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Review

Cast nephropathy in the ICU: Early recognition and extracorporeal strategies to improve outcomes

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ABSTRACT

Cast-induced acute kidney injury (AKI) is a frequent yet under-recognized cause of kidney dysfunction in the intensive care unit. It arises when filtered proteins or pigments – free light chains (FLCs) in multiple myeloma, myoglobin in rhabdomyolysis, bilirubin in severe cholestasis, or hemoglobin in intravascular hemolysis – precipitate within kidney tubules, forming obstructive casts and triggering oxidative and inflammatory injury. Early recognition is essential because traditional markers (creatinine, urine output) rise late. Emerging biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and the tissue inhibitor of metalloproteinases-2 · insulin-like growth factor binding protein-7 ([TIMP-2]·[IGFBP7]) panel, detect tubular stress earlier and can guide timely intervention. This narrative review summarizes pathophysiology, diagnostic tools, and extracorporeal strategies tailored to the offending molecule and patient stability. For myeloma cast nephropathy, high cut-off membranes provide robust early FLC clearance but require albumin monitoring; medium cut-off and polymethylmethacrylate membranes offer sustained removal with lower albumin loss. In rhabdomyolysis, continuous kidney replacement therapy with high-flux or newer membranes supports hemodynamic stability and myoglobin clearance; hemoadsorption may be considered in severe cases. In bile cast nephropathy, artificial extracorporeal liver support (e.g., molecular adsorbent recirculating system, fractional plasma separation and adsorption), single-pass albumin dialysis, and hemoadsorption reduce bilirubin and bile acids, while plasma exchange remains reserved mainly for hyperviscosity syndromes. Across etiologies, extracorporeal approaches are most effective when combined with disease-specific treatments, such as chemotherapy for myeloma or targeted therapy for hemolysis. Emerging evidence suggests that integrating artificial intelligence-driven diagnostic tools with these therapeutic strategies may further enhance early recognition and individualized management of renal injury. A patient-centered, pathophysiology-driven strategy can shift extracorporeal therapies from rescue measures to proactive tools that improve kidney recovery and survival. Prospective studies should refine timing, modality selection, and biomarker-based algorithms to optimize outcomes in cast-induced AKI.

Introduction

Cast-induced acute kidney injury (AKI) is a clinically important but frequently under-recognized cause of kidney dysfunction in critically ill patients.[1] It develops when circulating proteins or pigments precipitate within kidney tubules, forming obstructive casts that impair filtration and trigger tubular injury.[1,2] This process can occur in several clinical settings, including plasma cell dyscrasias, severe muscle injury, cholestatic liver disease, and intravascular hemolysis.

Early recognition is critical since traditional markers such as serum creatinine reflect established injury rather than early tubular stress.[3] Novel biomarkers have the potential to identify patients at risk before overt AKI occurs,[4] allowing more timely intervention.[4] Decision-making in these complex clinical scenarios remains challenging, particularly regarding the selection of the most appropriate extracorporeal modality, the optimal timing of initiation, and the management of patient hemodynamic stability.[5] The choice of modality depends on the culprit molecule, patient stability, and therapeutic goals, and is

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most effective when combined with disease-specific treatments such as chemotherapy in multiple myeloma (MM).[6] Integrating structured decision-support frameworks and emerging AI-assisted tools may help reduce ambiguity in these processes and improve the precision of therapeutic strategies.[7]

This review summarizes current knowledge on the mechanisms, early recognition, and extracorporeal strategies for cast-induced AKI. By linking pathophysiology with practical treatment approaches, we aim to provide a framework that helps clinicians deliver timely, targeted care in this complex condition. Importantly, this review adopts a unified and comparative framework that integrates extracorporeal strategies across the main etiologies of cast-induced AKI (free light chains [FLCs], myoglobin, bilirubin, and hemoglobin). While previous reviews have typically addressed these entities separately, our approach highlights shared pathophysiological mechanisms and therapeutic principles, aiming to facilitate cross-contextual understanding and clinical translation.

Methods

We searched for all published observational studies, randomized controlled trials, systematic reviews, and meta-analyses related to extracorporeal strategies in cast-induced AKI, from database inception to May 4, 2024. The PubMed database was searched using the following MeSH terms and keywords: ("cast nephropathy" OR "light chain nephropathy" OR "multiple myeloma" OR "rhabdomyolysis" OR "bile cast nephropathy" OR "hemoglobinuria" OR "hemolysis") AND ("acute kidney injury" OR "kidney injury" OR "acute renal failure" OR "renal dysfunction" OR "extracorporeal therapy" OR "dialysis" OR "hemodialysis" OR "continuous renal replacement therapy" OR "hemofiltration" OR "plasmapheresis" OR "extracorporeal blood purification"). We manually screened reference lists of relevant articles for additional studies of interest. Duplicate publications were excluded by cross-referencing titles, authors, and study characteristics. Given the narrative nature of this review, we did not adhere to a rigid systematic review protocol but focused on identifying studies providing mechanistic insights, clinical outcomes, and practical considerations regarding extracorporeal management in cast-induced AKI. Throughout this review, the term "kidney" is used instead of "renal" to align with preferred terminology in most contemporary U.S.-based medical journals. Because this work is a narrative review, a PRISMA flow diagram was not included. However, for clarity and transparency, the main studies discussed are summarized in Table 1.[8] Given the narrative nature of this review, the analysis aimed to integrate evidence across distinct etiologies of cast-induced AKI, emphasizing comparative insights and shared therapeutic strategies.

