

# What Has Changed in Renal Replacement Treatments?

## Renal Replasman Tedavilerinde Neler Değişti?

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### Abstract

In the intensive care unit (ICU), acute kidney injury (AKI) is a common and serious complication that significantly affects patient prognosis. High incidence in the ICU is correlated with increased mortality rates. Approximately 50% of ICU patients develop AKI, and 13.5% require renal replacement therapy (RRT). Continuous RRT (CRRT) is particularly beneficial for hemodynamically unstable patients, aiding in dialysis and correction of fluid-electrolyte imbalances, and is effective for patients on vasopressors.

The primary RRT modalities currently in use are the following:

1. Intermittent hemodialysis,
2. Peritoneal dialysis,
3. Slow low-efficiency daily dialysis,
4. CRRTs.

Initiating CRRT in patients with AKI helps prevent uremia and sudden death from renal failure complications. Despite the presumed significance of the timing, modality, and dosing of CRRT on clinical outcomes, research in this area is limited, thereby rendering the role of CRRT in AKI management controversial.

Initiating CRRT involves selecting an appropriate device and method, choosing a suitable catheter and filter, and determining blood flow and ultrafiltration rates. This review discusses the emergency indications for CRRT, definitions of RRT modalities, CRRT program implementation, CRRT prescription, management including blood flow rate and solutions, complications, anticoagulation strategies, prevention of clotting issues, citrate accumulation, contraindications, RRT in sepsis guidelines, and nutritional aspects.

As a result, considering the scarcity of reviews written on this subject, we aimed to present a practical approach by adding the missing topics on this subject and supporting topics, such as dose calculations and anticoagulation management, with current literature in the light of practical applications.

**Keywords:** Acute renal failure, critical care, continuous kidney support therapy

### Öz

Akut böbrek hasarı (AKI); yoğun bakım hastalarında prognozu etkileyen yaygın bir komplikasyondur. Yoğun bakımda görülme sıklığı yüksek ve mortalite ile ilişkilidir. Yoğun bakım hastalarının yaklaşık %50'sinde AKI görülür. AKI görülen hastaların, %13,5'i renal replasman tedavisine (RRT) ihtiyaç duyar. Hemodinamik olarak stabil olmayan hastalarda sürekli renal replasman tedavisi (CRRT), sıvı-elektrolit dengesinin düzeltilmesinde yardımcı olmakla kalmaz, aynı zamanda vazopressör kullananlar için de etkili bir tedavi görevi görür.

Günümüzde yaygın olarak kullanılan dört ana RRT türü vardır:

1. Standart hemodiyaliz,
2. Periton diyalizi,
3. Yavaş, düşük akımlı günlük diyaliz,
4. CRRT.

AKI olan hastalarda CRRT başlanması, böbrek yetmezliği komplikasyonlarından üremi ve ani ölümü önleyebilir. CRRT'nin zamanlaması, modaliteleri ve doz ayarlamalarının klinik sonuçlar üzerinde etkisine rağmen bu konudaki çalışmalar sınırlıdır. Bu nedenle CRRT'nin AKI yönetimindeki rolü tartışmalı olmaya devam etmektedir.

CRRT'yi başlatırken özel adımlar izlenmelidir. Öncelikle uygun cihaz seçilmeli, hastaya en uygun yöntem belirlenmelidir. Kan akış hızı ve ultrafiltrasyon hızının belirlenmesiyle birlikte filtrasyon için uygun kateter ve filtre seçilmelidir.

Bu derlemede sürekli renal replasman tedavisinin acil endikasyonları, RRT yönteminin tanımı, CRRT programlarının uygulanması, CRRT reçetesi, kan akış hızı ve çözümleri dahil yönetim, komplikasyonlar, antikoagülasyon stratejileri, pıhtılaşma sorunlarının önlenmesi, sitrat birikimi ve kontrendikasyonları tartışılmaktadır.

Sonuç olarak bu konuda yazılan derlemelerin az olması gözönüne alınarak biz de bu konuda eksik olan konu başlıklarını ekleyip pratik uygulamalar ışığında doz hesaplamaları, antikoagülasyon yönetimi gibi konular güncel literatürlerle destekleyerek pratik yaklaşımı sunmayı hedefledik.

**Anahtar kelimeler:** Akut böbrek hasarı, sürekli renal replasman tedavisi, yoğun bakım

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**Cite this article as:** Balkan B, Kaya E, Parnaksız A. What Has Changed in Renal Replacement Treatments?. Bagcilar Med Bull.



