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Contemporary Management of Severe Acute Kidney Injury and Refractory Cardiorenal Syndrome:

JACC Council Perspectives

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APPENDIX For supplemental tables, please see the online version of this paper.

Abstract

Acute kidney injury (AKI) and cardiorenal syndrome (CRS) are increasingly prevalent in hospitalized patients with cardiovascular disease and remain associated with poor short- and long-term outcomes. There are no specific therapies to reduce mortality related to either AKI or CRS, apart from supportive care and volume status management. Acute renal replacement therapies (RRTs), including ultrafiltration, intermittent hemodialysis, and continuous RRT are used to manage complications of medically refractory AKI and CRS and may restore normal electrolyte, acid-base, and fluid balance before renal recovery. Patients who require acute RRT have a significant risk of mortality and long-term dialysis dependence, emphasizing the importance of appropriate patient selection. Despite the growing use of RRT in the cardiac intensive care unit, there are few resources for the cardiovascular specialist that integrate the epidemiology, diagnostic workup, and medical management of AKI and CRS with an overview of indications, multidisciplinary team management, and transition off of RRT.

Keywords

acute kidney injury; cardiorenal syndrome; dialysis; heart failure; hemofiltration; renal replacement therapy; ultrafiltration

The prevalence of acute kidney injury (AKI) and chronic kidney disease (CKD) in patients with acute cardiovascular disease is growing, highlighting an increasingly complex patient population at significant risk of adverse outcomes despite multispecialty provider input and optimal supportive care (1,2). Cardiorenal syndrome (CRS) represents a subset of AKI or CKD that develops in the context of worsening cardiovascular disease, recognizing that not all renal dysfunction developing in patients with cardiovascular disease is due to CRS (Central Illustration) (3,4).

PREVALENCE OF AKI IN CARDIAC INTENSIVE CARE UNIT PATIENTS

AKI occurs in approximately 1 in 4 patients hospitalized with cardiovascular disease, including up to 47% of patients with acute decompensated heart failure and 15% to 30% of patients with acute coronary syndrome (ACS) (3,5-7). In the cardiac intensive care unit (CICU), the reported prevalence of AKI is 25% to 50% (with up to one-third having severe AKI) and up to 38% having underlying CKD, emphasizing the substantial burden of CRS (1,2,8-11). These rates are comparable to general intensive care unit patients, in whom the incidence of AKI was 57% in a large, multinational study (12). AKI requiring dialysis (AKI-D) occurs in 20% of patients with AKI and in 1% to 3% of patients hospitalized with heart failure or ACS (5,13-15). AKI-D is more common in CICU patients (5% to 8%) and may exceed 13% in patients with cardiogenic shock (1,2,9,16,17).

The severity of underlying CKD is 1 of the strongest risk factors for AKI, reflecting reduced renal reserve and impaired ability of the kidneys to respond to stress (3,7,18). Older age, hypertension, diabetes mellitus, heart failure, and sepsis are also important risk factors for AKI, as are higher severity of illness, hypotension and/or shock, and the need for vasopressors (3,6,7,12,18). Larger infarct size and higher Killip Class are

associated with a higher risk of AKI among patients with ACS (6,7). Furthermore, the use of iodinated radiocontrast material during cardiovascular interventional procedures is an important contributor to AKI risk, with contrast-associated AKI occurring in approximately 15% of patients with ACS who undergo percutaneous coronary intervention (19,20). Thus, common CICU admission diagnoses, comorbidities, and procedures represent significant risk factors for AKI (12).

OUTCOMES ASSOCIATED WITH AKI IN CICU PATIENTS.

AKI and CKD are consistently associated with higher short- and long-term mortality across populations of patients with acute cardiovascular disease and critical illness, including a persistent hazard for death and adverse cardiovascular events among hospital survivors (3,5,7,8,10-15,17,19,21-23). Elevated levels of creatinine, blood urea nitrogen, and cystatin C, which reflect a lower glomerular filtration rate, demonstrate a direct graded relationship with mortality in patients with acute cardiovascular disease, particularly among hospitalized patients with heart failure (3,23-25). Increases in serum creatinine during hospitalization for acute heart failure have frequently been associated with higher short-term mortality, although this mortality risk is dependent on other factors, such as the presence of residual congestion (3,4). The need for dialysis is a major risk factor for mortality among CICU patients and patients with AKI, and patients who develop AKI-D have poor short- and long-term outcomes, including high rates of mortality and dialysis dependence (11,16,26). In 1 study, patients admitted to the CICU for dialysis initiation had a mortality risk similar to patients admitted with cardiogenic shock or cardiac arrest (16). Mortality risk in patients with AKI depends on the severity of AKI, age, overall illness severity, presence and severity of other organ failures, and degree of renal function recovery. Low urine output, more severe volume overload, and greater net fluid accumulation are additional risk factors (12,22,27).

PATHOPHYSIOLOGY OF AKI AND CRS IN CARDIAC CRITICAL ILLNESS.

CRS was initially defined as worsening kidney function (i.e., AKI) that occurred during treatment for acute decompensated heart failure with persistent congestion and diuretic resistance; more recently, CRS has been envisioned as a spectrum of acute or chronic disorders of heart and kidney function characterized by mutual deterioration (4). CRS can be conceptually distinguished from other forms of AKI based on its intrinsic relationship with worsening cardiac function and often presents with a reversible decrease in kidney function without overt tubular injury (4). CRS has been sub-classified into 5 types based on chronicity and the primary organ dysfunction driving the syndrome (Figure 1) (4,28). Numerous inter-related pathophysiological mechanisms are involved in the reciprocal worsening of cardiac and renal functions seen in patients with CRS, including hemodynamic, neurohumoral, and inflammatory processes that potentially lead to reductions in glomerular filtration rate and tubular injury (Figure 1) (4,28).

Acute CRS is defined as an abrupt worsening of cardiac (CRS type 1) or kidney (CRS type 3) function that leads to AKI or acute heart failure, respectively. Right-sided heart failure often drives CRS type 1 by producing venous congestion, which reduces renal perfusion pressure and triggers intrarenal mechanisms that decrease renal function (3,29). AKI can trigger worsening heart failure and CRS type 3 via direct myocardial injury from oxidative

stress, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, and the harmful effects of fluid overload, uremia, electrolyte imbalance, and acidemia (28). Among other important mechanisms, the pro-inflammatory state of chronic heart failure can cause renal tubular injury, leading to fibrosis and CKD (CRS type 2) (28). CKD can likewise cause or intensify heart failure via volume and pressure overload and can aggravate cardiomyopathy due to uremic toxins and acidemia (CRS type 4) (28). CRS type 5 involves simultaneous acute or chronic cardiac and renal dysfunction secondary to a systemic disorder (e.g., sepsis). Chronic CRS (CRS types 2 and 4) often co-exists simultaneously with acute CRS (CRS types 1 and 3), reflecting acute chronic cardiac and renal dysfunction, making it difficult to distinguish CRS subtypes in patients presenting with combined heart and kidney failure (3,4).

DIAGNOSIS, WORKUP, AND STAGING OF AKI IN CICU PATIENTS.

Standard criteria for AKI have been developed by the Kidney Disease: Improving Global Outcomes group, which classifies AKI into 3 progressive stages based on changes in serum creatinine and urinary output over hours to days (Figure 2) (30). Elevated levels of urinary tubular injury biomarkers have been validated to predict the development and progression of AKI, and these tests can improve prognostication when added to conventional functional indexes of AKI (31,32). A common sign of severe AKI is an acute reduction in urine output (unless masked by diuretic use), and oliguric AKI is more likely to progress and require dialysis. Any acute decrease in urine output in a CICU patient should be promptly evaluated to identify and treat reversible causes (33).

For patients presenting with AKI or CRS, careful evaluation is needed to determine the etiology, including a detailed history and physical examination, volume status assessment, urinalysis, and urine microscopy, and a careful review of medication history to evaluate the use of renally eliminated and nephrotoxic drugs (Figure 2) (21). An essential step in the evaluation of patients with CRS is the assessment of filling pressures (congestion) and forward flow (perfusion) based on physical examination, echocardiography, and/or invasive hemodynamics (Figure 2) (3). Other causes of AKI, such as hypovolemia, nephrotoxins, or acute tubular necrosis due to hypotension and/or shock are not necessarily classified as CRS (3). A urinary albumin to creatinine ratio can be useful to evaluate for the presence and severity of CKD. A renal ultrasound can assess kidney size and echogenicity and exclude hydronephrosis as a cause of AKI.

