

---

## REVIEW ARTICLE

---

# Current management of severe acute kidney injury and refractory cardiorenal syndrome

Jacob C. Jentzer, Małgorzata Kruszwicka

Jentzer JC, Kruszwicka M. Current Management of Severe Acute Kidney Injury and Refractory Cardiorenal Syndrome : A literature review. *J Kidney Treat Diagn*. 2022; 5(4):36-38.

### ABSTRACT

According to this literature review, Cardiorenal Syndrome (CRS) and Acute Kidney Damage (AKI) are becoming more common in hospitalized patients with cardiovascular illness and continue to be linked to poor short- and long-term outcomes. Apart from supportive care and volume status management, there are no specific medications to lower mortality linked to either AKI or CRS. Prior to renal recovery, normal electrolyte, acid-base, and fluid balance may be

restored with the help of acute Renal Replacement Therapies (RRTs), which include ultrafiltration, intermittent hemodialysis, and continuous RRT. The risk of mortality and long-term dependency on dialysis is elevated in patients who require acute RRT, underscoring the significance of careful patient selection. There are minimal resources available for the cardiovascular specialist despite the expanding use of RRT in the cardiac intensive care unit.

**Key Words:** Acute kidney injury, Cardiorenal syndrome, Dialysis, Heart failure, Hemofiltration

### INTRODUCTION

A growing patient population at significant risk of negative outcomes is being highlighted by the prevalence of Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD) in patients with acute cardiovascular disease. This is true despite the involvement of multispecialty providers and the provision of the best supportive care. Recognizing that not all renal impairment emerging in people with cardiovascular illness is caused by CRS, Cardiorenal Syndrome (CRS) is a subset of AKI or CKD that occurs in the setting of increasing cardiovascular disease. Heart and kidney function deteriorate as a result of the hemodynamic, inflammatory, and neurohumoral abnormalities that interact to cause Cardiorenal Syndrome (CRS). Multidisciplinary care is required for the treatment of individuals with CRS, beginning with medical therapy and preventing further Acute Renal Impairment (AKI). Renal replacement therapy, especially Continuous Renal Replacement Therapy (CRRT), may be required for medically unresponsive CRS and severe AKI [1]. About 1 in 4 individuals with cardiovascular illness who are hospitalised develop AKI, including up to 47% of those with acute decompensated heart failure and 15% to 30% of those with Acute Coronary Syndrome (ACS). The prevalence of AKI is reported to range from 25% to 50%

in the Cardiac Critical Care Unit (CICU), with up to 38% having underlying CKD, highlighting the significant burden of CRS. These rates are comparable to those experienced by patients in regular critical care units, where the incidence of AKI was 57% in a significant international study. 20% of AKI patients and 1% to 3% of patients with heart failure or ACS who are hospitalised develop AKI that requires dialysis (AKI-D). AKI-D is more frequent in CICU patients (5%–8%) and may be higher in individuals with cardiogenic shock (13%–14% on average) [2]. One of the most significant risk factors for AKI, representing diminished renal reserve and impaired capacity of the kidneys to adapt to stress, is the severity of underlying CKD. Age, hypertension, diabetes mellitus, heart failure, sepsis, increased illness severity, hypotension and/or shock, and the requirement for vasopressors are additional significant risk factors for AKI. Patients with ACS have a higher risk of AKI when their infarct size is larger and their Killip Class is higher. Additionally, about 15% of patients with ACS who have percutaneous coronary intervention get contrast-associated AKI as a result of the use of iodinated radiocontrast material during cardiovascular interventional procedures. As a result, frequent CICU admission diagnoses, comorbidities, and procedures serve as important risk factors for AKI. In populations of patients with acute cardiovascular disease and critical illnesses, AKI and CKD are consistently linked to greater short-

---

Editorial Office, *Journal of Kidney Treatment and Diagnosis*, Windsor, Berkshire, England

Correspondence: Jacob C. Jentzer, Editorial Office, *Journal of Kidney Treatment and Diagnosis*, Windsor, Berkshire, England, e-mail [kidney@eclinicalsci.org](mailto:kidney@eclinicalsci.org)