Pathophysiological Framework

Cast-induced AKI results from the intratubular precipitation of nephrotoxic molecules that overwhelm the solubility and reabsorptive capacity of the nephron.[2,9,10] Once formed, casts obstruct tubular lumens, increase intratubular pressure, and compromise glomerular filtration. This obstruction is compounded by ischemia, oxidative stress, and local inflammation, leading to progressive tubular injury and, in severe cases, irreversible kidney damage.[11] Although the inciting agents differ, the pathophysiology converges on a shared cascade. In MM, excessive circulating FLCs (22–45 kDa) are filtered by the glomerulus and bind Tamm–Horsfall protein in the distal nephron, forming insoluble complexes that block tubular flow.[6,12] In rhabdomyolysis, myoglobin (17.8 kDa) released from damaged muscle cells precipitates more readily under acidic urine and hypovolemic conditions, while its heme group generates reactive oxygen species that induce lipid peroxidation and mitochondrial dysfunction.[13] In severe cholestasis, bilirubin and bile acids exceed tubular thresholds, resulting in bile casts and direct cytotoxicity to epithelial cells. In intravascular hemolysis, excess cell-free hemoglobin surpasses haptoglobin binding, filters into the nephron, and precipitates in tubules; heme-driven oxidative stress and nitric oxide scavenging further reduce kidney perfusion and aggravate injury.[14] The severity of kidney dysfunction depends not only on the concentration of the offending molecule but also on the tubular microenvironment, including urine pH, volume status, and the presence of co-factors such as Tamm–Horsfall protein.[15] Inflammatory responses and endothelial dysfunction amplify tubular stress and accelerate AKI progression. Because structural damage often develops silently, early recognition is critical. Conventional markers such as serum creatinine or urine output rise only after significant loss of function.[3] Novel biomarkers – including neutrophil gelatinase–associated lipocalin (NGAL), cystatin C, and the tissue inhibitor of metalloproteinases-2 · insulin-like growth factor binding protein-7 ([TIMP-2]·[IGFBP7]) panel – offer earlier signals of tubular stress and can help identify patients at risk before overt clinical deterioration.[16] Detecting injury in this window may allow timely initiation of supportive care, disease-specific therapy, and, when appropriate, extracorporeal strategies aimed at reducing nephrotoxic burden and preserving kidney recovery.[17] The shared mechanism leading to cast-induced AKI is summarized in Figure 1.

MM and Cast Nephropathy

Cast nephropathy remains a major cause of AKI in patients with MM, occurring in approximately 30 %–50 % of cases.[18] A high concentration of circulating FLCs, typically above 500 mg/L, is considered the threshold strongly associated with the development of myeloma cast nephropathy.[19] Because of their physicochemical properties, FLCs form complexes with tubular Tamm–Horsfall glycoprotein, leading to the formation of obstructive casts.[20] These casts increase intratubular pressure, reduce glomerular filtration, and cause tubular epithelial injury through ischemia and inflammation. Without prompt recognition and intervention, this cascade often culminates in AKI.[20] The mainstay of therapy for cast nephropathy is clone-directed treatment aimed at reducing the production and precipitation of FLCs. Adjuvant measures include the induction of high urine flow (unless contraindicated by oliguric AKI or heart failure).[1] Alkalinization of urine with isotonic sodium bicarbonate may also be considered to counteract FLC precipitation, though it should be avoided in hypercalcemic patients because of the risk of calcium phosphate precipitation. Loop diuretics should not be used unless there is significant fluid overload.[21] Traditionally, plasmapheresis (therapeutic plasma exchange, TPE) has been used to lower circulating FLC levels in MM-related AKI. Some studies suggested a linear

Table 1
Summary of key studies included in the review.

Study (Year)	Etiology/focus	Design/population	Intervention/comparator	Main findings	Comments/limitations
Zucchelli et al.[27](1988)	Myeloma cast nephropathy	Controlled trial, 29 MM patients with AKI	Plasma exchange + chemotherapy *vs.* conventional therapy	Early reduction of FLCs associated with improved renal recovery	Small sample, pre-modern therapy
Johnson et al.[28](1990)	Myeloma cast nephropathy	Observational, 24 MM patients	Plasmapheresis + hemodialysis with chemotherapy	Improved renal function in responders	Retrospective, non-standardized protocol
Clark et al.[29](2005)	Myeloma cast nephropathy	RCT, 97 MM-AKI patients	Plasma exchange *vs.* conventional therapy	No significant benefit of plasma exchange alone	Heterogeneous chemotherapy
Ronco et al.[53](2005)	Rhabdomyolysis	Conceptual paper	CRRT for myoglobin removal	High-volume hemofiltration improves myoglobin clearance	Theoretical, no clinical data
Evenepoel et al.[75](2006)	Bile cast nephropathy	Experimental comparison	MARS *vs.* PROMETHEUS albumin dialysis	Both systems effective for bilirubin removal	Technical comparison only
Burnette et al.[30](2011)	Myeloma cast nephropathy	Case report	Bortezomib + plasma exchange	Improvement with clone-directed therapy + PE	Anecdotal evidence
Finkel et al.[26](2016)	Myeloma cast nephropathy	Expert commentary	Evaluation and management of LCCN	Emphasized early chemotherapy; extracorporeal therapy as adjunct	Narrative expert opinion
Fabbrini et al.[43](2016)	Myeloma cast nephropathy	Position paper (SIN)	HCO, MCO, PMMA membranes	Pragmatic approach: HCO early, then MCO/PMMA	Consensus statement
Sens et al.[42](2017)	Myeloma cast nephropathy	Prospective cohort, $n = 38$	PMMA hemodialysis + chemotherapy	71 % renal recovery at 60 days	Non-randomized, small cohort
Hutchison et al. (EuLITE)[23](2019)	Myeloma cast nephropathy	Multicenter RCT, $n = 90$	HCO *vs.* high-flux HD + chemotherapy	No clear survival or renal benefit	Limited sample, delayed enrollment
Weidhase et al.[105](2020)	Rhabdomyolysis	RCT	HCO-CVVHD *vs.* CVVHDF (high-flux)	Greater myoglobin clearance with HCO; unclear clinical benefit	Short follow-up
Bridoux et al. (MYRE)[21](2021)	Myeloma cast nephropathy	Multicenter RCT, biopsy-proven LCCN	HCO *vs.* high-flux HD + chemotherapy	Higher dialysis independence at 6–12 month with HCO	Albumin loss; benefit tied to effective chemo
Tarragón et al.[31](2021)	Myeloma cast nephropathy	Systematic review & meta-analysis	5 studies (HCO *vs.* conventional)	Greater FLC reduction; trend toward better renal outcomes	Heterogeneous evidence
Kodadek et al. (AAST)[48] (2022)	Rhabdomyolysis	Expert consensus	Critical care management	CRRT reserved for severe AKI; use McMahon score	Consensus, no trial data
Schaaf et al.[37](2023)	Myeloma cast nephropathy	Retrospective, $n = 55$	MCO hemodialysis	70 % κ-FLC and 37 % λ-FLC reduction; albumin stable	Short-term study
Koniman et al.[38](2023)	Myeloma cast nephropathy	Systematic review (3 series, 17 patients)	MCO dialyzers	Consistent FLC reduction, well tolerated	Limited evidence
Tomescu et al. [84] (2021); Dhokia et al.[85](2019)	Bile cast nephropathy	Case series	Cytosorb + CRRT or Cytosorb	Reduced bilirubin and cytokines; hemodynamic improvement	Observational, small sample
Forni et al.[54](2024)	Rhabdomyolysis	Expert consensus	Hemoadsorption in severe rhabdomyolysis	Feasible and safe; evidence level low	Consensus-based
Gadour et al.[79](2024)	Liver-related AKI	Meta-analysis	SPAD, PROMETHEUS, MARS *vs.* standard care	Better biochemical control; survival benefit uncertain	High heterogeneity
Heybeli et al.[33](2025)	Myeloma cast nephropathy	Narrative review	HCO/MCO/PMMA/HFR dialysis strategies	Extracorporeal therapies as adjuncts to early clone control	Updated synthesis
Lukkanalikitkul et al.[36](2025)	Chronic dialysis (reference)	RCT (HD population)	MCO *vs.* online HDF	Improved middle-molecule clearance with MCO	Not AKI-specific

