Review Article

Continuous Renal Replacement Therapy: Principles, Modalities, and Prescription

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ABSTRACT. The mortality rate of critically ill patients with severe acute kidney injury (AKI) remains high. The associated sepsis and septic shock, as well as the presence of multiorgan failure, further increase the risk of death. Renal replacement therapy (RRT) represents the cornerstone of the management of severe AKI. Continuous RRT (CRRT) has been considered the predominant form of dialysis in the intensive care unit due to its accurate volume control, steady acid–base, and electrolyte correction and achievement of hemodynamic stability. This narrative review covers an introduction to CRRT, its physiologic principles, modalities, requirements, indications, and different elements of adequate prescription.

Introduction

Continuous renal replacement therapy (CRRT) is a slow and smooth continuous extracorporeal blood purification, which simulates the continuity of kidney functions. It is usually implemented over 24 h to several days with an aim of gentle removal of fluid overload and excess uremic toxins. Untreated severe acute kidney injury (AKI) in critically ill patients is associated with high mortality rate. Renal replacement therapy (RRT) represents the cornerstone of the management of severe AKI. CRRT has been considered the predominant form of RRT in the intensive care unit (ICU) due to its accurate volume control, steady acid–base, and electrolyte correction and achievement of hemodynamic stability. CRRT has multiple benefits (Table 1), and is usually prescribed in critically ill and hemodynamically unstable adult and pediatric patients with AKI and/or multiorgan failure, sepsis/shock, acute brain injury, or other causes of increased intracranial pressure or generalized brain edema in the ICU, where such patients cannot tolerate the relatively fast removal of fluids (and solutes) by conventional hemodialysis (HD).

CRRT witnessed significant improvement since the technique was implemented by Peter Kramer of Göttingen (Germany) in 1977. The technique was established when Kramer was trying to introduce a catheter into the femoral vein for initiating HD. Accidentally, the catheter
went into the femoral artery, when Kramer realized the value of the arterial–venous pressure difference (i.e., blood flow driven by mean arterial pressure) in providing ultrafiltration and convection/hemofiltration concept and the need of replacement solutions, which was known as “continuous arteriovenous hemofiltration (CAVH).” Later, in 1987, Peter Robert Uldall (Toronto, Canada) introduced the “continuous veno-venous hemofiltration (CVVH)” by providing a pump and replacing the need of the arterial pressure, a technique which avoided (a) the potential risks and complications of puncturing a major artery (e.g., infection, distal thrombosis, and disconnection/bleeding) and (b) the possible slow or altered blood flow rates due to frequent hypotension in critically ill or shocked patients.

**Principles and Modalities of Continuous Renal Replacement Therapy**

CRRT is based on four main physiologic principles. These are (a) diffusion, (b) ultrafiltration, (c) convection, and (d) adsorption. In clinical practice, there is more than one principle implemented in achieving the goals of required treatment (e.g., diffusion, ultrafiltration, and convection). CRRT can be performed in one or more of the following four modalities: (1) slow continuous ultrafiltration (SCUF), (2) CVVH, (3) continuous veno-venous hemodiafiltration (CVVHDF), and (4) continuous veno-venous HD (CVVHD). Other therapeutic modalities that can be used in conjunction with CRRT include therapeutic plasma exchange and hemoperfusion/adsorption.

**Requirements for Continuous Renal Replacement Therapy**

The performance and delivery of CRRT depends on an efficient vascular access (e.g., internal jugular or femoral vein), specifically designed HD machines, and high-flux membranes/dialyzers. Synthetic and biocompatible membranes/dialyzers are capable of efficiently removing excess fluids and clearing small- and middle-large-sized uremic toxins, and some have high adsorptive affinity to proteins, endotoxins, and inflammatory mediators (e.g., cytokines). Following high convective volume of ultrafiltration, the replacement/substitution solutions, which can be infused before (precirculation), after the dialyzer (postdilution) or mixed infusion (precirculation and postdilution), are sterile physiological fluids that consist of balanced electrolyte solutions of either lactate- or bicarbonate-base which resemble the composition of the ultrafiltrate (but without the removed uremic wastes). The long duration of this extracorporeal blood purification technique, where the blood is in direct contact with blood tubes and dialyzer membrane for longer period than conventional HD, requires continuous anticoagulation to prevent clotting and extend the circuit life. Heparin has been widely used, but it has been associated with increased risk of bleeding. Regional citrate anticoagulation (RCA) is the more preferred and recommended method of anticoagulation.