Received: 06-July-2022, Manuscript No. *puljkt*22-5396; Editor assigned: 08-July-2022, PreQC No. *puljkt*22-5396 (PQ); Reviewed: 15-July-2022, QC No. *puljkt*22-5396 (Q); Revised: 18-July-2022, Manuscript No. *puljkt*22-5396 (R); Published: 25-July-2022, DOI: 10.37532/*puljkt*22.5(4).36-38



This open-access article is distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC) (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits reuse, distribution and reproduction of the article, provided that the original work is properly cited and the reuse is restricted to noncommercial purposes. For commercial reuse, contact [reprints@pulsus.com](mailto:reprints@pulsus.com)

and long-term mortality, including a persisting risk for death and severe cardiovascular events among hospital survivors. Elevated levels of creatinine, blood urea nitrogen, and cystatin C, which are markers of a decreased glomerular filtration rate, have been linked directly to a graded increase in mortality in patients with acute cardiovascular illness, especially those with heart failure who are hospitalised. Although this mortality risk depends on other factors like the presence of residual congestion, increases in serum creatinine after hospitalisation for acute heart failure have commonly been linked to greater short-term mortality [3,4]. Patients with AKI and those who require dialysis have poor short- and long-term outcomes, including high death rates and dependence on dialysis, making them substantial risk factors for mortality among CICU patients and patients with AKI. According to one study, patients who were admitted to the CICU with the purpose of starting dialysis had a mortality risk similar to those who were there for cardiogenic shock or cardiac arrest. AKI severity, age, the severity of the overall illness, the existence and severity of additional organ failures, and the degree of renal function recovery all affect a patient's chance of dying. Additional risk factors include low urine production, significant volume overload, and increased net fluid buildup. With persistent congestion and diuretic resistance, worsening kidney function (AKI) during treatment for acute decompensated heart failure was the original definition of CRS. More recently, CRS has been conceptualised as a spectrum of acute or chronic disorders of the heart and kidney function characterised by reciprocal deterioration. CRS can be conceptually separated from other types of AKI due to its inherent connection to decreasing cardiac function and the fact that it frequently manifests as a reversible decline in kidney AKI or acute heart failure are the results of a sudden key function without obvious tubular injury. Based on its chronicity and the major organ malfunction that causes it, CRS has been subclassified into five different categories. The reciprocal deterioration of cardiac and renal functioning seen in patients with CRS is caused by a variety of interrelated pathophysiological processes, deterioration in the cardiac (CRS type 1) or renal (CRS type 3) functions, respectively. Venous congestion caused by right-sided heart failure, which lowers renal perfusion pressure and sets off intrarenal mechanisms that impair renal function, frequently causes CRS type 1 [5]. Through direct myocardial injury from oxidative stress, sympathetic nervous system activation, renin-angiotensin-aldosterone system activation, and the negative consequences of fluid overload, uremia, electrolyte imbalance, and acidemia, AKI can lead to progressive heart failure and CRS type 3 in patients. In addition to other significant causes, persistent heart failure's pro-inflammatory state can result in renal tubular damage, which can lead to fibrosis and CKD (CRS type 2). Additionally, uremic toxins and acidemia from CKD can exacerbate cardiomyopathy and cause heart failure through volume and pressure overload (CRS type 4). CRS type 5 is characterised by concurrent acute or chronic cardiac and renal failure brought on by a systemic disease (e.g., sepsis). It can be challenging to differentiate between CRS subtypes in patients who come with combined heart and kidney failure because chronic CRS (CRS types 2 and 4) frequently coexists with acute CRS (CRS types 1 and 3), signifying acute chronic cardiac and renal dysfunction. The Kidney Disease: Improving Global Outcomes group has produced standard criteria for AKI, which divides the condition into three progressive stages based on changes in blood creatinine and urine output over the course of hours to days. When combined with traditional functional indices of AKI, elevated levels of urine tubular damage biomarkers have been shown to be able to predict the onset and progression of AKI. Acute decrease in urine production is a common indicator of severe AKI (unless diuretics are

