precedes validation, calibration is omitted, predictor-outcome overlap is present, or assays require complex processing. Likewise, improvement in experimental creatinine or histology does not establish dose, therapeutic window, infection safety, or effectiveness in adults with sepsis. The field should therefore prioritize fewer, better-defined clinical questions and prospectively evaluate whether a test changes a decision that matters.

9.2. Barriers to the Clinical Translation of Targeted Therapies

Translation can fail because of delayed enrollment, biological mismatch, a narrow therapeutic window, competing mortality, assay turnaround time, or variability in source control, fluids, vasopressors, medications, and KRT. Outcome definitions may also inadequately account for death as a competing event or may reward transient creatinine changes without demonstrating durable kidney recovery. The neutral REVIVAL result underscores that exploratory subgroup findings or secondary kidney signals should not be treated as confirmatory evidence.

Future trials should use stable classifiers, define the index time before treatment allocation, specify the linked intervention, and test a prespecified treatment-by-phenotype interaction. Enrichment may improve trial efficiency, but overly narrow selection can reduce generalizability. Clinical-impact studies of prediction tools should compare a defined alert-response pathway with usual care and report adherence, unintended consequences, resource use, and patient-centered kidney outcomes [45,46].

9.3. Research Priorities

- Standardize the operational definition of sepsis onset, baseline creatinine, urine-output windows, correction for fluid dilution, handling of KRT, and classification of preexisting CKD.
- Validate biomarkers and prediction models across countries, hospitals, assay platforms, and urine-processing methods, with transparent calibration and prespecified thresholds.
- Define the prediction index time explicitly, ensure that predictors precede outcomes, and report missing-data handling, calibration, model updating, and potential target leakage.
- Move from prognostic clusters to treatment-response subphenotypes through prospectively stratified randomized trials, stable classifiers, adequate interaction power, and prespecified treatment-by-subphenotype tests rather than comparisons of subgroup-specific P values.
- Link electronic alerts to actionable pathways and evaluate whether nephrotoxin review, hemodynamic reassessment, intensified monitoring, or specialist consultation improves outcomes.
- Use dynamic, patient-centered endpoints, including persistent AKI, time to kidney recovery, KRT-free survival, MAKE90, AKD trajectories, quality of life, and readmission.
- Link single-cell and spatial-omics discoveries to measurable blood or urine companion biomarkers and to human-derived organoid or organ-on-chip models. Translation should proceed iteratively from mechanistic plausibility and a measurable companion biomarker, through standardized multicenter validation and externally validated prediction, to prospectively specified treatment-interaction testing and randomized clinical-impact trials. Preclinical studies establish plausibility but not patient benefit; single-center biomarker studies require standardized external validation; validated prediction models require trials of model-triggered care; reproducible molecular subphenotypes require prospective treatment-interaction testing; and randomized trials require implementation evaluation and long-term follow-up. Neutral or negative results should refine classifiers, thresholds, and trial design rather than be treated as terminal failures [17,22,27–29,41,45,46].

10. Conclusion

SA-AKI should be approached as a heterogeneous, time-dependent syndrome rather than a uniform consequence of renal hypoperfusion. Current care should emphasize timely infection control, balanced and physiologically individualized fluid and perfusion management, repeated medication-safety review, serial kidney-trajectory assessment,

and KRT for accepted indications. Emerging urinary extracellular-vesicle, multi-omics, endothelial, inflammatory, and machine-learning tools can refine dynamic risk stratification, but none should direct routine therapy without SA-AKI-specific validation and clinical-impact testing. The next meaningful advance will not be another high-AUC marker in isolation; it will be a reproducible phenotype measured at the correct time, linked to a feasible intervention, and shown in a prospective trial to improve kidney recovery, KRT-free survival, MAKE90, and long-term quality of life.

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