**Indications for Continuous Renal Replacement Therapy**

Initiation of CRRT is indicated in patients...
with (a) hemodynamic instability/shock, (b) diuretic-resistant fluid overload, (c) severe metabolic acidosis (pH <7.2), and (d) refractory hyperkalemia (K+ >6.5). CRRT has also been considered in drug toxicity and in the prevention of radiocontrast-induced nephropathy, though the latter has not been confirmed in a meta-analysis study.\(^9\) The goals of CRRT include (i) clearance of uremic toxins, (ii) correction of electrolytes disturbance, (iii) acid–base balance, (iv) hemodynamic stabilization, (v) fluid balance, (vi) nutritional support, and (vii) removal and/or modulation of inflammatory mediators in septic patients.\(^8\)

### Preventable Limitations of Continuous Renal Replacement Therapy

Despite the general safety and valuable advantages, CRRT has some limitations. These include the requirement of a large-bore central vascular access (a risk source of infection), hypotension (decreased organ perfusion), continuous anticoagulation (inappropriate doses or inadequate control of anticoagulants may lead to bleeding, which is associated with a decrease in hemoglobin level and/or drop in blood pressure and possible need of blood transfusion, or clot formation which is associated with short circuit life, interruption of prescribed dose, inadequate therapy, and increased cost), electrolyte imbalance (potassium, phosphorus, and magnesium), drug removal (e.g., antibiotics), and immobilization of the patient for prolonged periods.\(^10\)

However, most of these limitations can either be prevented or controlled.\(^11\) A drop-in blood pressure, though much less encountered than in intermittent HD, is usually compensated for by the patient or, in some cases, require inotropic support to maintain effective mean arterial pressure. Furthermore, CRRT prescription can be modified at any time during treatment based on hemodynamic situation. A well-established protocol of RCA, for example, can help in maintaining the patency of the extracorporeal circuit for a longer period and in avoiding uncontrolled bleeding. Implementation of infection control policies and procedures, including aseptic techniques, can help in preventing or reducing the vascular access catheter-associated infection. Regular monitoring and assessment of electrolytes and blood gases, and the selection of appropriate replacement solutions (e.g., bicarbonate-based buffer and required composition of electrolytes and supplements), not only can help in replacing plasma volume removed by ultrafiltration, but also can ensure the correction of electrolyte and acid–base imbalances. Drug removal in CRRT depends on its molecular weight, the sieving coefficient, and the degree of protein binding. Drugs with significant protein binding are removed minimally. Some drugs may be removed by adsorption to the membrane. Most of the commonly used drugs, including antibiotics, require monitoring and dose adjustments.\(^12\) Finally, CRRT patients are prone to hypothermia due to the significant volume of blood that is circulated outside the body, and the significant volumes of the substitution and dialysate fluid used. Although newer CRRT machines are equipped with blood warmers that can bring both dialysate and substitution fluids to 37°C (98.6°F), a close monitoring of body temperature of patients is recommended especially when using larger volumes of substitution and dialysate solutions that are stored in air-conditioned area.

### Prescription for Continuous Renal Replacement Therapy

The success of CRRT depends on the prescribed and achieved dose of replacement/substitution fluids, treatment duration, type of dialyzer, and method and dose of anticoagulation, in addition to a well-established CRRT management protocol (e.g., type, size, length, placement and care of central lines, and indications of when to start and when to stop CRRT). Furthermore, the delivery and performance of CRRT requires well-trained medical and nursing staff.