Prognostic biomarkers in CRS include clearance biomarkers (which reflect glomerular filtration rate), tubular injury biomarkers, natriuretic peptides reflecting congestion, and biomarkers suggesting neurohumoral activation or inflammation (34). Natriuretic peptide levels can be elevated in all CRS subtypes, and a normal natriuretic peptide level suggests a cause of AKI other than CRS type 1. Increases in clearance biomarkers are characteristic of AKI, but reductions in glomerular filtration rate occur before biomarker changes, emphasizing the importance of oliguria as an early warning sign of AKI (32,33). Serum cystatin C is a clearance biomarker analogous to serum creatinine with higher sensitivity for AKI and additive prognostic value beyond serum creatinine levels (35,36).

MEDICAL MANAGEMENT OF AKI AND CRS BEFORE INITIATION OF RENAL REPLACEMENT THERAPY.

Management of AKI and CRS generally involve optimization of hemodynamics and fluid balance, and avoidance or discontinuation of potential nephrotoxins (Central Illustration). Common nephrotoxic medications include certain antimicrobial drugs (particularly aminoglycosides), nonsteroidal anti-inflammatory drugs, and iodinated radiocontrast. All renin-angiotensin-aldosterone system inhibitors can reduce the glomerular filtration rate and should be held during severe AKI (20,21). Because of the potentially beneficial effects of renin-angiotensin-aldosterone system inhibitors in patients with cardiovascular disease, continuing these medications initially may be reasonable during mild AKI and CRS, but caution is needed. Apart from preventative measures, there are no universally accepted therapies that consistently improve renal function recovery or clinical outcomes in patients with AKI or CRS (3,4,21). Cautious fluid administration guided by markers of fluid responsiveness can be considered (3). Excessive fluid administration should be avoided to prevent harmful volume overload (22,27).

Loop diuretics are useful for patients with CRS and AKI to prevent or treat fluid overload, and successful diuresis can potentially lead to improved renal function by relieving renal venous congestion (4,22). For most patients, intravenous bolus dosing or continuous infusion of loop diuretics at equivalent doses will produce similar diuresis, with a comparable safety profile and no demonstrated difference in clinical outcomes (37). In our clinical experience, the greater control of diuresis allowed by a continuous loop diuretic infusion may be advantageous for selected patients, such as those with hemodynamic instability who may not tolerate bolus dosing, as well as in patients in whom careful diuretic titration or high diuretic doses are required. Although loop diuretics can transiently reduce glomerular filtration rate, they are not considered directly nephrotoxic (3).

Although diuretics have not been demonstrated to reduce mortality or prevent the need for dialysis in patients with AKI, patients who respond to diuretics appear to have better outcomes (38). A loop diuretic challenge or furosemide stress test can be performed in patients with AKI by measuring the urine output after a dose of 1.0 to 1.5 mg/kg of intravenous furosemide (39-42). Patients who have a urine output <200 ml over the first 2 h are at increased risk of progressive AKI and potential need for renal replacement therapy (RRT); a 6-h urine output <600 ml is predictive of the need for RRT in patients with stage III AKI (39-42). Intravenous furosemide doses up to 200 to 240 mg can occasionally produce diuresis in patients with severe AKI who fail to respond to a standard furosemide challenge.

The addition of a second diuretic, frequently a thiazide-type diuretic, to ongoing loop diuretic therapy can potentially overcome diuretic resistance and increase urine output (Figure 3) (43-46). Close monitoring of electrolytes is warranted when using combination diuretic therapy due to the elevated risk of electrolyte disturbances (43). Although tolvaptan and aldosterone antagonists can augment diuresis in selected patients with CRS, these agents have not improved kidney function or clinical outcomes in patients with acute heart failure (46-49). A randomized study in 60 loop diuretic-resistant patients hospitalized with heart failure demonstrated similar augmentation of urine output with the addition of oral metolazone, intravenous chlorothiazide, or oral tolvaptan (46). Small-volume hypertonic

saline may also improve diuretic responsiveness and renal function in patients with CRS, potentially by amelioration of neurohormonal activation (50).

The optimal systemic hemodynamic goals for the prevention and treatment of AKI and CRS are unknown, although avoidance of hypotension and low-output states is prudent (30). No specific vasoactive drug has been shown to prevent or treat AKI or CRS, including inotropes or vasodilators (3,4,21). Dopamine has cardiac inotropic and direct kidney effects that can enhance kidney function and diuresis in some patients, but dopamine has not improved clinical or renal outcomes in patients with AKI (51). Dopamine has not consistently improved kidney function, diuresis, or clinical outcomes in patients with CRS, although a possible beneficial effect of low-dose dopamine has been observed in patients with CRS with systolic heart failure (52-54). Inotropic therapy is most likely to be effective in patients with CRS with hypotension or objective evidence of reduced cardiac output, and empirical use of inotropes should be avoided due to their potential toxicity (44,45).

ULTRAFILTRATION IN REFRACTORY CRS.

Isolated ultrafiltration (aquapheresis) is a potential option for management of diuretic-resistant heart failure and refractory CRS (Central Illustration), although patients with severe kidney dysfunction (e.g., serum creatinine >2.5 mg/dl) may benefit from another RRT modality that provides clearance (44,45,55). No widely accepted standard criteria exist for initiating ultrafiltration in patients with heart failure, but it is reasonable to consider ultrafiltration for fluid-overloaded patients with severe diuretic resistance despite adequate kidney function (44,45,55). No studies have prospectively examined the optimal timing of ultrafiltration initiation in patients with heart failure and CRS, although ultrafiltration appears to be more beneficial if applied within 24 h of admission (55,56). The use of ultrafiltration may provoke less neurohormonal activation than diuretic therapy, which leads to greater sustainability of beneficial effects (57,58). Reversal of renal venous congestion using ultrafiltration can improve diuretic responsiveness, particularly in patients with significant right-sided heart failure (59,60).

Ultrafiltration is a safe alternative to diuretic therapy in patients with heart failure or CRS who are not medically refractory, and studies have generally shown greater decongestion and lower rates of subsequent rehospitalization with ultrafiltration, but no improvement in renal function or mortality (55,56,61,62). In the CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), ultrafiltration was associated with a greater rise in serum creatinine without improved fluid removal or clinical outcomes in CRS patients compared with a stepped diuretic algorithm that involved escalating doses of furosemide infusion ± metolazone (Table 1) (62). For most patients with CRS, a stepped diuretic algorithm similar to that used in the CARRESS-HF and AVOID-HF (Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure) trials (Table 1) is a reasonable first-line strategy (56,62). Some patients will respond to diuretic doses greater than those used in CARRESS-HF, but the safety profile is uncertain, and transitioning to ultrafiltration is reasonable for patients who do not respond adequately to high-dose diuretic therapy (43-45).

USE OF RRT IN CRITICALLY ILL CARDIAC PATIENTS.

Traditionally, the decision to initiate urgent RRT in critically ill patients with AKI or CRS is based on the standard "AEIOU" indications: acidosis, electrolyte derangements, intoxications, volume overload, and uremia (Table 2) (63). The most common indication for continuous RRT (CRRT) initiation in CICU patients is medically refractory volume overload with hemodynamic instability (64). We support standard RRT initiation guidelines, although there may be some unique CICU-specific indications for initiating RRT (Table 2) (63,64).

A meta-analysis that examined the timing of RRT initiation did not demonstrate any significant differences in mortality, renal recovery, or other outcomes in patients with severe AKI who were randomized to early or late RRT initiation (65). The AKIKI (Artificial Kidney Initiation in Kidney Injury) study randomized 620 critically ill patients with stage 3 AKI to immediate RRT initiation or deferred RRT initiation until patients developed severe hyperkalemia, metabolic acidosis, pulmonary edema, severe azotemia, or oliguria for >72 h (66). No difference in mortality was observed, and nearly one-half of the delayed RRT group did not require RRT (66). By contrast, the randomized ELAIN (Early versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury) study demonstrated lower mortality in 231 critically ill, predominantly post-operative patients with stage 2 AKI and elevated markers of tubular injury (plasma neutrophil gelatinase-associated lipocalin [NGAL] >150 ng/ml) who received immediate RRT initiation versus deferral of RRT initiation until the development of stage 3 AKI (67). The totality of evidence suggests that patients with AKI who do not have a specific indication for RRT initiation may safely be observed initially, even in the presence of oliguria (i.e., urine output <400 to 500 ml/day). The development of diuretic refractory symptomatic fluid overload should prompt consideration of RRT (63).

BASICS OF RRT.

RRT removes metabolic wastes and excess water, balances electrolytes, and replenishes buffers in patients with severe AKI and patients with end-stage renal disease (30,63). In the United States, hemodialysis is used most commonly for acute RRT. The apparatus for performing RRT consists of a dialyzer with a semipermeable membrane, replacement fluid or dialysate (dialysis solution), sterile tubing for the transport of blood and dialysate, and a machine to power and monitor the procedure using sensors and alarms (Figure 4). The semipermeable dialyzer membrane allows the bidirectional exchange of solutes and fluid between a patient's blood and dialysate without loss of large molecular weight substances or cells.