used to conceal it), and oliguric AKI is more likely to worsen and require dialysis. To find and address reversible reasons of any sudden decrease in urine production in a patient in the CICU, quick evaluation is required [6]. A thorough evaluation is required for patients who present with AKI or CRS in order to identify the underlying cause. This evaluation should include a thorough review of the patient's medical history in order to assess the use of renally eliminated and nephrotoxic medications, as well as a thorough history and physical examination, volume status assessment, urinalysis, and urine microscopy. Assessment of filling pressures (congestion) and forward flow (perfusion) by physical examination, echocardiography, and/or invasive hemodynamics is a crucial step in the evaluation of patients with CRS. Other causes of AKI, such as hypovolemia, nephrotoxins, or acute tubular necrosis brought on by shock or hypotension are not always categorised as CRS. The presence and severity of CKD can be assessed using the urine albumin to creatinine ratio. A renal ultrasonography can measure the size of the kidneys and AKI cannot be caused by hydronephrosis or echogenicity. Clearance biomarkers (which indicate glomerular filtration rate), tubular damage biomarkers, natriuretic peptides expressing congestion, and biomarkers indicating neurohumoral activation or inflammation are among the prognostic biomarkers in CRS. All CRS subtypes can cause high natriuretic peptide levels, and a normal level suggests an AKI cause other than CRS type 1. AKI is characterised by an increase in clearance biomarkers, however glomerular filtration rate declines occur before biomarker changes, highlighting the significance of oliguria as an early indicator of AKI. A clearance indicator similar to serum creatinine, serum cystatin C has a greater sensitivity for AKI and additional predictive significance above serum creatinine levels [7].

#### **AKI and CRS medical treatment prior to beginning renal replacement therapy**

Optimization of hemodynamics, fluid balance, and avoidance or cessation of possible nephrotoxins are typically required for the treatment of AKI and CRS (Central Illustration). Several antimicrobial medicines, particularly aminoglycosides, nonsteroidal anti-inflammatory drugs, and iodinated radiocontrast are frequently nephrotoxic. During severe AKI, all renin-angiotensin-aldosterone system inhibitors should be avoided since they can lower glomerular filtration rate. It may be reasonable to initially continue these drugs during mild AKI and CRS due to the possible benefits of renin-angiotensin-aldosterone system inhibitors in patients with cardiovascular disease, but caution is advised. There are no universally recognised medicines that reliably enhance renal function recovery or clinical outcomes in patients with AKI or CRS aside from prophylactic measures. Consider cautious fluid administration aided by indicators of fluid responsiveness [7].

It is best to avoid administering too much liquids to avoid damaging volume overload. For individuals with CRS and AKI, loop diuretics are helpful in preventing or treating fluid overload, and effective diuresis may improve renal function by reducing renal venous congestion. For the majority of patients, continuous infusion of loop diuretics or intravenous bolus dosage will result in a similar amount of diuresis, with a similar safety profile and no discernible difference in clinical results. According to our clinical experience, certain patients, such as those who require careful diuretic titration or high diuretic doses or those who have hemodynamic instability and may not tolerate