### Continuous renal replacement therapy versus intermittent and extended hemodialysis

Patients with severe AKI in the ICU usually
require RRT in the form of intermittent HD (IHD) or extended HD (slow low-efficiency dialysis, SLED) or CRRT. The current evidence and KDIGO guidelines support the implementation of CRRT in hemodynamically unstable patients and those with increased intracranial pressure. Moreover, there is increasing evidence that CRRT is associated with a trend of short- and long-term dialysis independence. However, there is no supportive evidence of mortality difference between all these modalities of RRT.

The KDIGO guidelines recommend the use of CRRT and intermittent hemodialysis (IHD) as complementary therapies in AKI patients.

Life of the filter/dialyzer

Short-lived dialyzers due to clotting are associated with blood loss, inadequate dialysis due to frequent interruption of treatment, and increased costs due to extra number of used sets. The major causes of short-lived dialyzers are lack or inappropriate prescribed dose of anticoagulation, slow or inadequate blood flow rate (due to improper vascular access or frequent machine alarms), and/or high filtration fraction (FF). FF is the volume of plasma removed from the dialyzed blood by ultrafiltration. For example, a filtration fraction of 25% represents 25% of the plasma water removed by ultrafiltration. The official definition of FF is “the percentage ratio of ultrafiltration rate to plasma flow rate, where plasma flow rate equals blood flow rate × (1 – hematocrit).” Practically, FF should not exceed 20%–25%. Higher FF corresponds to higher postfilter hematocrit, which will tend to degrade the life of the filter and promote clot formation.

Anticoagulation

The aim of anticoagulation is to maintain patency of the extracorporeal circuit and minimize patient complications of anticoagulation therapy. Appropriate anticoagulation is a subtle balance between clotting and bleeding. Strategies to prevent clotting include general measures, such as saline flushes and online predilution, and different anticoagulants, such as unfractionated and low-molecular-weight heparin, heparin-coated membranes (e.g., oXiris), and RCA, which are valuable in patients at high risk of bleeding and in those with heparin-induced thrombocytopenia. RCA has been shown to be safe and effective for the anticoagulation of CRRT in most ICU patients.

RCA is based on the ability of citrate to prevent coagulation by binding and chelating free ionized calcium in the extracorporeal circuit, which is needed for the formation of the fibrin/clot in the intrinsic and extrinsic coagulation cascade. One molecule of citrate binds two calcium anions, forming citrate–calcium complex. About 60% of this complex is lost in the dialysate effluent. Some complexes, however, enter systemic circulation and are metabolized in the liver, where one citrate molecule is transformed into three bicarbonate molecules, and calcium is released into the circulation. However, this amount of released calcium does not replace that is lost in the dialysate effluent, hence calcium is replaced and infused through a separate central blood line. The dialysate and replacement solutions should be calcium free to avoid interaction and reduction of the anticoagulation effect. RCA requires close monitoring, especially upon initiation of RCA anticoagulation. RCA has been associated with significantly less bleeding, less need for blood transfusion, and extended life of the extracorporeal circuit. The KDIGO guidelines suggested using RCA rather than heparin in patients who do not have contraindications for citrate.

Continuous renal replacement therapy dose

The adequate dose of CRRT may be represented by the volume of blood purified per unit of time. In clinical practice, the dose of CRRT is the effluent flow rate, which equals ultrafiltrate (in SCUF and CVVHF modalities) and ultrafiltrate and dialysate (in CVVHD and CVVHDF modalities).