Metabolic clearance through the semipermeable membrane occurs primarily via diffusion (Figure 5) and convection (Figure 6), which can be used either alone or together during CRRT. Diffusive clearance is determined by the concentration gradient between the solute in the blood and dialysate, which is maximized during hemodialysis by countercurrent blood and dialysate flow. Convective clearance uses a hydrostatic pressure gradient to extract plasma water and small molecular weight solutes, leading to ultrafiltration of isotonic fluid. Fluid removed by convection during ultrafiltration increases intravascular plasma osmolality and oncotic pressure, which mitigates the potential hypotensive effects of rapid volume

removal, whereas solute removal by diffusion during hemodialysis can result in decreased plasma osmolality and hypotension from fluid shifts (68).

RRT MODALITIES.

Intermittent RRT modalities, such as intermittent hemodialysis (IHD), last 3 to 6 h/day, whereas CRRT ideally runs 24 h/day (Table 3). Standard modalities of CRRT include slow continuous ultrafiltration, continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), or continuous venovenous hemodiafiltration (CVVHDF). Aquapheresis is a volume removal procedure without the intent of solute removal by ultrafiltration that can be performed via a portable machine and peripheral venous access (55). Hybrid slow RRT modalities with intermediate or extended treatment durations, such as sustained low-efficiency dialysis, can be provided using standard IHD machines, with lower resource use, less need for anticoagulation, and less patient immobility compared with CRRT (69). The choice of RRT modality depends on the expertise of the treating physician, local availability, hemodynamic stability, vascular access, and indication (Table 3); data comparing different RRT modalities in patients with CRS are lacking (63,70).

The choice of acute RRT modality (IHD vs. CRRT) does not appear to influence survival or subsequent renal recovery in patients with AKI (71). CRRT uses a lower blood flow rate than IHD, which allows better hemodynamic tolerance; aquapheresis can be performed using a blood flow rate as low as 40 ml/min (55). Because hemodynamic instability during RRT is influenced by the rate of fluid and solute removal, the major advantage of CRRT is slower and more controlled solute and fluid removal compared with IHD (Table 3) (63). The longer duration of CRRT compared with IHD allows greater daily fluid removal, making CRRT particularly useful in the presence of massive hypervolemia (63). CRRT is associated with improved cardiovascular stability, more consistent daily fluid removal, and better metabolic control compared with IHD (Table 3) (72,73). IHD is more effective for rapid fluid and solute removal and is preferred for patients with acute pulmonary edema, intoxications, or severe acid-base and electrolyte imbalances (e.g., hyperkalemia) (Table 3). Other potential advantages of IHD include improved patient mobility, a lower nursing workload, and lower costs (Table 3) (74-76). Hemodynamic effects, fluid removal, metabolic control, 30-day mortality, and RRT liberation are similar between CRRT and hybrid RRT modalities and between different CRRT modalities (77,78).

Vascular access via an arteriovenous fistula is the preferred approach for maintenance IHD in patients with end-stage renal disease, but this approach is not effective for initiating acute IHD or CRRT. Venous access via a large-bore, high-flow, dual-lumen central venous dialysis catheter in the right internal jugular or femoral vein is necessary for acute CRRT or IHD. Catheter placement in the subclavian or brachial vein should be avoided to prevent subsequent venous stenosis (63). CRRT is preferred for management of AKI-D in patients receiving extracorporeal membrane oxygenator support, which is performed either using a dedicated catheter and separate circuit or via attaching a CRRT circuit to the venous limb of the extracorporeal membrane oxygenator circuit (79). Separate CRRT cannulation is the simplest setup to manage but requires additional large-caliber venous access.

EFFECTS OF CRRT ON DRUG PHARMACOKINETICS.

Depending on the mode, drug clearance during CRRT is determined by the ability of the drug to pass through the filter, pre-filter fluid administration (which reduces clearance), rate of blood flow, dialysate flow, and ultrafiltration rate (80-83). During CVVHDF, clearance occurs through a combination of convective and diffusive clearance, whereas drug clearance by ultrafiltration or aquapheresis is not clinically significant (80). Few published studies have characterized the effect of CRRT on the pharmacokinetics of common drugs used in the CICU (Supplemental Table 1).

For drugs with substantial renal excretion, dose reduction is necessary for patients with AKI, and dosing must be further adjusted when initiating or discontinuing RRT. Although dosing recommendations during IHD are available for many drugs, drug dosing recommendations for patients on CRRT are currently not included in the labeling for drugs approved by the Food and Drug Administration (84). Expert consultation is recommended to determine drug dosing specific to the CRRT modality being used. The clearance of drugs may be higher with prolonged CRRT than IHD, depending on the CRRT modality and dose. Close attention to appropriate drug dosing is necessary when CRRT is interrupted or discontinued for more than a brief period, or during transition onto or off of IHD. Patients who receive IHD require a diet that is restricted in fluid, sodium, potassium, and phosphorous, as well as modified in protein, whereas patients receiving CRRT may not need these electrolytes restricted and may require electrolyte and protein supplementation (30).

Cardiac medications such as intravenous inotropes, vasopressors, and vasodilators are not substantially cleared by either CRRT (Supplemental Table 1) or IHD. Milrinone accumulates during AKI, with a half-life of up to 20 h in patients on CVVH, leading to drug accumulation and toxicity even at low doses (85). Renally excreted antiarrhythmic drugs can accumulate to toxic levels in patients with AKI, and clearance by either CRRT or IHD is unreliable, so alternative drugs should be used in patients with AKI-D. The most commonly used drugs requiring altered dosing for patients with AKI-D are antimicrobial agents, which typically require higher and/or more frequent doses for patients on CRRT compared with that of IHD (82,83).

CRRT BEDSIDE MANAGEMENT AND TROUBLESHOOTING.

The CVVH prescription consists of 4 parts: blood flow rate, replacement fluid rate, replacement fluid composition, and net patient fluid removal (Supplemental Table 2). In CVVHD and CVVHDF, dialysate composition and dialysate flow rate are also prescribed. Blood flow rate is typically set at 150 to 250 ml/min in adults, because lower blood flow rates promote hemostasis and filter clotting; higher blood flow rates can lead to pressure alarms and CRRT interruption. CVVH removes a large volume of plasma ultrafiltrate via convection, exchanging it with a balanced replacement fluid mirroring the solute content of normal plasma (Figure 6). The dose of CVVH is the total effluent rate (roughly equivalent to the replacement fluid rate) and is typically set at 25 to 35 ml/kg/h; higher dose CRRT regimens have not been shown to improve outcomes in patients with AKI (86). Replacement fluid can be administered 100% pre-filter or split pre- and post-filter (Figure 6). Pre-filter fluid administration dilutes the blood in the filter, which reduces the risk of

filter clotting at the expense of clearance, whereas post-filter fluid administration favors clearance at the expense of clotting risk. The bicarbonate concentration in the replacement fluid can be increased in patients with severe metabolic acidosis, but patients who receive high-bicarbonate replacement fluid are at increased risk of adverse outcomes (87). The net patient fluid removal (ultrafiltration) rate is adjusted to achieve fluid balance goals. Although higher ultrafiltration rates may be used temporarily for patients with severe volume overload, daily average net ultrafiltration rates >1.75 ml/kg/h may be associated with worse outcomes (88). High ultrafiltration rates can also dehydrate the filter and increase the risk of clotting (Supplemental Table 2).

Frequent monitoring of CRRT is necessary, and troubleshooting strategies for common CRRT circuit issues are outlined in Table 4. Monitoring transmembrane pressure helps to track filter patency, and a rising transmembrane pressure is a harbinger of filter clotting that may warrant electively returning the patient's blood (before blood is wasted within a clotted filter) and replacing the circuit (Table 4). Frequent electrolyte monitoring every 6 to 12 h is necessary, including calcium, phosphorous, and magnesium. Phosphorous is cleared efficiently by CRRT, and patients may require phosphorous repletion during CRRT. Hypotension occurs in up to two-thirds of patients who are started on CRRT, many of whom are already in shock and require vasopressors (64,89). Hemodynamic intolerance to ultrafiltration in volume-overloaded patients with hypotension can be ameliorated in some patients by administration of hyperoncotic albumin (if hypoproteinemic), blood transfusion (if anemic), and/or lower extremity wrapping. CRRT can induce hypothermia and potentially mask fevers, warranting a high index of suspicion for infection.