AKI: Acute kidney injury; AAST: American Association for the Surgery of Trauma; CRRT: Continuous renal replacement therapy; CVVHDF: Continuous veno-venous hemodiafiltration; FLC: Free light chain; HD: Hemodialysis; HCO: High-cutoff membrane; HDF: Hemodiafiltration; HFR: Hemodiafiltration with reinfusion; LCCN: Light-chain cast nephropathy; MCO: Medium-cutoff membrane; MARS: Molecular adsorbent recirculating system; MM: Multiple myeloma; PE: Plasma exchange; PMMA: Polymethylmethacrylate; PROMETHEUS: Fractional plasma separation and adsorption; RCT: Randomized controlled trials; SIN: Italian Society of Nephrology; SPAD: Single-pass albumin dialysis.

relationship between FLC reduction and kidney recovery, but no absolute threshold for response has been established.[21–23] Consequently, the International Myeloma Working Group does not recommend TPE as a standard therapy for kidney failure in MM, and its role is now largely confined to hyperviscosity syndromes (ASFA guidelines, Grade 1B).[22] In cases of extreme monoclonal IgM production (>4000 mg/dL), TPE can rapidly reduce serum viscosity and relieve neurological, visual, or hemorrhagic complications.[24] However, randomized controlled trials and systematic reviews have shown that TPE alone does not significantly improve kidney outcomes in cast nephropathy unless combined with effective anti-myeloma therapy.[25] Interestingly, a Mayo Clinic study reported partial responses in about 86 % of patients with cast nephropathy who received TPE in addition to chemotherapy.[24] This limited efficacy has led to the exploration of advanced extracorporeal modalities designed

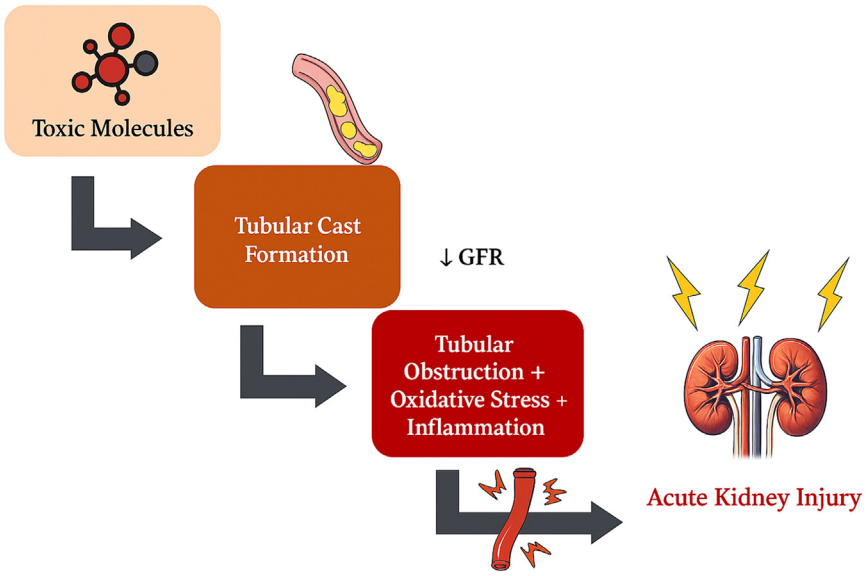

Figure 1. Pathophysiological cascade of cast-induced AKI. Excess circulating nephrotoxic molecules – including free light chains, myoglobin, bilirubin, and hemoglobin – are filtered at the glomerulus and precipitate within renal tubules, forming obstructive casts. These casts impair tubular flow and induce oxidative stress and inflammation, leading to reduced glomerular filtration rate (↓GFR) and the development of AKI.
AKI: Acute kidney injury; GFR: Glomerular filtration rate.

to remove FLCs more efficiently while maintaining hemodynamic stability and minimizing adverse effects. FLCs are relatively small proteins (22.5–45 kDa). Based on their molecular weight, high-cutoff hemodialysis (HCO-HD) has been proposed as an extracorporeal method for FLC removal. In this technique, hemofilters with larger pore sizes (approximate 10 nm) are used for repeated dialysis sessions over several weeks.[26]

Several studies have investigated extracorporeal techniques for the removal of circulating FLCs in patients with light-chain cast nephropathy (LCCN). Early reports by Zucchelli et al.[27] and Johnson et al.[28] demonstrated that rapid reduction of serum FLC levels was associated with improved kidney recovery. Later, Clark et al.[29] and Burnette et al.[30] emphasized the importance of combining effective antimyeloma therapy with extracorporeal clearance methods. The MYRE randomized clinical trial[21] compared HCO-HD with conventional high-flux dialysis in biopsy-proven LCCN and found no significant difference at 3 months, but a higher rate of dialysis independence at 6 and 12 months in the HCO group. Conversely, the EuLITE trial[23] did not confirm a survival or kidney benefit of HCO hemodialysis compared to conventional therapy, highlighting the need for careful patient selection and standardized treatment protocols. Collectively, these findings suggest that extracorporeal FLC removal may be beneficial when used as an adjunct to modern, clone-directed therapy, though its role remains to be fully defined.

HCO dialyzers have a sieving curve shifted to the right compared with high-flux dialyzers, as illustrated in Figure 2. HCO membranes have shown efficacy in the initial management of patients with MM-related cast nephropathy when the circulating sFLC burden is markedly elevated, typically above 500 mg/L.[31] By enabling the removal of large middle molecules, including both κ-FLC and λ-FLCs, HCO membranes reduce intratubular FLC concentrations and limit further cast formation.[32] However, their use is associated with significant albumin loss, requiring careful monitoring and replacement to prevent hypoproteinemia, as well as higher treatment costs.[32]

A meta-analysis of five studies found that HCO-HD achieved greater reductions in FLC levels compared with conventional HD, with a trend toward higher dialysis independence, although no significant improvement in overall kidney or patient survival was demonstrated.[31] More recent reviews confirm that HCO-HD can achieve up to approximate 90 % FLC reduction after several sessions when combined with anti-myeloma therapy, though its impact on kidney recovery remains uncertain[33] (Table 2).