In 2000, Ronco et al. have shown that higher delivered dose (35 and 45 mL/kg/h) using postdilution hemofiltration is superior to 25 mL/kg/h in improving the survival rate (15%—
20% reduction in mortality rate). However, later studies of higher prescribed doses of 48 versus 20 mL/kg/h20 or 20 versus 35 mL/kg/h21 showed no difference in survival rates. These studies were followed by three major multicentric randomized controlled trials (RCTs): ATN-CVVHDF in the USA,22 RENAL-CVVHDF in Australia and New Zealand,23 and IVOIRE-CVVHF in France, Belgium, and the Netherlands24, which confirmed that increasing dose intensity above 20–25 mL/kg/h does not deliver clinical benefits to critically ill patients with severe AKI. Furthermore, two meta-analyses have evaluated the volume intensity in AKI. Van Wert et al25 assessed 12 studies with 3999 patients and showed no benefit of more intensive RRT with regard to survival or dialysis dependence among survivors. Clark et al26 tested high-volume hemofiltration (>50 mL/kg/h) for septic AKI patients and found no difference in mortality between high-dose and standard-volume hemofiltration, but significantly higher rates of hypophosphatemia and hypokalemia in high-volume hemofiltration-treated patients. Other studies have confirmed the higher rates of hypophosphatemia; hypokalemia; loss of amino acid or protein, vitamins, selenium, and folic acid; and the clearance of some antibiotics, resulting in difficulty to adjust the dose of antibiotics with possible periods of inadequate antibiotic levels.27,28 In addition, the RENAL study found that high-volume hemofiltration required more filters per day, indicating more clotting events and frequent interruption occurred during therapy.23

However, it is important to differentiate between prescribed and delivered doses. Interruption of CRRT treatment, due to circuit clotting, machine alarms, change of replacement solutions, radiological investigations, and/or surgical procedures, can have substantial impact on the actual delivered dose, which determines the outcome. This should be considered when prescribing the CRRT dose. KDIGO clinical practice guidelines recommend that “In clinical practice, in order to achieve a delivered dose of 20–25 mL/kg/h, it is generally necessary to prescribe in the range of 25–30 mL/kg/h, and to minimize interruptions in CRRT.” Equally important, “The dose should be frequently assessed and prescription should be adjusted accordingly.”

Vascular access

The vascular access is essential in achieving adequate blood flow rate, which reduces the chances of extracorporeal clot formation and interruption of CRRT treatment, and optimizing the delivered dose. Catheters are the mainstay vascular access in performing CRRT. Proper management of catheters is crucial in achieving adequate blood flow rate and in avoiding or minimizing infections, mechanical problems, and CRRT machine alarms.

Placing vascular access should be at the highest blood flow rate location. Parienti et al29 showed, in aRCT, catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring RRT that catheter survival is best with right internal jugular vein, followed by femoral vein and left internal jugular vein. The KDIGO guidelines8 recommended the sites of catheter placement by order of preference as follows: right internal jugular vein, femoral vein, left internal jugular vein, subclavian vein (dominant side), and subclavian vein (nondominant side).

The diameter of the preferred catheter depends on RRT modality. For example, in CVVHD modality, where blood flow rate ranges from 100–150 mL/min, 11–12 French size is recommended, whereas in CRRT with extracorporeal CO2 removal by artificial lung using extracorporeal membrane oxygenation (ECMO) with high blood flow rate of 400–500 mL/min, 14–16 French size is required.14

Continuous renal replacement therapy initiation and termination

The optimal time of initiation and termination of CRRT treatment remains controversial and not well determined. This is possibly due to the lack of a definition of “timing.” For example, is early start related to the onset of symptoms, biomarker thresholds, relative to the onset of AKI, relative to ICU admission, or
based on AKI classification criteria? There are numerous contributing factors, but no broad consensus to guide. The KDIGO guidelines recommend that “Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist,” and “Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests, rather than single BUN and creatinine thresholds alone, when making the decision to start RRT.”

In 2016, two large prospective RCTs assessed the impact of different RRT timing in severely ill ICU patients with AKI without potentially life-threatening complications. These are the Artificial Kidney Initiation in Kidney Injury (AKIKI) study, which was performed in France, and the Early versus Late Initiation of RRT in Critically Ill Patients with AKI (ELAIN) trial, which was conducted in Germany. The multicentric AKIKI trial, which was conducted on 620 ICU patients on mechanical ventilation and/or catecholamine infusion with KDIGO stage 3 AKI, showed no significant difference in 60-day mortality, which was found between early and delayed RRT. However, a post hoc analysis of this study showed that, when patients in the late group treated with RRT were analyzed separately, mortality was significantly higher in the late group in comparison with the early group.