Clotting of the CRRT circuit can be prevented by adjusting the CRRT prescription or adding an anticoagulant to extend the life of the CRRT filter (Table 4). To perform CRRT without anticoagulation, high blood flow rates and pre-filter replacement fluid are used (Table 4). Heparin can be administered either systemically or regionally by infusing the heparin pre-filter (Supplemental Table 2). As an alternative to heparin, regional administration of citrate solution pre-filter prevents filter clotting by chelating calcium akin to banked blood. Although citrate is more effective for anticoagulation during CRRT and is associated with less bleeding than heparin, the use of citrate requires close monitoring of ionized calcium levels and additional central venous access for administration of a calcium infusion to maintain normal systemic ionized calcium levels (90,91). Accumulation of citrate can cause significant toxicity with worsening anion-gap metabolic acidosis and ionized hypocalcemia that triggers hypotension. Patients with liver failure and profound shock cannot efficiently clear citrate and may require lower citrate doses to avoid toxicity (92). An elevated ratio of total to ionized calcium >2.4 suggests citrate accumulation and an increased risk of death (93).

ASSESSMENT OF RENAL RECOVERY AND CRRT DISCONTINUATION.

Rates of CRRT discontinuation success vary widely (21% to 60%) among intensive care unit patients (94-96). In 1 study, 48% of CICU patients with AKI-D who survived hospitalization were ultimately transitioned to IHD (64). There are currently no widely accepted specific criteria to guide renal function recovery assessment for the discontinuation of CRRT. As an

indicator of renal recovery in CRRT patients, urine output had a sensitivity of 66% and a specificity of 74% in a meta-analysis of observational studies that used different 24-h urine output thresholds (95-98). In a retrospective study of 1,006 intensive care unit patients who received CRRT, urine output was the strongest predictor of successful CRRT discontinuation (odds ratio: 1.08 per 100 ml/day increase; area under the curve: 0.81) (95). A cutpoint of 400 ml/day without the use of diuretics had a positive and negative predictive value of 80.9% and 76.5%, respectively. In a randomized study of 71 patients on CRRT, those who received a furosemide infusion after CRRT discontinuation had higher urine volume, with no differences in renal recovery or repeat need for CRRT (99). We suggest that urine output ≥400 ml over 24 h in the absence of diuretic administration is a reasonable predictor of renal recovery for patients on CRRT (Central Illustration); diuretics should be used primarily to enhance urine output after CRRT discontinuation. Although angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be held during AKI until recovery occurs, resuming these important drugs after AKI recovery appears to be associated with better long-term outcomes (100,101).

TRANSITIONS TO IHD.

The suitability for transitioning from CRRT to IHD should be assessed daily by the CICU and nephrology teams. There are no set criteria or timing standards for transitions from CRRT to IHD in either AKI or CRS, but potential considerations in CICU patients include the resolution of the initial indication for CRRT (Table 2), hemodynamic stability on minimal doses of vasoactive agents, and/or near-euvolemia with the anticipated ability to tolerate daily fluid removal goals with IHD. It is not known whether the criteria for transitioning from CRRT to IHD should differ for patients with end-stage renal disease versus patients with AKI-D or CRS, but caution should be taken in patients with AKI-D because recurrent hypotension associated with the transition to IHD could adversely affect renal recovery (Table 3). At least one-third of patients cannot be successfully liberated from CRRT, typically due to persistent hypotension that results in intolerance of IHD (64,95,102). Initiation of oral midodrine or droxidopa can allow weaning from intravenous vasopressors and prevent hypotension during IHD, but these alpha-agonists are potentially harmful to patients with cardiovascular disease (103).

PROGNOSIS AND PREDICTORS OF OUTCOME AMONG CICU PATIENTS REQUIRING RRT.

Although the indication for CRRT influences the observed mortality, the provision of CRRT is associated with poor outcomes among CICU patients, with hospital mortality rates of at least 40% to 50% and 1-year mortality >70% (26,64,104). Among 199 CICU patients who received CRRT at a single center, 53% died in the hospital and 50% of hospital survivors required dialysis at discharge, which produced a dialysis-free hospital survival of 22% (64). Hospital survivors had 39% 1-year mortality, and overall 1-year survival was only 29% (64). In a multicenter study of 178 CICU patients who received dialysis (including CRRT and IHD), 42% died in the hospital (26). Among general intensive care unit patients who received CRRT in randomized clinical trials, the pooled hospital mortality was 58% (71). Short-term mortality was 30% in patients treated with ultrafiltration or CRRT for refractory CRS, but 1-year mortality was 95%; patients who responded to ultrafiltration without needing CRRT had better outcomes (105,106). Patients with acute coronary syndromes who

required CRRT had a 41% hospital mortality rate, which contrasted with >60% mortality for patients with cardiogenic shock and AKI-D (14,17,26). Among patients who received CRRT, those with end-stage renal disease might have had lower short-term mortality than those with AKI-D (89). Predictors of higher hospital mortality in patients who receive CRRT include older age, hypotension (particularly early after CRRT initiation), greater vasopressor requirements, greater fluid overload, worse right ventricular function, higher overall illness severity, frailty, hyperphosphatemia, and worse oxygenation (64,89,104,106-110).

MULTIDISCIPLINARY TEAM-BASED CARE FOR RRT PATIENTS.

Acute RRT constitutes a resource-intensive intervention that requires specialized skills and a dynamic individualized approach to the patient's changing clinical status in the context of the patient's acute illness and underlying comorbidities (111). Appropriate delivery of CRRT requires simultaneous attention to the patient's clinical status, fluid and electrolyte balance, hemodynamics, drug dosing, and anticoagulation (Central Illustration), as well as assessing the technical components of the CRRT circuit (Table 4). There is no single evidence-based approach to the staffing or care for patients undergoing CRRT, and each institution should determine the optimal composition of the multidisciplinary team as well as adequate nurse staffing ratios. We believe that multidisciplinary CICU teams caring for patients receiving CRRT should ideally include providers with expertise in critical care medicine, cardiovascular medicine, critical care nursing, pharmacy, nutrition, and nephrology. The American Society of Nephrology Acute Kidney Injury Advisory Group emphasizes the importance of nephrologists in supporting CRRT in collaboration with critical care physicians (112). Regular, structured, multidisciplinary evaluation of CRRT quality is essential (113). Nonrandomized studies suggest that having specialized CRRT nurses can free the general critical care nurse to focus on other aspects of patient care (114,115). A single-center retrospective observational study in South Korea that evaluated 1,104 patients who underwent RRT before and after the implementation of a specialized CRRT team, which consisted of a nephrologist and 2 nurses, found that time to CRRT initiation, downtimes, and in-hospital mortality rates decreased after implementation of the specialized CRRT team (114).

END-OF-LIFE ISSUES IN PATIENTS RECEIVING RRT.

End-of-life issues should be considered for any critically ill patient with severe or medically refractory CRS or AKI. Early consultation with a palliative medicine specialist can be beneficial for symptom control, patient and family emotional support, and assistance with goals of care discussions even when an aggressive care plan is desired. Prognosis and quality of life are often poor even among those patients who are successfully liberated from CRRT (64,105,106,116). Patients with cardiomyopathy or heart failure have a poor prognosis on maintenance IHD, and the high rates of post-discharge mortality, rehospitalization, and dialysis dependence among hospital survivors should be discussed with the patient and family members when considering initiation of acute RRT (117). Overall goals of care should be clarified before the initiation of RRT, allowing individualized decision-making regarding a patient's quality of life and prospects for recovery. Although older patients with AKI-D with higher severity of illness and more nonrenal organ failures are at higher risk of

death, there are no established criteria for declaring futility of RRT in medically refractory AKI and CRS (3).

The presence of end-stage heart failure is associated with poor outcomes, particularly in patients who are not candidates for advanced heart failure therapies. The presence of severe kidney dysfunction often makes patients ineligible for a left ventricular assist device or heart transplantation because of a high post-operative mortality. RRT may not be appropriate for these patients unless kidney recovery can be expected (118,119). Patients and families may be faced with choosing between continuing supportive care, including prolonged CRRT in the CICU without the certainty of recovery or deciding to forego artificial life–prolonging technologies and allowing natural death. Many patients who receive CRRT are intubated and unable to directly participate in goals of care discussions, so providers and families need to make these crucial decisions on their behalf (64). Ideally, decisions to forgo CRRT and allow natural death are made after determining the medical appropriateness of supportive therapies in the context of the goals, preferences, values, and anticipated prognosis of the patient. Although withdrawing any supportive therapy is emotionally challenging for patients and providers, discontinuing RRT is bioethically equivalent to never having started RRT, especially as a patient's clinical trajectory and personal goals evolve.