In response to these limitations, medium-cutoff (MCO) membranes, such as Theranova, have been developed.[34] MCO membranes offer effective clearance of middle molecules, including FLCs, while minimizing albumin loss and reducing treatment costs.[34] In addition, MCO therapy has been associated with favorable modulation of the inflammatory milieu, lowering cytokines such as IL-6 and TNF-α, which may improve tolerability and reduce dialysis-related inflammation.[34,35] A randomized trial demonstrated superior clearance of larger middle molecules, such as λ-FLCs, with MCO compared to high-flux dialyzers, while preserving albumin levels.[36] A retrospective study of 55 patients reported relative reductions of 70 % in κ-FLC and 37 % in λ-FLCs, confirming the efficiency of MCO at a lower cost than HCO-HD.[37] A systematic review further identified three case series including 17 patients treated with MCO, all showing encouraging results.[38]

Polymethylmethacrylate (PMMA) filters represent another valuable option in the extracorporeal management of cast nephropathy.[1] PMMA membranes have strong adsorptive properties, enabling sustained FLC removal over repeated dialysis sessions without significant albumin loss.[39] This makes them particularly useful in the subacute phase, when the FLC burden is declining under chemotherapy. The extended adsorption dialysis (EAD) system using PMMA has shown effective FLC clearance while preserving albumin, offering a practical long-term strategy for dialysis-dependent patients.[40] In acute myeloma, however, the high FLC load may saturate the filter rapidly. To address this, the DELETE system employing a double-filter circuit has been proposed.[41] Another technique, hemodiafiltration with ultrafiltrate regeneration (HFR-SUPRA®), combines convection with adsorption on an ultrafiltrate cartridge. Case series have reported mean FLC reduc-

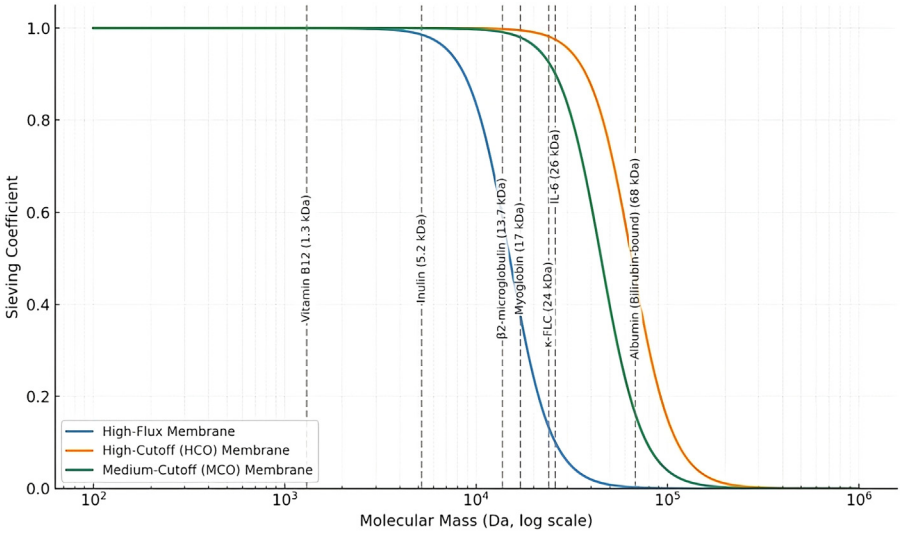

Figure 2. Sieving curves of high-flux, HCO, and MCO dialysis membranes. The sieving coefficients of different membranes are compared across a range of solute molecular weights. High-flux membranes provide clearance of small solutes but limited removal of middle molecules. HCO membranes extend clearance to larger molecules, including free light chains (κ-FLC, 24 kDa), at the expense of albumin leakage. MCO membranes offer an intermediate profile, ensuring effective removal of middle molecules while minimizing albumin loss. Vertical dashed lines indicate the molecular weights of representative solutes: Vitamin B12 (1.3 kDa), Inulin (5.2 kDa), β2-microglobulin (13.7 kDa), Myoglobin (17 kDa), κ-FLC (24 kDa), IL-6 (26 kDa), and Albumin (68 kDa, bilirubin-bound).
FLC: Free light chains; HCO: High-cutoff; MCO: Medium-cutoff.

Table 2
Dialysis membranes for MM-related cast nephropathy.

Membrane	Mechanism	Albumin loss	Typical clinical use	Advantages	Limitations	Evidence
HCO	High-permeability filtration (approximate 10 nm)	High	Acute phase, sFLC >500 mg/L	High initial clearance	Requires albumin replacement, expensive	Meta-analyses: increased FLC clearance, uncertain renal benefit
MCO (Theranova)	Extended middle molecule clearance	Low	Subacute/prolonged therapy	Good balance efficiency/safety, less costly	Less clinical experience	RCTs + retrospective series, promising
PMMA	Direct adsorption	Minimal	Subacute phase, declining FLC burden under chemotherapy	Preserves albumin, suitable for long-term use	Rapid saturation if high FLC load	Prospective series, real-world data

HCO: High-cutoff membranemembrane; MCO: Medium cut-off membrane; MM: Multiple myeloma; PMMA: Polymethylmethacrylate membrane; RCTs: Randomized controlled trials; sFLC: Serum free light chains.

Table 3
Extracorporeal modalities.

Technique	Mechanism	Clinical use	Advantages	Limitations	Evidence
DELETE system	Double-filter adsorption	Acute phase with very high FLC load	Increased adsorption capacity	Experimental	Case reports
HFR-SUPRA®	Hemodiafiltration + adsorption (ultrafiltrate cartridge)	Alternative when albumin preservation is needed	Combined versatile approach	Small studies only	Approximate40 % FLC reduction/session
TPE (Plasma exchange)	Whole plasma removal (non-selective)	Hyperviscosity syndromes (IgM > 4000 mg/dL)	Rapid viscosity reduction, symptom relief	No renal benefit without chemotherapy	ASFA: recommended only for hyperviscosity

ASFA: American Society for Apheresis; FLC: Free light chains; HFR-SUPRA®: Hemodiafiltration with reinjection–SUPRA (hemodiafiltration plus adsorption cartridge); IgM: Immunoglobulin M; TPE: Therapeutic plasma exchange.

tions of 39%±16 % per session using such adsorption-based approaches[33] (Table 3).