The ELAIN trial, which was a single-center homogeneous trial conducted over a similar time period screening 604 almost exclusively postsurgical and trauma patients to include 231 ICU patients with KDIGO stage 2 AKI and exhibiting a plasma NGAL level >150 ng/mL, showed that early strategy resulted in lower 90-day mortality, more rapid recovery of renal function, and a significantly shorter duration of hospital stay. Long-term (12 months) follow-up showed persistent beneficial effect on survival rate in the group which received early versus late start CRRT. These findings require confirmation in larger, multicentric, RCTs involving different patient groups requiring RRT.

Following these two studies, there were different meta-analysis studies with conflicting results of early versus late start of CRRT. A more recent French RCT was conducted in one group which received RRT within 12 h after documentation of failure-stage AKI (early strategy) and another group received RRT after a delay of 48 h if renal recovery had not occurred (delayed strategy). This study, which assessed the primary outcome as death at 90 days, showed no difference between early and late start of CRRT. However, there were some limitations in this trial. These include the reliance on RIFLE classification of AKI, where studies have shown that RIFLE is not as sensitive as the most recent classification system. The second limitation is the choice of a delay of only 48 h, which may not be sufficiently long to allow the recovery of renal function or to detect a difference between early and delayed RRT.

The Acute Disease Quality Initiative workgroup suggested that a more personalized approach can be developed on the basis of dynamic assessments of different clinical parameters that reflect the mismatch of demand and capacity. More recently, the Cochrane Database of Systematic Reviews studied the timing effect of RRT initiation for AKI on death (day 30 or after 30 days) and recovery of renal function according to the modality of RRT (continuous RRT vs. continuous and intermittent RRT), etiology of AKI (surgical versus nonsurgical), clinical–biochemical criteria, length of stay in ICU, and the adverse effects. This review, which included five randomized studies enrolling 1084 participants, concluded that early RRT may reduce the risk of death and may improve the recovery of kidney function in critically ill patients with AKI. However, there was an increased risk of adverse events with early RRT.

Discontinuation of CRRT, as per the KDIGO guidelines, is “when RRT 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.” These guidelines also state that “using diuretics is not recommended to enhance kidney function recovery, or to reduce the duration or...
frequency of RRT. Recent studies showed that improvement in urine output and daily urinary creatinine evaluation remain reliable markers of renal recovery, but detailed clinical indicators for discontinuation of RRT include off vasopressors, increased urinary output ≥500 mL/24h (without diuretics), hemodynamic stability, no more fluid overload, and a possible need to shift to IHD when patients become stable or have left the ICU.

Conclusions

Severe AKI, especially when it is caused or associated with sepsis, carries increased risk of progression to chronic kidney disease and end-stage renal failure. In addition, it is associated with prolonged hospitalization, financial burden, and increased mortality rate. Critically ill patients with AKI and/or multiorgan failure in ICU require special modalities of therapies to ensure hemodynamic stability, euvoletic status, and acid–base and electrolyte balance, with an aim of speeding up renal recovery and avoiding deleterious consequences. CRRT stands as a valuable supportive therapeutic modality for such patients. CRRT provides slow, smooth, and gentle dialysis treatment compared to IHD. It is indicated in hemo-dynamically unstable and brain edema patients. The prescribed dose is 20–25 mL/kg/h, but to deliver this dose, higher doses are required. RCA is the recommended method of anticoagulation. Filtration fraction should not exceed 20%–25%, and its calculation is very useful to prolong the life of the dialyzer. Vascular access (catheters) should be placed at the highest blood flow location and in order sequence of right internal jugular vein, femoral vein, and left internal jugular vein. CRRT management also includes proper timing of initiation and termination, where early start may have better survival and renal recovery rates but may be associated with more complications. Finally, removal of endotoxins and inflammatory mediators in different settings of associated sepsis may have positive impact on early renal recovery and improved patient survival rate.

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