The decision to forego or withdraw RRT for patients with unrecovered AKI-D or end-stage renal disease will result in death, with the time frame depending on the severity of the underlying illness and the degree of residual renal function. For patients who discontinue long-term maintenance IHD, death usually occurs within 7 days due to uremia and hyperkalemia, and hospice care is often appropriate (120). Death may occur sooner after withdrawal of CRRT for critically ill patients, particularly in the setting of discontinuing other supportive therapies (e.g., vasopressors or mechanical ventilation). A primary concern during withdrawal of life-sustaining measures is adequate control of end-of-life symptoms, most notably dyspnea due to volume overload. Family support and aggressive symptom management through pharmacotherapy is critical to proactively alleviate suffering at the end-of-life, allowing a peaceful death.

CONCLUSIONS

AKI and CRS are increasingly prevalent in patients with cardiovascular disease and remain associated with poor short- and long-term outcomes, with few established treatments available for clinicians. Patients with AKI-D and those requiring CRRT represent a growing subset of patients within the CICU environment who are at incrementally higher risk of post-discharge death and dialysis dependence. The successful provision of CRRT in the CICU environment requires an integrated multidisciplinary care team. There is a pressing need for future research to evaluate the optimal approach to the management of the growing population of cardiac patients with AKI-D and refractory CRS, including new therapies for AKI and CRS, and improved strategies for CRRT initiation, management, and transitions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

ACS	acute coronary syndrome
AKI	acute kidney injury
AKI-D	acute kidney injury requiring dialysis
CICU	cardiac intensive care unit
CKD	chronic kidney disease
CRS	cardiorenal syndrome
CRRT	continuous renal-replacement therapy
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis
CVVHDF	continuous venovenous hemodiafiltration
IHD	intermittent hemodialysis
RRT	renal replacement therapy

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HIGHLIGHTS

- AKI is increasingly common in hospitalized patients with cardiac disease.
- Initial medical therapy of acute CRS involves a stepped diuretic regimen.
- The need for RRT in AKI and CRS is associated with poor outcomes.
- Outcomes are similar for patients treated with different acute RRT strategies in the setting of AKI.

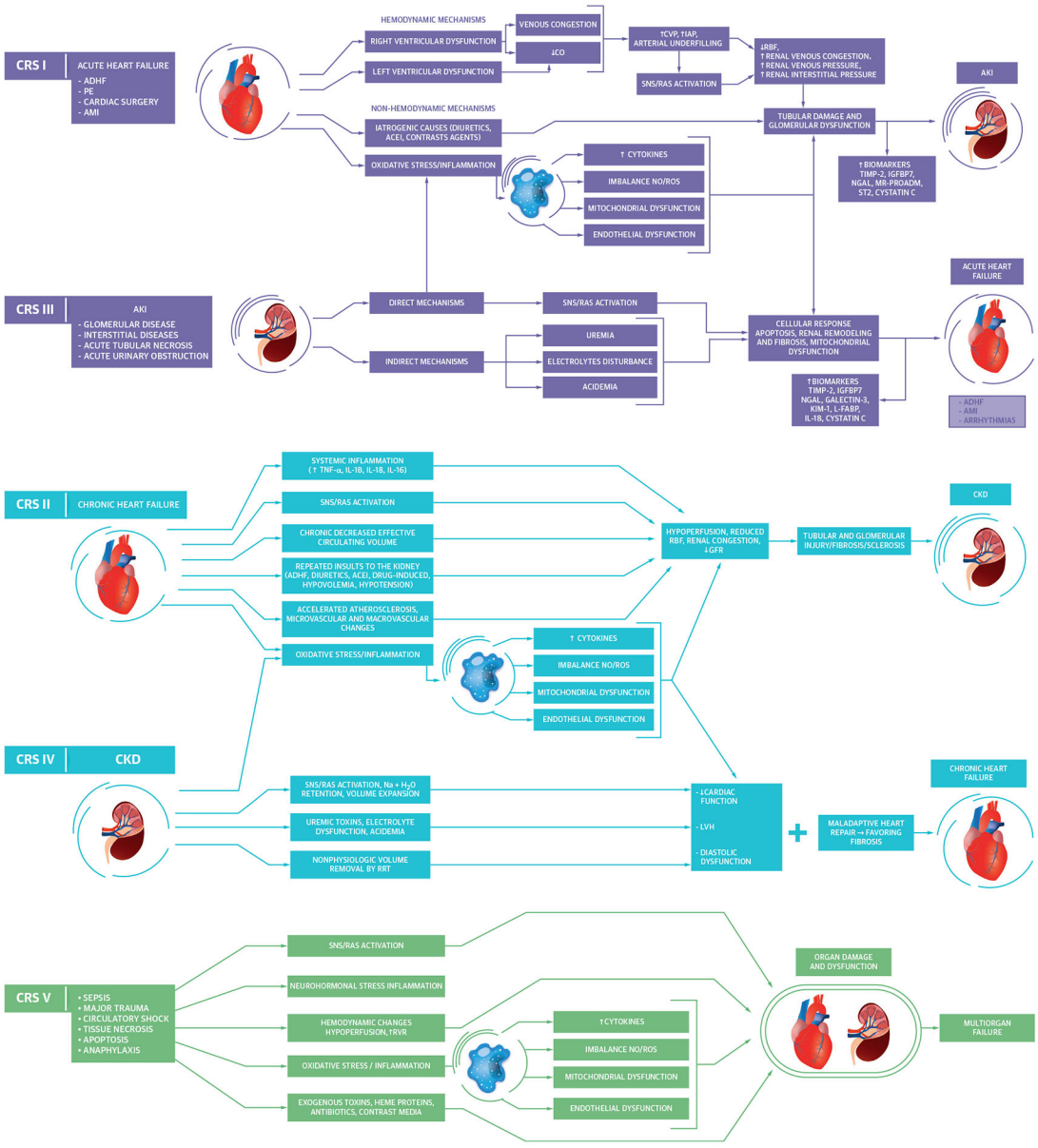


FIGURE 1. Pathophysiological Interactions Between the Heart and Kidney in CRS

Acute cardiorenal syndrome (CRS) (types 1 and 3) occurs when acutely worsening heart or kidney function, respectively, leads to worsening function of the other organ. Chronic CRS (types 2 and 4) occurs when chronic heart or kidney dysfunction, respectively, leads to worsening dysfunction of the other organ. Secondary CRS (type 5) occurs when a systemic process leads to simultaneous heart and kidney dysfunction (28,34). ACEI = angiotensin-converting enzyme inhibitor; ADHF = acute decompensated heart failure; AKI = acute kidney injury; AMI = acute myocardial infarction; CKD = chronic kidney disease; CO = cardiac output, CVP = central venous pressure; GFR = glomerular filtration rate; H_2O = water; IAP = intra-abdominal pressure; IGFBP7 = insulin-like growth factor binding protein 7; IL = interleukin; KIM-1 = kidney injury molecule 1; L-FABP = liver-type fatty acid binding protein; LVH = left ventricular hypertrophy; MR-PROADM = mid regional

pro adrenomedullin; Na = sodium; N-GAL = neutrophil gelatinase-associated lipocalin; NO/ROS = nitric oxide/reactive oxygen species; PE = pulmonary embolism; RBF = renal blood flow; RRT = renal replacement therapy; RVR = renal venous resistance; SNS/RAS = sympathetic nervous system/renin angiotensin system; ST2 = suppression tumorigenicity 2; TIMP-2 = tissue inhibitor of metalloproteinase 2; TNF = tumor necrosis factor.