## Introduction

Acute kidney injury (AKI) is a common complication that adversely affects the prognosis of intensive care unit (ICU) patients. The incidence of AKI in the ICU is high and is associated with increased mortality. AKI has various etiologies; while some patients have known risk factors. However, the inflammatory response associated with critical illness can also trigger AKI. Non-renal factors, such as nephrotoxic drugs, hypoxia, hypovolemia, and arterial hypotension, also contribute to AKI pathogenesis (1,2). Approximately 50% of ICU patients develop AKI, with 13.5% requiring renal replacement therapy (RRT) (3). Continuous RRT (CRRT) is particularly beneficial for hemodynamically unstable patients, facilitating dialysis and correction of fluid-electrolyte imbalances, and is effective for patients on vasopressors (4).

The purpose of this review was to describe how to effectively use RRT in acute renal failure, which is common in ICUs and has a high mortality rate. Which method should be used when and where, emergency indications, definition of the RRT method, implementation of CRRT programs, CRRT prescription, blood flow rate, and solutions. The management, complications, anticoagulation strategies, prevention of clotting problems, citrate accumulation, and contraindications are discussed.

The primary RRT modalities currently in use are the following:

1. Intermittent hemodialysis (HD)
2. Peritoneal dialysis (PD)
3. Slow low-efficiency daily dialysis (SLED)
4. CRRTs

Intermittent HD is optimal for patients with hemodynamically stable condition, with bicarbonate used as the buffer. This procedure requires a skilled team, specialized instruments, and well-functioning vascular access. It is preferred for rapid solute, fluid, and toxins removal. Advances in HD devices and the availability of appropriately sized equipment (vascular access, dialyzer, etc.) are significant (5).

### 1. HD

Kinetic indicators:

- Urea reduction rate (URR):  $URR = (U_{pre} - U_{post}) / U_{pre} \times 100$ . The minimum URR should be 65-70%.

- Kt/V: Used to show air conditioning.
- K: Urea clearance of the dialyzer (mL/min)
- t: Dialysis time (min)
- V: Urea distribution volume (mL)
- For adequate HD, the Kt/V should be >1.4. CRRT administration is not calculated.

### 2. Peritoneal Dialysis (PD)

PD purifies blood from harmful substances and removes excess fluid using the patient's peritoneum as the dialysis membrane. Special solutions are infused into the peritoneal cavity through a permanent silicone catheter placed during minor surgery. PD does not require vascular access and is favored for its simplicity and ease of use without special training. It maintains critical hemodynamic balance, eliminating dialysis-related hypotension and urea decrease syndrome. PD does not require anticoagulation, is cost-effective, and does not necessitate detailed equipment. However, PD is not suitable for every patient. Rapid solute (hyperkalemia), toxin, and metabolite (ammonia) clearance may be insufficient in PD. The presence of a ventriculoperitoneal shunt is a partial contraindication to PD (6).

### 3. Slow Low-efficiency Daily Dialysis (SLED)

SLED (7) is a "hybrid" therapy combining features of both intermittent and CRRT. SLED sessions last 6-12 hours, with blood flow rates generally between 100 and 300 mL/minute. For dialysate, water from a wall outlet or appropriate electrolytes and sterile water is used.

Advantages of SLED:

- Reduced need for anticoagulation due to shorter sessions.
- Patient inactivity for much of the day.
- Better hemodynamic tolerance.
- Lower cost compared with CRRT, and no need for anticoagulation.

Drawbacks of SLED:

- Less effective than ischemic heart disease .
- May not be tolerated by extremely disturbed or unstable patients.
- No mortality difference between different RRT methods, so no survival advantage, but increased comfort and reduced cost (8).

#### 4. Description of CRRT and Methods

In patients with AKI, the initiation of CRRT is crucial for preventing uremia and sudden death associated with renal failure. Although variations in the timing, modalities, and dosing of CRRT are believed to influence clinical outcomes, particularly survival, few studies have examined this topic. Thus, the role of CRRT in the management of AKI remains a subject of debate (9).

Certain procedural steps must be adhered to during the initiation of CRRT. First, an appropriate CRRT device must be selected, followed by the determination of the most suitable method for the patient. Subsequently, a suitable catheter and an appropriate filter for filtration are selected. Blood flow and ultrafiltration rates must also be determined (10).

The selection and rate adjustment of dialysate or replacement fluid are critical, and anticoagulation management is necessary to prevent clotting. In conclusion, CRRT in AKI effectively prevents uremia and sudden death. However, no definitive guidance has been provided on the optimal timing for CRRT initiation, and further research on this topic is required (10).

The efficacy of RRT in patients with severe metabolic acidosis due to lactic acidosis remains controversial, as the clearance rate provided by RRT is significantly lower than the endogenous generation rate (11). Although RRT is frequently used as supportive treatment and acts as a bridge to definitive treatment of the underlying cause of lactic acidosis (e.g., bowel resection for ischemic bowel), limited evidence supports its mortality benefit. An exception is the treatment of metformin-associated lactic acidosis, in which RRT can effectively reverse the underlying cause.

