

Strategies for Continuous Renal Replacement Therapy De-escalation

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Key Words: Weaning Trial, Continuous Renal Replacement therapy, Biomarkers, Diuretics

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Introduction:

Acute Kidney Injury (AKI) is a common complication in hospitalized patients and occurs in more than half of patients in the intensive care unit (ICU) (1). Up to 15% of these patients may require renal replacement therapy (RRT) (2). CRRT is preferred in the ICU given increased fluid removal tolerability with associated hemodynamic instability. CRRT is increasingly used as renal supportive therapy for nutrition, AKI with hyponatremia, dialyzable drugs, poisoning and intoxicants. While studies have investigated optimal timing and indications for RRT initiation, few have looked at optimal timing and strategies for CRRT weaning. Evidence is currently limited to guide RRT de-escalation. Like Rapid Shallow Breathing Index (RSBI) for mechanical ventilation weaning, there is a need for a standardized CRRT weaning protocol as a recovery tool from ICU. Different institutions have different approaches and, even within an institution, individual variations (depending on the ICU unit) can occur. Ultimately, the decision should include a comprehensive assessment of the patient's recovery curve, immediate needs, goals of care, and the primary team's short-term goals. It should involve factors such as urine output monitoring, optimal diuretic use, adjusting medication dosing, and mobility goals. Several clinical variables serve as potential tools to guide CRRT weaning such as urine output, diuretics, creatinine and electrolyte levels, and renal biomarkers. Here we will discuss different strategies we use at our institution and current evidence to guide the de-escalation of CRRT.

- a. Predictors of successful weaning and mitigation strategies
- b. Role of Diuretics in CRRT weaning trial (WT)
- c. Role of renal biomarkers
- d. Various RRT modalities, Hybrid therapies and Drug dosing

e. Special situations and poisonings

Predictors of successful weaning and mitigation strategies:

According to Kidney Disease Improving Global Organization (KDIGO) clinical practice guidelines for AKI in 2012, RRT should be stopped when “it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care” (3). However, this recommendation lacks specific guidance. At our and other institutions, CRRT weaning includes evaluating hemodynamic stability, volume status, solute control, daily obligate inputs and the need to improve patients’ mobility (Fig. 1). Typically, CRRT is maintained in patients requiring vasopressors given as it is tolerated better for fluid removal than other modalities. We use obligate inputs of more than two liters daily and oliguria as poor predictors of successful weaning as they indicate ongoing net positive fluid balance. Daily discussions with the primary team are necessary to understand ongoing ICU needs and to optimize fluid balance. Logistical capabilities of the institution, such as staffing of nurses and availability of machines for bedside HD/Hybrid therapies should be considered daily. CRRT is continued when future surgical procedures (especially in surgical ICUs) are anticipated. We define weaning success as one week of RRT independence (4).

Assessment of degree of kidney recovery is key to CRRT weaning. No clear guidelines or tools are available although, several variables have been evaluated in retrospective observational studies. A recent systematic review and meta-analysis found 23 studies and 16 variables for predicting successful RRT discontinuation (4). These variables can be categorized into

physiological parameters such as hemodynamics and urine output, biochemical markers to evaluate glomerular filtration rate (GFR), and novel kidney markers (4). Urine output before RRT cessation has been a consistent positive predictor of successful RRT discontinuation. In studies, urine output is quantified as 400mL/day or 8.5mL/kg/24 hours without diuretics, although variation in these thresholds do exist (5). Urine output after RRT cessation has also been assessed. Raurich et al. compared urine output pre and post CRRT stop and showed that 6-hour urine output after CRRT discontinuation was the main predictor associated with successful CRRT weaning (6). Katayama et al showed that for every 100 mL/day there is a nearly 10% likelihood of successful discontinuation from CRRT (2). As such, urine output serves as a real-time marker of renal function and a key predictor of CRRT independence.

Persistent hypotension is a frequent barrier to ICU discharge and CRRT transitioning. Hypotension in resuscitated patients can be related to sedatives, autonomic dysfunction, or vasoplegia from sepsis. Once the underlying cause of hypotension is addressed, midodrine can be a useful tool to facilitate weaning off intravenous vasopressors and CRRT (7).

Role of Diuretics in CRRT Weaning trial (WT)

The role of diuretics in AKI recovery remains unknown. Studies have shown an association of diuretic use with successful CRRT weaning. In this setting loop diuretics (e.g., furosemide) are particularly needed, either as large intermittent doses or as a continuous infusion. Response to loop diuretics represents a functional test since this requires the integrity of several nephrons from filtration to proximal tubular secretion and luminal patency. For loop diuretics to increase urine output, blood flow must be intact to the proximal tubule to deliver the loop diuretic, after

which they need to be actively secreted into the proximal lumen, and subsequently the thick ascending limb and collecting duct function all of which need to be intact. In this way, loop diuretics allow for an assessment of tubular integrity.