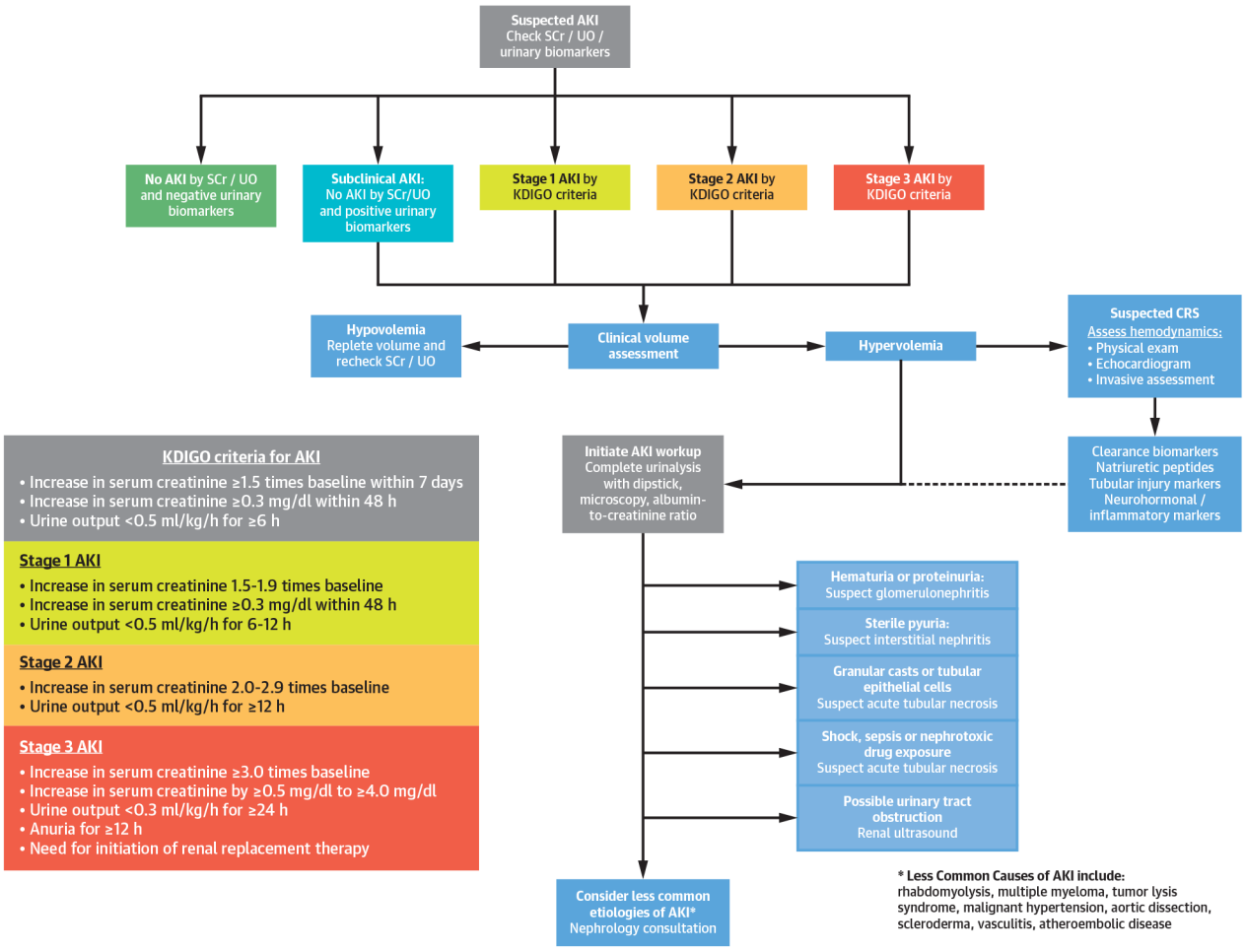


FIGURE 2. Diagnostic Approach to Patients With Suspected AKI

AKI is defined as an acute reduction in urine output or increase in serum creatinine level and is divided into 3 Kidney Disease: Improving Global Outcomes (KDIGO) AKI stages of increasing severity (21,30). The diagnostic approach for patients with AKI includes assessment of volume status and focused testing to exclude potential etiologies, including biomarker testing (21,30,32,34). Natriuretic peptides include B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP). Urinary biomarkers include TIMP-2 and IGFBP-7. Clearance biomarkers include serum creatinine (SCr), blood urea nitrogen (BUN), and cystatin C. Tubular injury biomarkers include KIM-1, L-FABP, and NGAL. Neurohormonal and/or inflammatory biomarkers include growth differentiation factor (GDF)-15, ST-2, and cancer antigen 125 (CA-125). UO = urinary output; other abbreviations as in Figure 1.

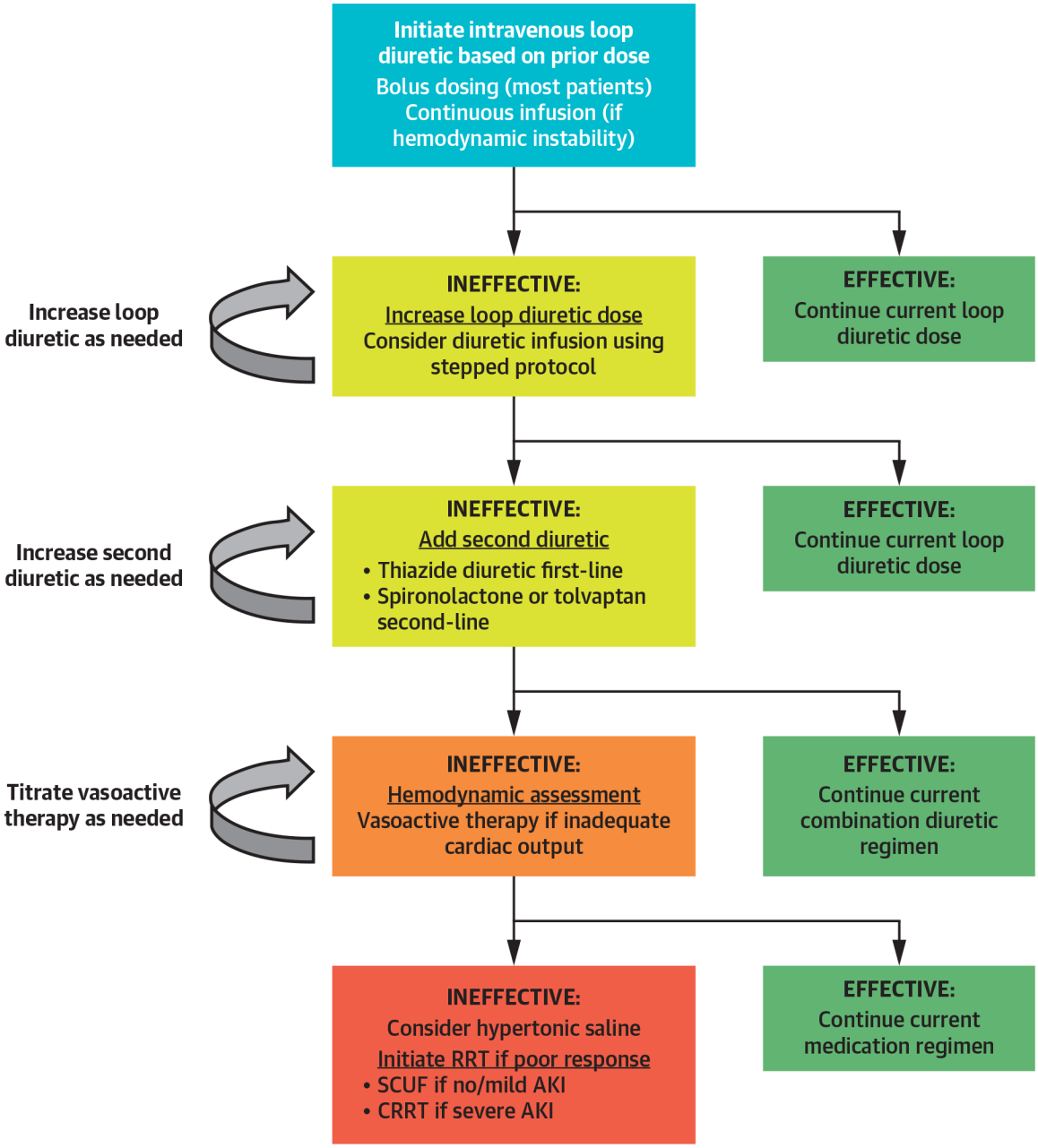


FIGURE 3. Volume Management in Patients With Acute Heart Failure and CRS

Escalating doses of loop diuretics are the first-line of therapy for volume removal, with combination diuretic therapy used for patients who do not respond adequately to loop diuretics (3). A target urine output of 3 to 5 l/day has been used in studies of stepped-diuretic therapy (56,62). Hemodynamic assessment and vasoactive therapy can be helpful in selected patients with poor response to diuretics, with extracorporeal volume removal for patients in whom medical therapy fails. CRRT = continuous renal replacement therapy; RRT = renal replacement therapy; SCUF = slow continuous ultrafiltration; other abbreviations as in Figure 1.