The integration of extracorporeal therapies with early disease-modifying chemotherapy, particularly bortezomib-based regimens, has significantly improved patient outcomes. In a prospective study by Sens et al.[42], early initiation of PMMA-based intermittent hemodialysis combined with chemotherapy resulted in a 71 % kidney recovery rate within 60 days, with most patients regaining dialysis independence. Hematologic responses were durable, and survival remained high at 6, 12, and 24 months.

The current consensus, reflected in the Italian Society of Nephrology (SIN) position paper[43] supports a pragmatic approach: employing HCO-HD in the early phase when sFLC levels are high, followed by transition to MCO or PMMA as FLC burden decreases under chemotherapy. This sequential strategy maximizes FLC clearance, minimizes albumin loss, and aligns with the underlying pathophysiology of cast nephropathy.

Overall, the early use of HCO or MCO membranes in combination with chemotherapy may be considered in selected patients, as an adjunctive measure to enhance FLC clearance. However, given the heterogeneity and limitations of existing trials, their impact on long-term dialysis independence remains uncertain. Although HCO membranes represent an effective extracorporeal option for FLC removal, their availability remains limited in many regions. In such settings, TPE may still play a role as an adjunctive therapy, particularly when access to HCO dialyzers is restricted. While randomized controlled trials have not con-

sistently demonstrated a significant benefit of TPE in improving kidney outcomes, it may facilitate a transient reduction in circulating FLCs when combined with effective antimyeloma therapy, especially in severe cases of myeloma cast nephropathy.

Rhabdomyolysis

Rhabdomyolysis is a recognized cause of pigment-induced AKI, occurring due to the massive release of intracellular muscle components, particularly myoglobin, into the bloodstream following skeletal muscle injury.[44] Myoglobin, with a molecular weight of 17.8 kDa, is freely filtered by the glomerulus, and under conditions of hypovolemia and aciduria, it precipitates within the kidney tubules, forming obstructive casts and generating oxidative stress that exacerbates tubular epithelial cell injury.[44,45] While the diagnosis of rhabdomyolysis often relies on elevated serum creatine kinase (CK) levels, it is important to recognize that CK levels correlate poorly with the actual risk of AKI or the need for dialysis. In this context, the McMahon score has been proposed as a prognostic tool to stratify patients based on their risk of developing AKI or requiring renal replacement therapy (RRT), incorporating variables such as age, CK levels, and laboratory parameters available at admission to predict clinical outcomes effectively.[45]

The pathophysiology of myoglobin-induced AKI involves both mechanical obstruction of the tubules and direct cytotoxic effects.[46] Myoglobin interacts with Tamm–Horsfall protein within the distal tubules, forming casts that obstruct urine flow, while its heme component catalyzes the formation of reactive oxygen species, leading to lipid peroxidation, mitochondrial dysfunction, and apoptosis of tubular epithelial cells.[44] Additionally, myoglobin scavenges nitric oxide, resulting in intrarenal vasoconstriction and reduced kidney perfusion, further aggravating ischemic injury.[44]

Management of rhabdomyolysis focuses on early and aggressive fluid resuscitation, aiming to maintain adequate intravascular volume and kidney perfusion while promoting diuresis to reduce the concentration of myoglobin within the tubules.[47,48] Alkalinization of urine and correction of electrolyte imbalances, particularly hyperkalemia and hyperphosphatemia, are also integral components of conservative management strategies aimed at mitigating the risk of AKI.[49]

Despite optimal conservative management, a subset of patients will progress to severe AKI requiring extracorporeal support. Continuous renal replacement therapy (CRRT) with high-flux membranes is the cornerstone of extracorporeal management in rhabdomyolysis-associated AKI, providing gradual clearance of circulating myoglobin while maintaining hemodynamic stability and facilitating the management of fluid and electrolyte disturbances.[50,51] The use of CRRT is particularly advantageous in critically ill patients with hemodynamic instability, where intermittent hemodialysis may not be feasible.

It is essential to acknowledge, however, that while high-flux hemofiltration theoretically enables the clearance of myoglobin.[52] the actual sieving coefficients for myoglobin can be highly variable in clinical practice due to factors such as filter characteristics, concentration polarization, and the presence of plasma proteins, which may limit the efficiency of clearance.[53] Nevertheless, the use of CRRT provides vital supportive care during the acute phase of illness, facilitating metabolic and volume control while the underlying muscle injury resolves.[53]

Emerging extracorporeal strategies, including super high-flux membranes and hemoadsorption techniques, are under investigation to enhance myoglobin removal further, although additional clinical studies are necessary to establish their efficacy and safety in routine practice.[54] In selected cases, a multiparametric approach integrating extracorporeal support, monitoring of biomarkers, and individualized hemodynamic management may improve outcomes in critically ill patients with rhabdomyolysis and AKI.[54,55] In summary, rhabdomyolysis-induced AKI requires timely recognition, prompt conservative management, and the judicious use of CRRT to support kidney function, with extracorporeal therapies playing a crucial role in managing the systemic complications of severe cases and facilitating recovery.

Table 4
Causes of hemolysis leading to hemoglobin cast nephropathy.

Cause	Mechanism underlying hemolysis
Autoimmune hemolytic anemia, Evans syndrome	Immune-mediated
Medications (rifampicin, quinine, TMP-SMX, vancomycin, bevacizumab)	Immune-mediated/cytotoxic
Snakebite, wasp sting	Cytotoxic
Toxins (termite oil, heavy metals)	Cytotoxic
Falciparum malaria	Parasitic invasion → intravascular hemolysis
Leptospira infection	Cytotoxic/hemolytic
Mechanical heart valves or valvular disease	Mechanical red cell fragmentation
NSAIDs	Immune-mediated
Sepsis / DIC	Immune-mediated, intravascular fragmentation
Hemoglobinopathies (favism, sickle cell anemia)	Genetic, oxidative hemolysis
Paroxysmal nocturnal hemoglobinuria	Complement-mediated
Transfusion incompatibility	Immune-mediated

DIC: Disseminated intravascular coagulation; NSAIDs: Non-steroidal anti-inflammatory drugs; TMP-SMX: Trimethoprim-sulfamethoxazole.

Intravascular Hemolysis

Intravascular hemolysis, which may occur in a variety of clinical conditions (Table 4), leads to the release of cell-free hemoglobin (Hb) into the circulation. Hb is freely filtered by the glomerulus and contributes to hemoglobin-induced AKI.[56]

Vancomycin, frequently used in the ICU, has been associated not only with immune-mediated hemolysis but also with direct tubular cast formation and obstruction, potentially leading to vancomycin-induced cast nephropathy independent of hemolysis.[57] Although clinical experience with extracorporeal therapy in this specific setting is lacking, recognition of this mechanism is important in ICU patients receiving high or prolonged vancomycin exposure.