Studies have shown an association of diuretic use with successful RRT weaning. Accuracy of urine output as a marker with diuretic use showed improved predictive accuracy in patients who received diuretics however a larger study by Uchino et al. suggested that diuretics may decrease the accuracy of urine output as a predictive marker (6,8). Given current variability in assessing diuretic use, we believe that loop diuretics may be useful to assess successful weaning and determine the need for CRRT. In addition, in assessing urine output, one should keep in mind the effect of large solute loads leading to solute diuresis. Lack of significant response to diuretics can indicate ongoing AKI and determine if CRRT should be reinitiated.

Role of Renal biomarkers

Renal biomarkers measuring GFR are other available tools. Serum urea and creatinine before CRRT withdrawal can be assessed during prolonged CRRT breaks to determine solute clearance needs. Low serum creatinine and low serum urea have been considered positive predictors. However, the accuracy of these parameters is imperfect given fluctuations in critically ill patients due to varying muscle mass, creatinine generation, the timing of CRRT withdrawal, delivered CRRT dose, tube feeds, diuresis, steroid use, or active bleeding. Urine creatinine clearance is the next best measure for GFR in the ICU. However, 24-hour urine collections can be time-consuming, affected by hemodynamic changes, and could delay time to predict

successful weaning. In that scenario, shorter timed creatinine clearance measurements can be considered.

Novel renal biomarkers such as cystatin C, NGAL, IL-18, IL-6, serum osteopontin, have been studied albeit with limited consistency in their prediction; It is important to note that current data on biomarkers stems from small, isolated, observational studies, with significant heterogeneity in their definitions of successful discontinuation, weaning criteria, and timing of measurement of biomarkers, and threshold values. Cystatin C remains the most commonly studied biomarker and was found to be an independent positive predictor for weaning off CRRT (4,9). Limitations exist that may restrict cystatin C use in certain clinical situations such as with corticosteroid use, thyroid dysfunction, and underlying malignancy.

Various RRT modalities, Hybrid therapies and Drug dosing

Novel hybrid therapies are worth considering as modalities to transition off CRRT (10). Hybrid therapies vary in nomenclature (PIRRT/SLED/EDD/AVVH) depending upon the machine or the practice location. Hybrid therapies serve as an excellent option in situations where patients are unable to be transitioned to intermittent hemodialysis. Studies have not shown a difference in mortality, hemodynamic stability, solute clearance, or dialysis dependence between CRRT and hybrid therapies (10). However, to date, a clear consensus is lacking on hybrid therapies aspects such as frequency, duration, intensity, and type of RRT machine. In addition, isolated ultrafiltration techniques (e.g., aquapheresis) can be helpful in patients with tenuous hemodynamics and fluid overload without significant clearance need. Drug dosing is also

variable among RRT modalities. Like CRRT, for hybrid therapies, while more complex, the dose of effluent provides the best estimate of drug clearance.

CRRT in Special Situations:

AKI with hyponatremia

Hyponatremia with AKI is challenging given an increased risk of overcorrection. CRRT is increasingly utilized given the ability to control the rate of sodium increase with hypotonic fluids or customization of dialysate (11). In these situations, CRRT can be transitioned to intermittent hemodialysis once sodium levels reach 125-130meq/L depending upon the patients' comorbidities and transplant status (11).

Hyperammonemia

There is no clear consensus on the initiation or weaning from CRRT for hyperammonemia. It is often started in patients unable to tolerate lactulose with associated hemodynamic instability (12). Based on our experience, CRRT can be weaned once mental status, ammonia levels, and hemodynamics improve, and the patient can have oral intake. In cases of fulminant liver failure, CRRT or intermittent HD (iHD) can be used as a bridge to transplant, especially if the patient is severely hyponatremic and there are risks of overcorrection following liver transplantation.

Poisonings

CRRT is used for the removal of toxins especially with associated hemodynamic instability. CRRT membranes are preferred for large toxin removal given greater clearance of large molecules (20000-40000 KDa) than conventional high flux HD membranes (13). CRRT further prevents the

rebound of toxins removed from intravascular space, a frequent issue with intermittent hemodialysis (13). Clear data is lacking regarding CRRT cessation in poisoning, but the decision should involve toxin characteristics such as molecular weight, degree of protein binding, the volume of distribution, water solubility, and endogenous clearance.