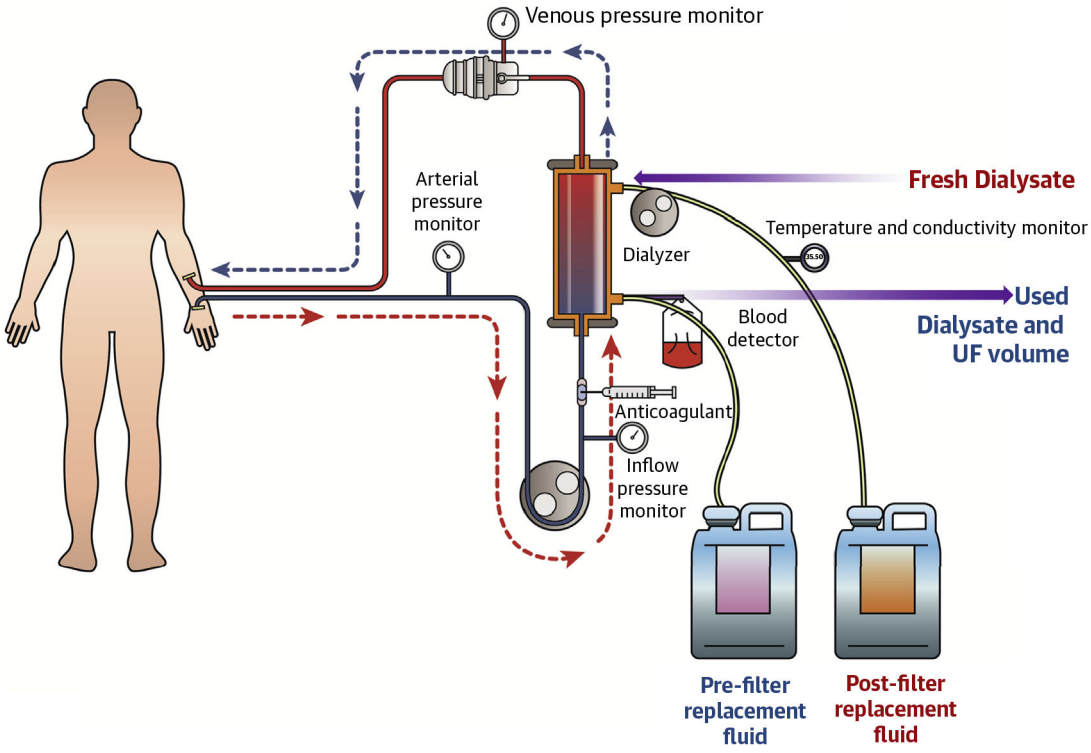


FIGURE 4. Components of a Dialysis Circuit

The dialysis circuit is composed of a dialyzer with a semipermeable membrane, replacement fluid or dialysate (dialysis solution), sterile tubing for the transport of blood and dialysate, and a machine to power and monitor the procedure using sensors and alarms. A continuous venovenous hemofiltration (CVVH) circuit contains the same components, except that dialysate is not used. UF = ultrafiltration.

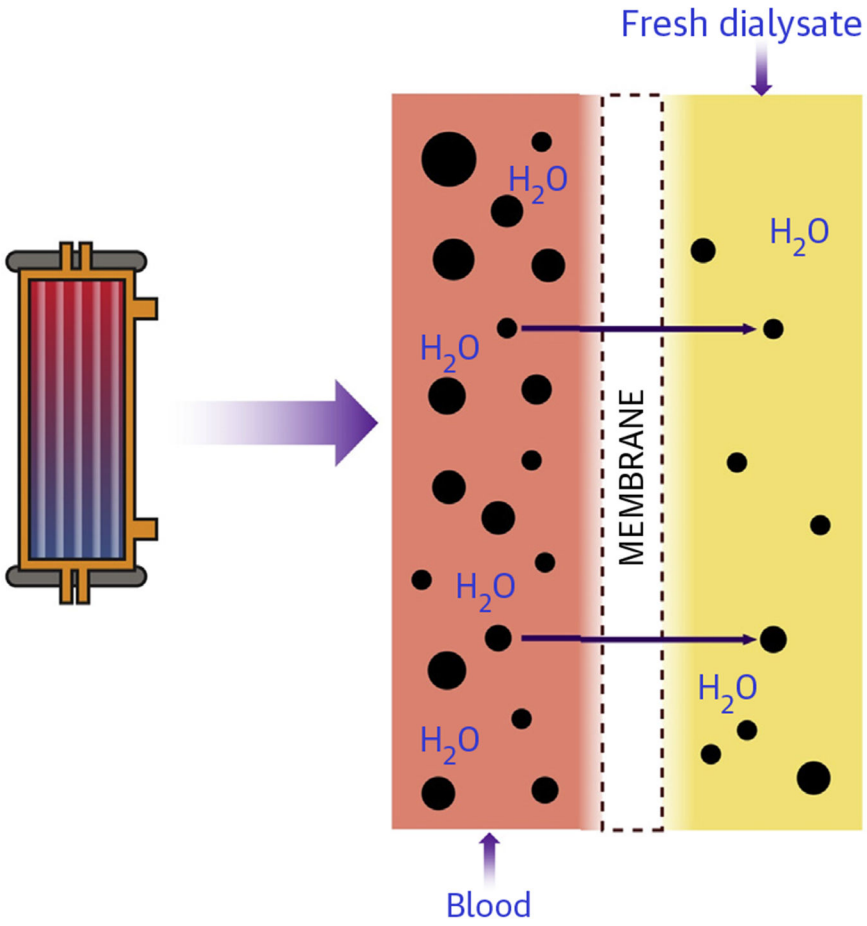


FIGURE 5. Solute Clearance by Diffusion During Hemodialysis

Blood and dialysate are separated by the semipermeable membrane, and solutes move across the membrane down a concentration gradient. With diffusive solute clearance, dialysate runs countercurrent to the blood flow to remove solutes.

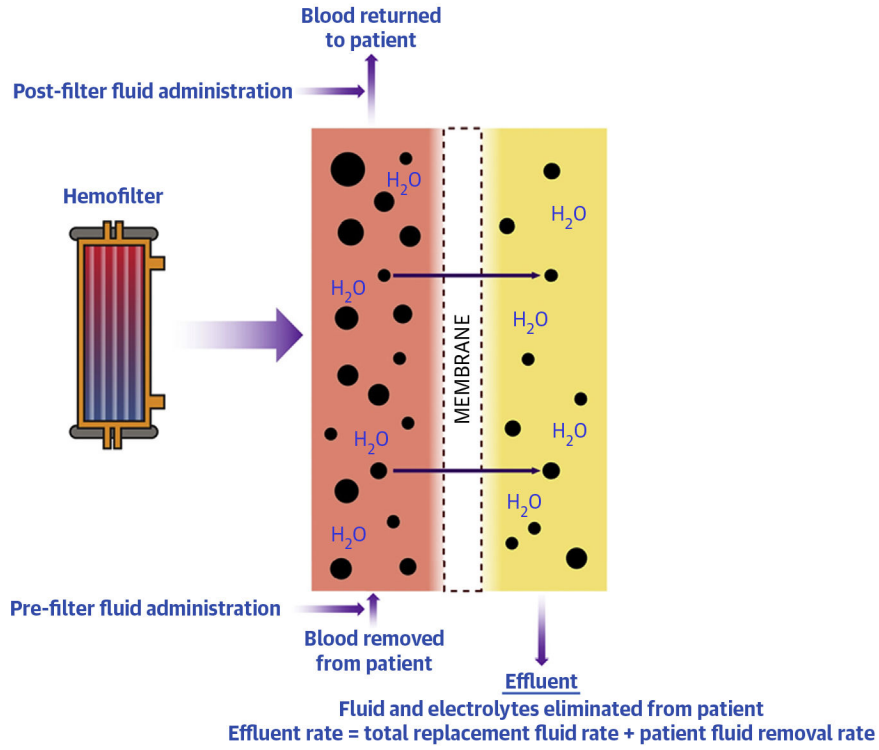
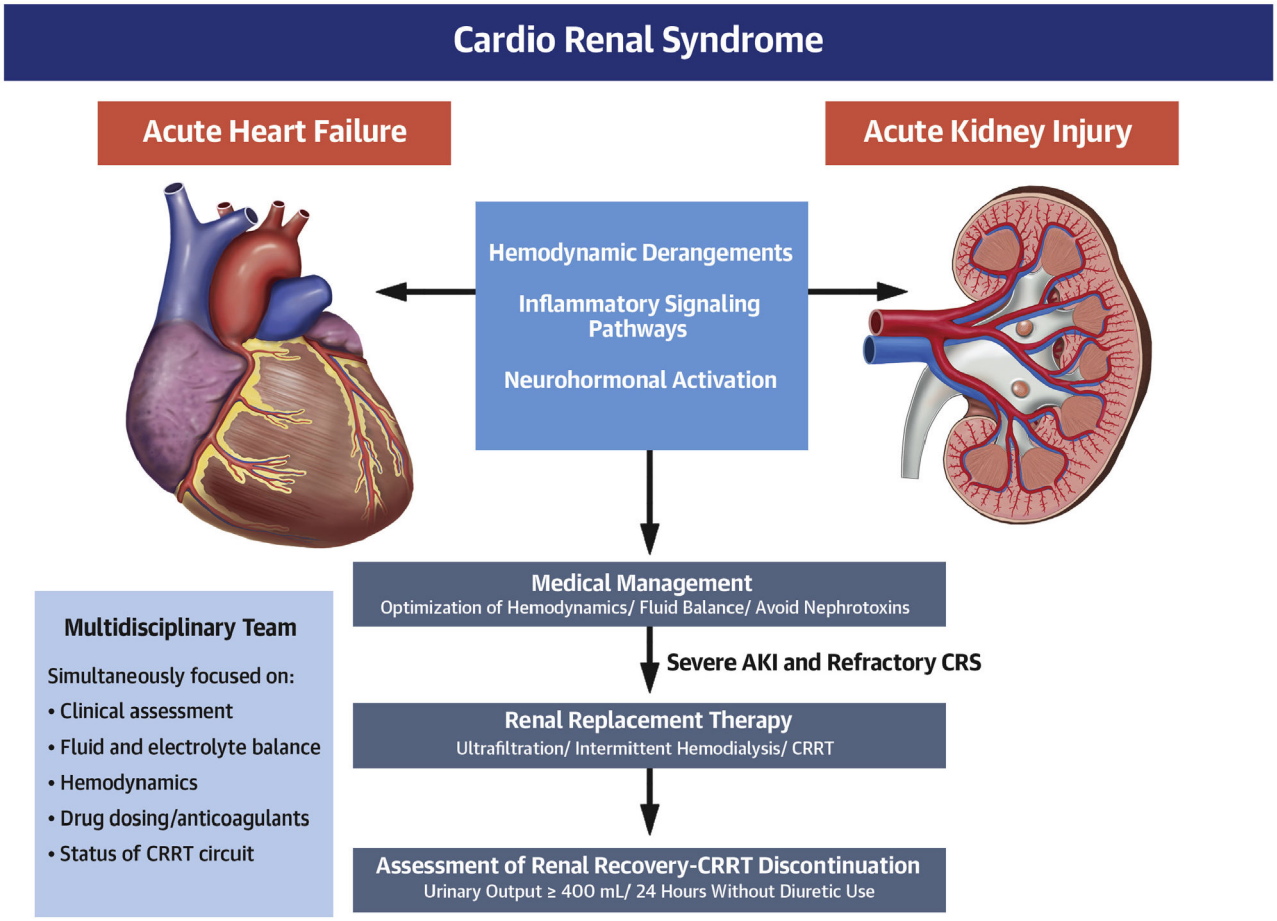