The pathophysiology of hemoglobin-induced AKI involves multiple mechanisms, including tubular obstruction, oxidative injury, and nitric oxide scavenging.[58] Free Hb filtered by the glomerulus can precipitate within the kidney tubules, forming obstructive casts, while its heme component catalyzes the production of reactive oxygen species, leading to lipid peroxidation and mitochondrial dysfunction in tubular epithelial cells.[59] Histopathologic confirmation of hemoglobin casts has been comprehensively characterized by Dvanajscak et al.[60], in

one of the largest clinicopathologic series to date, which emphasized the diagnostic significance of identifying hemoglobin casts in biopsy-proven hemolysis-associated AKI.

Additionally, free Hb binds to and depletes nitric oxide, resulting in intrarenal vasoconstriction, reduced kidney perfusion, and further exacerbation of ischemic injury.[61] Current management of intravascular hemolysis focuses on supportive care and disease-specific therapies to treat the underlying cause of hemolysis.[62] The use of complement C5 inhibitors such as eculizumab or ravulizumab has proven effective in preventing hemolysis in patients with paroxysmal nocturnal hemoglobinuria by inhibiting terminal complement activation.[63] While extracorporeal techniques specifically targeting free Hb removal are still under investigation, some promising approaches include hemoadsorption and advanced filtration techniques designed to capture and remove circulating cell-free Hb and heme complexes, thereby reducing oxidative stress and tubular injury.[61]

However, these strategies require further validation through clinical studies to establish their safety and efficacy in routine practice.[56] Extracorporeal therapy may be considered in patients with severe or sustained intravascular hemolysis, particularly when there is significant accumulation of circulating free hemoglobin and evidence of ongoing tubular injury or systemic involvement. Although kidney biopsy remains the gold standard for confirming the diagnosis through histologic demonstration of hemoglobin casts, it is not always required in patients with a typical clinical and biochemical profile or in those for whom biopsy poses a high procedural risk. In such settings, prompt recognition of hemolysis, initiation of disease-specific therapy, and consideration of extracorporeal techniques, such as hemoadsorption or advanced filtration, may help attenuate hemoglobin-mediated nephrotoxicity and improve outcomes.

In cases of severe hemolysis with AKI, supportive management with CRRT may be necessary to manage fluid overload, electrolyte disturbances, and uremia while addressing the underlying cause of hemolysis.[64] The choice between intermittent hemodialysis and CRRT should be guided by the patient's hemodynamic status, with CRRT preferred in hemodynamically unstable patients. Most of the cases described in the literature showed recovery of kidney function after a few dialysis sessions.[65]

Intravascular hemolysis-induced AKI requires a multifaceted approach, combining disease-specific treatments with supportive care and RRT as needed. While extracorporeal techniques targeting free Hb removal are evolving, the current cornerstone of management remains the early identification of hemolysis and the prompt initiation of targeted therapy to prevent ongoing kidney injury and systemic complications.[61]

Severe Cholestasis (Bile Cast Nephropathy)

Severe cholestasis can result in bile cast nephropathy, an underrecognized cause of AKI in patients with liver dysfunction, characterized by the intratubular precipitation of bilirubin and bile acids.[66] The pathophysiology involves hyperbilirubinemia (>20 mg/dL),[66] exceeding the reabsorptive and solubility capacity of kidney tubules. Bile casts obstruct tubular lumen and exert cytotoxicity. Kidney biopsies usually show Hall's stain-positive bile casts and tubular injury, but bleeding risk in liver failure limits its use.[67] Evidence suggests cholemic casts may also precipitate in urine,[68] offering a safer diagnostic alternative, though not yet standardized. The link between hyperbilirubinemia and kidney dysfunction has been recognized since Quincke and Nothnagel.[69] Bilirubin and bile acids promote oxidative stress, mitochondrial dysfunction, apoptosis, and obstruction, culminating in AKI. Bilirubin-albumin complexes (approximate 67–69 kDa) resist clearance with conventional dialysis, requiring specialized extracorporeal therapies.[70]

Extracorporeal liver support (ECLS) systems have emerged as important therapeutic modalities in managing bile cast nephropathy, limiting hyperbilirubinemia and support the failed kidney.[70] Artificial ECLS utilize column chromatography, incorporating selective membranes of various pore sizes and adsorbent affinities to filter out serum toxins.[71] Among the devices, two Molecular Adsorbent Recirculating System (MARS) and Fractional plasma separation and adsorption (PROMETHEUS), are the first and the most studied, although show a complexity to use.[72]

MARS combines albumin dialysis with conventional dialysis and adsorption to facilitate the removal of albumin-bound toxins, including bilirubin and bile acids, while also improving the albumin-binding capacity, reducing ammonia levels, and correcting acid-base disturbances.[73–75] It uses three interconnected circuits (blood, albumin, and dialysate) in which toxins transfer from plasma to exogenous albumin, which is subsequently regenerated through adsorption on charcoal and anion-exchange columns.[76,77] The PROMETHEUS system integrates plasma separation, albumin adsorption, and high-flux hemodialysis.[78] It uses a specific albumin-permeable filter that allows protein-bound toxins to pass into a secondary circuit, where they are adsorbed before the purified plasma is returned to the patient.[79] Unlike MARS, PROMETHEUS uses the patient's own albumin, eliminating the need for external sources.[79] Other emerging systems include the Double Plasma Molecular Absorption System (DPMAS), which employs dual resin columns to clear bilirubin, bile acids, ammonia, phenols, and inflammatory mediators with >40 % bilirubin reduction.[80–82] and coupled plasma filtration adsorption (CPFA), which combines plasma filtration and adsorption in a single circuit, allowing simultaneous removal of protein-bound and water-soluble toxins.[83]

Simpler approaches, such as single-pass albumin dialysis (SPAD), adapt standard CRRT machines by dialyzing blood against an albumin-enriched solution, while Cytosorb® cartridges containing adsorbing polymeric beads can reduce bilirubin, bile acids, ammonia, and pro-inflammatory cytokines.[84–86] Cytosorb® is increasingly used in ICU settings, often combined with CRRT or extracorporeal membrane oxygenation. Plasma exchange (PEX), either conventional or high-volume, enables nonspecific detoxification by removing the entire plasma fraction and replenishing it with fresh plasma, thereby also restoring albumin and coagulation factors.[87] Among these artificial liver support systems, MARS remains the most extensively studied, providing selective removal of albumin-bound molecules (<50 kDa). Beyond bilirubin clearance, MARS can improve hemodynamic and metabolic stability in acute-on-chronic liver failure (ACLF), although robust evidence for renal recovery or survival benefit is still lacking.[88,89] Overall, MARS remains the most validated platform, yet randomized trials have not demonstrated a clear survival benefit for any system, underscoring the

Table 5
Comparative characteristics of artificial extracorporeal liver support (ECLS) systems used in severe cholestasis and bile cast nephropathy.