Conclusion

Currently, standardized indexes are nonexistent for CRRT weaning. We believe that once hemodynamic stability is achieved and the underlying etiology of critical illness is improved, CRRT cessation should involve a complex multidisciplinary approach. Several predictors exist based on observational studies and include renal biomarkers, novel biomarkers, urine output, and diuretic use. Of all parameters, increased urine output has consistently emerged as a positive predictor. Hybrid modalities can serve as an excellent tool for transitioning off CRRT. In other circumstances, CRRT weaning is unique to the underlying etiology of RRT initiation in cases of hyponatremia, toxins, or hyperammonemia. Larger research studies are needed in this topic for creation of predictive models and a uniform consensus on the weaning of CRRT.

Disclosures: B. Jaar reports Honoraria: American Board of Internal Medicine – Nephrology; Scientific Advisor or Membership: Clinical Journal of the American Society of Nephrology, American Board of Internal Medicine, National Kidney Foundation, BMC Nephrology, BMC; Medicine Other Interests/Relationships: UpToDate royalties as an author. All remaining authors have nothing to disclose.

Funding: None

Acknowledgements: The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or *Kidney360*. Responsibility for the information and views expressed herein lies entirely with the author(s).

Authorship: S Gautam: Conceptualization; Writing - original draft; Writing - review and editing

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Figure 1

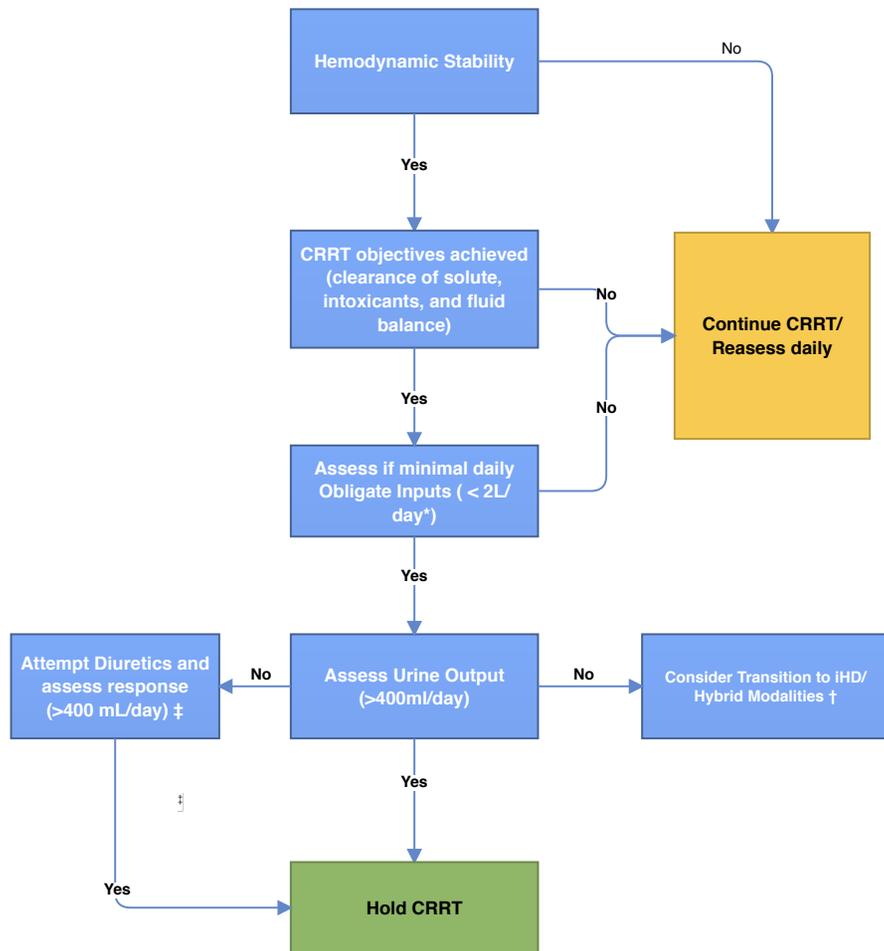


Figure 1. Guide to wean patients from CRRT

*Identify a target fluid balance (intake minus output) to reach for the patient, often variable with each patient (net even for some, while net negative for others), <2L/day may not be universal to all patients especially if requiring tube feeds/parenteral nutrition in addition to intravenous medications

†Can do intermittent hemodialysis or transition to hybrid modalities while on low dose pressor support if needed

‡Loop diuretics can be carefully attempted in patients on low dose vasopressor support even while on CRRT or low dose vasopressors but one needs to be mindful that it can cause hypotension