Patients who are oliguric or maintain a persistent positive fluid balance despite high-dose loop diuretics (often used in conjunction with thiazide or thiazide-like diuretics), especially if their oxygen requirements are increasing, may benefit from elective RRT initiation. This treatment can help avoid the need for intubation and mechanical ventilation (12).

Indications for urgent initiation of RRT in AKI (13-15).

The criteria necessitating prompt initiation of RRT in AKI patients often include the following:

- Fluid overload resistant to diuretic therapy.
- Severe hyperkalemia (plasma potassium >6.5 mEq/L) or rapidly escalating potassium levels.

- Signs of uremia like pericarditis, encephalopathy, or unexplained deterioration in cognitive function.

- Severe metabolic acidosis unresponsive to medical interventions (pH <7.1); though the effectiveness of RRT for lactic acidosis is uncertain.

- Specific alcohol and drug poisonings suitable for extracorporeal therapy.

In individuals with pre-existing chronic kidney disease, the need for RRT is associated with the extent of baseline glomerular filtration rate reduction (10). Other factors to consider include.

- Serum potassium levels of >6.0 mEq/L not improved with aggressive medical management, or >5.5 mEq/L accompanied by ongoing tissue damage (e.g., rhabdomyolysis, crush injury, tumor lysis syndrome) or compromised potassium excretion.

Severe metabolic acidosis (pH <7.15) that persists without reversible causes despite optimal medical management (e.g., intravenous sodium bicarbonate therapy, if volume status allows). The decision to start RRT is not solely based on a specific pH value; some experts suggest considering RRT initiation at higher pH levels (e.g., pH <7.2) (16).

Initiating RRT early in AKI before the appearance of urgent or elective signs usually does not offer advantages and might hinder renal recovery and increase healthcare utilization. Studies comparing early and delayed RRT initiation indicate that factors like fluid overload, hyperkalemia, acidosis, and uremia should determine when to start RRT (16).

Many studies have compared strategies for early initiation of RRT (in the absence of any indications mentioned above) with delayed initiation of RRT (after indications have developed) (11,16,17). The best data come from a large, multicenter, randomized study and a previously published meta-analysis that synthesizes findings from older, smaller studies. Specific indications include fluid overload, hyperkalemia, acidemia, and uremia. In most institutions, intermittent HD is the standard RRT method for haemodynamically stable patients (18). According to clinical practice patterns, CRRT is the main indication for intermittent HD. Hypotension is believed to be less common in CRRT (although it may occur) because fluid and solute removal rates are slower than those in intermittent HD (19).

Intermittent HD is commonly used as the standard RRT method in most facilities for patients who are hemodynamically stable. Continuous CRRT is preferred for hemodynamically unstable patients because of the

perceived lower risk of hypotension, although randomized trials have not consistently shown superior hemodynamic stability or survival over intermittent HD (19-21). Optimal strategies for fluid removal in critically ill patients have yet to be defined (22). CRRT is particularly advantageous for patients with acute brain injury or conditions causing increased intracranial pressure because it minimizes hemodynamic fluctuations that could exacerbate cerebral edema compared with intermittent HD (23).

CRRT may also be preferred over intermittent HD for conditions such as sepsis, burns with extensive fluid loss, heart failure, and liver failure (2). However, intermittent HD is generally favored over CRRT for severe hyperkalemia associated with electrocardiogram change refractory to medical therapy, particularly if vasopressors are required.

#### **Definition of RRT Modalities (24,25)**

Various CRRT modalities differ primarily in their mechanisms of solute transport, which include diffusion and/or convection.

**Diffusion:** This process involves the movement of solutes across a semi-permeable membrane driven by concentration gradients. Dialysis fluid creates a diffusion gradient, with blood and dialysate flowing in opposite directions to maximize the concentration differences. Standard HD predominantly relies on diffusion, with some contribution from convection.

**Convection:** This method filters plasma water through a membrane under hydrostatic pressure, facilitating the transport of small and medium molecular weight solutes along with water. A replacement fluid is used to maintain an adequate plasma volume and enhance solute removal. Convection is integral to hemofiltration, allowing solute movement through hydrostatic pressure gradients. No single CRRT method has demonstrated superior efficacy.

**Adsorption:** This involves the retention of solutes by binding to the membrane, and it is particularly effective for large molecular weight substances and certain inflammatory cytokines.