System	Principle/mechanism	Targets	Advantages	Limitations
MARS	Albumin dialysis + adsorption + conventional dialysis	Bilirubin, bile acids, ammonia, protein-bound toxins	Selective (<50 kDa), improves hemodynamics and renal function	Complex setup, requires exogenous albumin
PROMETHEUS	Plasma separation + albumin adsorption + high-flux HD	Albumin-bound + water-soluble toxins	Uses patient's own albumin, broad detoxification	Technically complex
DPMAS	Dual resin adsorption (HA330-II, BS330)	Bilirubin, bile acids, ammonia, inflammatory mediators	>40 % bilirubin reduction, no plasma replacement	Limited availability, needs further validation
CPFA	Plasma filtration + resin adsorption + CRRT	Albumin-bound + water-soluble toxins	Simultaneous dual clearance, integration with CRRT	Anticoagulation challenges
SPAD	Albumin-enriched dialysate in CRRT	Bilirubin, protein-bound toxins	Simple, uses standard CRRT machines	Discards albumin after each pass
Cytosorb®	Resin cartridge adsorption (55 kDa cutoff)	Bilirubin, bile acids, cytokines, ammonia	Easy to integrate with CRRT/ECMO, modulates inflammation	Not specific for bilirubin, needs multiple sessions
PEX/HVP	Plasma removal & replacement	Non-selective toxin removal + replenishes albumin & coagulation factors	Widely available, rapid detoxification	Non-specific, removes beneficial molecules too

CRRT: Continuous renal replacement therapy; CPFA: Coupled plasma filtration adsorption; DPMAS: Double plasma molecular adsorption system; ECMO: Extracorporeal membrane oxygenation; HD: Hemodialysis; HA330-II/BS330: Specific resin cartridges; MARS: Molecular adsorbent recirculating system; PEX/HVP: Plasma exchange/high-volume plasma exchange; PROMETHEUS: Fractional plasma separation and adsorption; SPAD: Single-pass albumin dialysis.

importance of individualized selection based on patient stability, bilirubin burden, and available resources.

While all these systems share the common goal of removing albumin-bound toxins, their mechanisms, efficiency, and clinical validation differ. MARS offers reliable detoxification with established safety but requires complex setup and significant albumin consumption; PROMETHEUS achieves higher clearance through fractionated plasma separation but at the cost of greater albumin loss and hemodynamic instability; SPAD and Cytosorb® provide simpler, more accessible options but rely mostly on limited case-based evidence. The main characteristics, targets, and limitations of these ECLS systems are summarized in Table 5.

Artificial ECLS devices – particularly MARS, PROMETHEUS, CPFA, and Cytosorb® enable the removal of bilirubin, bile acids, and inflammatory mediators, thereby reducing systemic toxicity and potentially mitigating kidney injury. Many of these systems can be integrated with CRRT to enhance hydrophilic toxin clearance and maintain metabolic balance. Although clinical experience is encouraging, robust randomized trials are still lacking to define the optimal timing, modality, and patient selection. Overall, MARS and Cytosorb® can effectively reduce bilirubin and inflammatory mediators; however, evidence supporting renal function improvement remains limited to small series and case reports. Their use should therefore be individualized and considered adjunctive or experimental pending stronger clinical validation.

Biomarkers and Early Diagnosis in Cast-induced AKI

Early diagnosis of cast-induced AKI is critical for optimizing patient outcomes, allowing timely intervention before irreversible tubular injury occurs. Traditional markers such as serum creatinine and urine output often reflect established kidney dysfunction rather than early cellular stress, delaying therapeutic decisions.[3]

In critically ill patients, a kidney biopsy is often avoided because of coagulopathy or hemodynamic instability. In these cases, the diagnosis of cast-induced AKI can frequently be supported by characteristic laboratory patterns: markedly elevated serum FLCs with non-albumin proteinuria in MM, extreme CK and myoglobin levels in rhabdomyolysis, plasma-free hemoglobin and decreased haptoglobin in hemolysis, and severe conjugated hyperbilirubinemia (>20 mg/dL) in cholestasis.[90] In this context, biomarkers including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, [TIMP-2]· [IGFBP7] have emerged as valuable tools for the early detection of tubular injury across various clinical scenarios.[91] When combined with biomarker evidence of tubular stress (e.g., NGAL, [TIMP-2]· [IGFBP7]), these findings can guide early therapy even in the absence of biopsy confirmation. NGAL and cystatin C are sensitive indicators of tubular damage, with NGAL released by injured tubular epithelial cells and cystatin C reflecting glomerular filtration and proximal tubular reabsorption dynamics.[92] Elevated NGAL levels can indicate early tubular injury in patients with MM before overt rises in creatinine, allowing earlier initiation of therapies such as chemotherapy and extracorporeal removal of FLCs.[93] Similarly, cystatin C allows earlier detection of glomerular filtration impairment, particularly relevant in ICU patients where rapid kidney support decisions are needed. [TIMP-2]· [IGFBP7], markers of cell cycle arrest, signal early nephron stress before functional decline, with TIMP-2 linked to distal and IGFBP7 to proximal tubular injury.[94]

While NGAL, cystatin C, and [TIMP-2]·[IGFBP7] are all promising biomarkers for early detection and risk stratification of AKI, their clinical roles differ. NGAL rises rapidly (within hours) after tubular injury and is useful for early identification, particularly in sepsis or contrast exposure. Cystatin C provides a more accurate estimate of glomerular filtration rate and is less influenced by muscle mass, making it suitable for dynamic monitoring during renal recovery. [TIMP-2]·[IGFBP7] reflects cell-cycle arrest and is best suited for identifying patients at high risk of imminent AKI who may benefit from preventive measures or timely initiation of extracorporeal therapy. A comparative summary of their mechanisms, diagnostic windows, and limitations is provided in Table 6, supporting a biomarker-guided approach to AKI management in the ICU.

In MM-related cast nephropathy, these biomarkers help identify patients at risk for AKI and support early initiation of extracorporeal FLC removal, potentially avoiding dialysis.[18] The

Table 6
Comparative overview of AKI biomarker.