bolus dosing, may benefit from the greater control of diuresis made possible by a continuous loop diuretic infusion. Patients who react to diuretics seem to have better outcomes, even though diuretics have not been shown to lower mortality or avoid the need for dialysis in patients with AKI. Patients with AKI can undergo a loop diuretic challenge or a furosemide stress test by monitoring their urine output following a dose of 1.0 to 1.5 mg/kg of intravenous furosemide. Patients with a urine output of 200 ml or less over the first two hours are more likely to develop stage III AKI and require Renal Replacement Therapy (RRT); patients with a urine output of 600 ml or less after six hours are more likely to require RRT. Continuous loop diuretic therapy may be able to overcome diuretic resistance and boost urine output with the addition of a second diuretic, often a thiazide-type diuretic. Due to the heightened risk of electrolyte abnormalities, careful electrolyte monitoring is necessary when utilising combined diuretic medication. Aldosterone antagonists and tolvaptan can increase diuresis in some CRS patients, but they have not been shown to enhance clinical outcomes or kidney function in people with acute heart failure. The addition of oral metolazone, intravenous chlorothiazide, or oral tolvaptan increased urine output similarly in a randomised study of 60 loop diuretic-resistant patients hospitalised for heart failure. Small-volume hypertonic saline may also enhance renal function and diuretic responsiveness in CRS patients, possibly through enhancing neurohormonal activation [8]. Though it is prudent to avoid hypotension and low-output conditions, the ideal systemic hemodynamic targets for the prevention and treatment of AKI and CRS are unknown. No specific vasoactive medication, not even inotropes or vasodilators, has been demonstrated to prevent or treat AKI or CRS. Dopamine can increase kidney function and diuresis in some people due to its direct kidney effects and cardiac inotropic effects, but it has not been shown to improve clinical or renal outcomes in AKI patients. Although a putative positive effect of low-dose dopamine has been noted in patients with CRS who had systolic heart failure, dopamine has not consistently improved kidney function, diuresis, or clinical outcomes in people with CRS. In critically ill patients with AKI or CRS, the decision to begin urgent RRT is traditionally based on the "AEIOU" indicators of acidosis, electrolyte disturbances, intoxications, volume overload, and uremia. Medically refractory volume overload coupled with hemodynamic instability is the most frequent reason for starting continuous RRT (CRRT) in CICU patients. Although there may be some specific CICU-specific indications for starting RRT, we support the generally accepted RRT commencement recommendations. There were no discernible changes in mortality, renal recovery, or other outcomes between patients with severe AKI who were randomised to early or late RRT commencement, according to a meta-analysis that looked at the timing of RRT initiation. In the AKIKI study (Artificial Kidney Initiation in Kidney Injury), 620 critically ill patients with stage 3 AKI were randomly assigned to receive immediate RRT or wait until they experienced severe hyperkalemia, metabolic acidosis, pulmonary edema, severe azotemia, or oliguria for more than 72 hours before starting RRT. There was no difference in mortality, and nearly half of the group receiving delayed RRT did not need RRT. Early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury, however, was associated with lower mortality, according to the randomized ELAIN research [9,10].

## REFERENCES

1. Jin K, Murugan R, Sileanu FE, et al. Intensive monitoring of urine output is associated with increased detection of acute kidney injury and improved outcomes. *Chest*. 2017;152:972-79
2. Forni LG, Chawla LS. Biomarkers in cardiorenal syndrome. *Blood Purif*. 2014;37:14-19
3. Feng Y, Zhang Y, Li G, Wang L. Relationship of cystatin-C change and the prevalence of death or dialysis need after acute kidney injury: a meta-analysis. *Nephrology (Carlton)*. 2014;19:679-84
4. Bove T, Belletti A, Putzu A, et al. Intermittent furosemide administration in patients with or at risk for acute kidney injury: meta-analysis of randomized trials. *PLoS One*, 13 (2018), Article e0196088
5. N Lumlertgul, S Peerapornratana, T Trakarnvanich, et al. Early versus standard initiation of renal replacement therapy in furosemide stress test non-responsive acute kidney injury patients (the FST trial). *Crit Care*, 22 (2018), 101
6. A Sakhuja, G Bandak, E F Barreto, et al. Role of loop diuretic challenge in stage 3 acute kidney injury. *Mayo Clin Proc*. 2019;94:1509-15
7. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol*. 2010;56:1527-34
8. Cox ZL, R Hung, Lenihan DJ, Testani JM. Diuretic strategies for loop diuretic resistance in acute heart failure: The 3T trial. *J Am Coll Cardiol HF*. 2020; 8:157-168
9. Gheorghiade M, Konstam MA, Burnett JC, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST clinical status trials *JAMA*. 2007;297:1332-43
10. Chen HH, Anstrom HH, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial *JAMA*. 2013;310:2533-43