FIGURE 6. Function of the CVVH Filter and Solute Clearance by Convection

Blood and ultrafiltrate are separated by the semipermeable membrane, and solutes move across the membrane down a hydrostatic pressure gradient. With convective solute clearance, solutes are removed from the blood by ultrafiltration and then balanced replacement fluid is administered. CVVH = continuous venovenous hemofiltration.



CENTRAL ILLUSTRATION. Pathophysiology, Medical Management, and Use of Renal Replacement Therapy in Severe Acute Kidney Injury and Refractory Cardiorenal Syndrome

Cardiorenal syndrome (CRS) involves the interplay between hemodynamic, inflammatory, and neurohumoral abnormalities to produce worsening heart and kidney function. Management of patients with CRS involves multidisciplinary care, starting with medical management and avoidance of further acute kidney injury (AKI). For medically refractory CRS and severe AKI, renal replacement therapy, including continuous renal replacement therapy (CRRT), may be necessary.

TABLE 1

Stepped Diuretic Algorithm Used in the CARRESS-HF and AVOID-HF Trials (56,62)

	Current Diuretic Regimen		Suggested Diuretic Regimen	
Step	**Furosemide Dose**	**Thiazide**	**Furosemide Dose (IV)**	**Metolazone**
1	≤80 mg/day	+/−	40 mg + 5 mg/h	0
2	81–160 mg/day	+/−	80 mg + 10 mg/h	5 mg QD
3	161–240 mg/day	+/−	80 mg + 20 mg/h	5 mg BID
4*	>240 mg/day	+/−	80 mg + 30 mg/h	5 mg BID

The starting diuretic dose is determined by the outpatient or current inpatient diuretic dose, and the patient is moved to a higher diuretic dose if urine output is <3 l/day on the current dose. All loop diuretic doses are given in furosemide equivalents, although an alternative loop diuretic could be used. *A vasodilator or inotrope can be added for patients who have urine output <3 l/day despite Step 4 diuretic dosing.

AVOID-HF = Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure; BID = twice daily; CARRESS-HF = Cardiorenal Rescue Study in Acute Decompensated Heart Failure; IV = intravenous; QD = every day.

TABLE 2

Potential General and CICU-Specific CRRT Indications

General Acute RRT Indications	Proposed CICU-Specific CRRT Indications
A: Severe metabolic acidosis (i.e., severe lactic acidosis with refractory shock and multiorgan failure)	Patients with severe cardiac and/or valvular dysfunction and borderline blood pressure with AKI and volume overload
E: Severe electrolyte disturbances, most commonly hyperkalemia	Cardiogenic shock or heart failure with pulmonary edema on mechanical ventilation and high FiO_2 (>80% to 90%) despite diuretic therapy
I: Intoxication with dialyzable drugs or toxins	Pre-cardiac surgical volume removal to improve likelihood of chest closure and prevent post-operative right ventricular failure
O: Medically refractory volume overload	Refractory cardiorenal syndrome with progressive AKI (e.g., stage 2 to 3 AKI plus volume overload with inadequate diuretic response)
U: Severe azotemia or symptoms of uremia	

When initiating renal replacement therapy (RRT), the broader clinical context, presence of conditions that can be modified by RRT, and trends of laboratory tests should be considered instead of a single universal threshold (e.g., blood urea nitrogen or creatinine) (63).

AKI = acute kidney injury; CICU = cardiac intensive care unit; CRRT = continuous renal replacement therapy; FiO_2 = fraction of inspired oxygen.

TABLE 3

Comparison Between CRRT Modalities (i.e., CVVH) and Intermittent RRT Modalities (i.e., IHD)

	Continuous RRT Modalities	Intermittent RRT Modalities
Indication	Hemodynamic instability	Severe acid-base and electrolyte imbalances
	Volume control	Intoxication
	Intracranial hypertension	Refractory filter clotting
Advantages	Hemodynamic stability	(Relatively) inexpensive
	Stable, effective, and predictable volume control	Flexible timing allows for mobility/transport
	Stable and predictable control of chemistry	Rapid correction of fluid overload
	Stable intracranial pressure	Rapid removal of dialyzable drugs
	Disease modification by cytokine removal	Minimizes anticoagulant exposure
	Potentially improved chances of renal recovery	Rapid correction of acidosis and electrolyte abnormality
Disadvantages	Anticoagulation requirements	Intradialytic hypotension
	Reduced patient mobility	Potential nephrotoxicity
	Higher potential for filter clotting	Risk of bowel and coronary ischemia
	Higher cost	

CVVH = continuous venovenous hemofiltration; IHD = intermittent hemodialysis; other abbreviations as in Table 1.

TABLE 4

Troubleshooting Common Alarms and Clinical Problems for Patients on CRRT

Alarm/CRRT Issue	Evaluation	Resolution/Intervention
Negative pressure access alarms (high inlet pressure)	Evaluate patient for hypovolemia, intrabdominal hypertension, and respiratory distress	Remedy contributing patient factors (e.g., bolus fluids or add sedation)
	Check catheter for kinking and clot formation	Reposition catheter
		Intra-catheter TPA administration
		Reverse inlet and outlet positions
		Place new catheter (longer if feasible)
Positive pressure access alarms (high outlet pressure)	Check catheter for kinking and clot formation	Adjust patient position
		Reposition catheter
		Intra-catheter TPA administration
		Reverse inlet and outlet positions
		Place new catheter (longer if feasible)
Transmembrane pressure alarms	Evaluate filter for evidence of clotting	Calculate and maintain filtration fraction <25% (e.g., increase pre-filter fluid or decrease net patient fluid removal)
	Check adequacy of circuit anticoagulation	
		Add circuit anticoagulation
		If clotting is imminent, return blood to patient
Refractory hyperkalemia	Assess patient for etiologies of elevated potassium: acidosis, hemolysis, tissue necrosis, drugs	Administer medical therapies including: insulin, bicarbonate, and laxatives
		Attempt lower K replacement fluid administration
		Increase prescription (replacement fluid rate)
		Consider performing IHD
Refractory acidosis	Assess patient for etiologies of acidosis: hypoperfusion/lactic acidosis, ketosis, hyperchloremia, organic acids, toxic alcohols	Increase prescription (replacement fluid rate)
		Increase replacement fluid bicarbonate concentration
		Consider isotonic (150 mEq/l) bicarbonate infusion

K = potassium; TPA = tissue plasminogen activator; other abbreviations as in Tables 1 and 3.