Biomarker	Pathophysiological target	Time to rise	Main clinical use	Strengths	Limitations
NGAL	Tubular damage marker (neutrophil granules)	2–6 h	Early AKI detection (sepsis, contrast nephropathy)	Rapid, sensitive, available assays	Less specific (rises with inflammation)
Cystatin C	GFR marker (filtered and reabsorbed in tubules)	12–24 h	Monitoring kidney function and recovery	Independent of muscle mass, stable	Delayed *vs.* NGAL, affected by thyroid disorders
[TIMP-2]·[IGFBP7]	Cell-cycle arrest markers	<4 h	Risk prediction of imminent AKI	Strong predictive value, FDA-approved test	Cost, availability, affected by inflammation

AKI: Acute kidney injury; FDA: Food and Drug Administration; GFR: Glomerular filtration rate; NGAL: Neutrophil gelatinase-associated lipocalin; [TIMP-2]·[IGFBP7]: Tissue inhibitor of metalloproteinases-2 · insulin-like growth factor binding protein-7.

risk of AKI, the need for RRT, and in-hospital mortality in rhabdomyolysis can be estimated using demographic, clinical, and laboratory data at admission, integrated in the McMahon risk score.[95] A score ≥6 indicates high risk of fluid overload, RRT, and mortality, although this tool is mainly prognostic and does not guide therapy.[48] Biomarkers provide complementary information, detecting tubular injury caused by myoglobin toxicity and refining risk stratification beyond the McMahon score.[48] In severe cholestasis, biomarkers may help distinguish functional from structural AKI in hyperbilirubinemic patients, guiding the use of ECLS or bilirubin adsorption therapies.[96] Experimental models show urinary NGAL correlates with tubular injury and response to treatment in bile cast nephropathy, but its role in humans remains to be clarified.[97] Biomarkers are also essential for evaluating extracorporeal blood therapies (EBTs). Efficiency reflects toxin removal (e.g., bilirubin clearance over time), while efficacy measures clinical benefit, such as kidney recovery or improved outcomes.[98] Their integration into clinical workflows supports a precision medicine approach, enabling early identification of high-risk patients, tailoring extracorporeal interventions, and guiding treatment escalation or de-escalation.[99]

Technical Considerations in Extracorporeal Strategies

The success of extracorporeal strategies in cast-induced AKI depends on multiple technical aspects, such as membrane selection, clearance efficiency, albumin loss management, and patient stability during treatment. The nephrotoxic molecules involved differ in molecular weight, FLCs (22–45 kDa),[18] myoglobin (17.8 kDa),[13] and bilirubin–albumin complexes (approximate 67–69 kDa),[66] and therefore require specific removal approaches. Among the mechanisms of clearance, HCO and MCO membranes enlarge pore size and overcome steric hindrance, allowing more efficient filtration than standard high-flux filters.[100] Adsorptive strategies using polystyrene resin or charcoal exploit van der Waals forces, hydrophobic interactions, and ionic bonds to capture middle- and large-weight molecules independently of their protein binding.[101] In bilirubin removal, polystyrene divinylbenzene nanoparticles show selective affinity for bilirubin, disrupting its bond with albumin and releasing free albumin into circulation through electrostatic binding.[102] HCO membranes are particularly effective in clearing large middle molecules such as FLCs during the initial high-burden phase of MM-related cast nephropathy, but their use is limited by significant albumin loss, which requires careful monitoring and supplementation.[32] MCO membranes represent a more sustainable alternative, providing effective clearance of middle molecules while minimizing albumin loss and reducing inflammatory cytokines, a property that may improve outcomes in critically ill patients.[32] PMMA filters combine efficiency and safety, as they remove FLCs through adsorption while sparing albumin, and are especially valuable during prolonged treatment or in patients whose FLC burden decreases under chemotherapy.[103] In rhabdomyolysis,CRRT with high-flux membranes is frequently used for myoglobin removal, although the clinical efficiency is often limited by low sieving coefficients. Newer approaches, including HCO and MCO membranes as well as adsorption-based therapies, are under evaluation to enhance clearance while maintaining hemodynamic stability.[104–106] Recently, a consensus task force on hemoadsorption in rhabdomyolysis confirmed the feasibility and safety of adjuvant hemoadsorption therapy in severe cases, but emphasized that the evidence remains of low quality, underlining the need for robust clinical trials with clearly defined endpoints.[54] For bile cast nephropathy, more advanced systems such as MARS and PROMETHEUS, as well as simpler resin adsorption devices, allow removal of albumin-bound bilirubin and bile acids that cannot be eliminated through conventional dialysis.[97] The choice of the most appropriate technique depends on the patient's condition, the expertise available, and the intended metabolic targets.[97] Finally, additional considerations such as treatment duration, anticoagulation protocols, and frequency of sessions are crucial to ensure the effectiveness of therapy while minimizing risks such as clotting or bleeding. The integration of all these technical aspects into the overall patient management plan is essential to achieve optimal outcomes in cast-induced AKI.[107] Extracorporeal therapies may also enhance the clearance of essential drugs, such as antibiotics, antivirals, or immunosuppressants, especially those with low protein binding and hydrophilic characteristics. Therefore, therapeutic drug monitoring and dosage adjustment should be considered whenever available.[108]

Conclusions

Cast-induced AKI is a severe condition that requires early recognition and individualized management to prevent irreversible injury and dialysis dependence. Extracorporeal therapies, tailored to the underlying cause, such as MM, rhabdomyolysis, severe cholestasis, or hemolysis, can lower the nephrotoxic burden, support kidney recovery, and improve survival. Advances in dialysis membranes, adsorption techniques, and biomarker-guided strategies allow efficient clearance of toxins while minimizing complications like albumin loss or hemody-

namic instability. Integrating these approaches with disease-specific and supportive therapies enables proactive management in critically ill patients. Overall, extracorporeal therapies represent a promising but still adjunctive approach whose renal benefits require confirmation in prospective studies. Looking ahead, prospective studies should determine which patient groups, such as those with myeloma- *vs.* rhabdomyolysis-associated AKI, benefit most from biomarker-guided timing of extracorporeal therapy. Ultimately, a precision medicine strategy that matches extracorporeal techniques to pathophysiology, patient stability, and toxin characteristics should become the cornerstone of care, improving both kidney outcomes and overall survival in this high-risk population.

CRediT Authorship Contribution Statement

Silvia De Rosa: Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Fiorenza Ferrari:** Writing – review & editing, Writing – original draft, Methodology. **Diana Zarantonello:** Writing – review & editing, Writing – original draft. **Alessia Dalpiaz:** Writing – review & editing, Writing – original draft. **Sergio Lassola:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Data Availability

No new data were generated or analyzed in this study. Data sharing is not applicable to this article as no datasets were created or used.

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