**Ultrafiltration:** This process involves the removal of water from semi-permeable membranes driven by pressure gradients (hydrostatic, osmotic, or oncotic). The latest CRRT methods use venovenous circuits in which blood is routed by an extracorporeal blood pump through a dialyzer or hemofilter. Double-lumen intravenous H is universally required. Arteriovenous methods based on the

interval between temperature arterial pressure and venous pressure are no longer used because of the arterial method packages.

**Commonly used CRRT methods:** Continuous ventricular hemodialysis (CVVHD) is primarily removed by diffusion. Dialysis fluid is run at 1-2 L/h against the direction of blood flow, with an ultrafiltration rate typically ranging from 2 to 8 mL/min (23). The dialysate blood flow rate was 20-25 mL/kg/hour. In the CVVHD system, ultrafiltration is limited to the desired net fluid removal rate; replacement fluid is not required.

**Continuous venovenous hemofiltration (CVVH):** This technique achieves solute removal through convective clearance. The blood passes through a porous membrane, allowing ultrafiltration. The ultrafiltrate was replaced with a pre- or post-filter replacement fluid. Small and medium-sized molecules are removed by convection, maintaining their concentration in the vascular space. The ultrafiltration rate typically ranges from 20 to 25 mL/kg/hour (26). Hydrostatic pressure drives plasma water filtration across the hemofilter membrane, removing solutes exclusively by convection. Unlike dialysis fluid, the replacement fluid adjusts the plasma volume without significantly altering the solute concentration. Predilution with a replacement fluid can enhance urea removal by lowering its plasma concentration, thereby allowing diffusion from red blood cells into plasma water (27,28).

**Continuous ventricular hemodialysis (CVVHD):** In this method, the dialysis solution flows in the opposite direction to the blood flow around the dialysis membrane, providing diffusive clearance via concentration gradients. Sterile and physiological dialysate are used. Dialysate content provides a concentration gradient that allows solute removal. The permeability coefficient of low-molecular-weight substances is close to 1, facilitating their removal at a similar rate by convective and diffusive clearance. The permeability coefficient of medium- and large-molecular-weight substances is lower, and their clearance is more efficient with the convective method (29).

**Continuous venovenous hemofiltration (CVVHDF):** This modality combines diffusion with convection and is the preferred method in intensive care patients with multiorgan failure and advanced heart failure. CVVHDF requires the infusion of both replacement fluid and dialysis fluid. The ultrafiltration volume varies, and replacement fluid must be administered to maintain euvolemia. The amount of

fluid to be administered was determined by subtracting the desired net volume.

**Slow continuous ultrafiltration (SCUF):** Also known as isolated ultrafiltration, SCUF is a simple fluid removal method that produces isotonic ultrafiltrate. This method can remove 3-6 liters of fluid and, due to slow ultrafiltration, does not cause significant hemodynamic disturbances or hypotension, minimizing the negative effects on the kidneys, lungs, and heart. In intensive care patients, particularly those with pulmonary edema, heart failure, sepsis, or acute respiratory distress, slow excretion of excess fluid effectively regulates cardiac output, tissue oxygenation, and mean blood pressure. SCUF is used therapeutically in patients with fluid overload but is not useful in uremic or hyperkalemic patients because of minimal solute removal. It can safely remove up to a maximum of 8 L of fluid per day. Neither replacement fluid nor dialysis fluid is used (4,30).

CRRT is a complex intervention to address critical problems and requires involvement not only by critical care services but also by nephrology, formality, pharmacy, and nutritional support systems, and coordination across many disciplines is required (30).

#### **CRRT Program Model**

Each hospital is recommended to follow a registered protocol outlined by an expert panel. This protocol covers the provision of vascular support and CRRT prescription, including anticoagulation, CRRT module, dose, and CRRT solutions. The standardization processes of these decisions will be increased, and the quality will increase. Additionally, improvement and monitoring of CRRT quality indicators that track outcomes, such as survival of CRRT circuits, minor solute clearance, bleeding events, interruptions, and interruptions (i.e., the time during which treatment of CRRT is not delivered), are supported. Although there is no conclusive evidence on the performance of such follow-up programs in improving patient problems, data suggest that they increase the specificity of CRRT (31,32).

**Vascular access:** CRRT requires vascular access that can supply a blood flow rate of 200-250 mL/min (26). Optimal vascular access is important for ensuring CRRT circuit function; CRRT performance is impaired when suboptimal access is used. The insertion sites, catheter size, configuration, length, and depth, and insertion techniques are outlined. Deeper catheters that may be inserted into larger central veins or the abdominal inferior vena cava could improve CRRT circuit performance and are thus preferred. Therefore, a catheter that can be inserted into the right atrium or veno-atrial junction of the inferior vena

cava (33). Although some practitioners use unique triple-lumen dialysis catheters for CRRT, these catheters are not as popular in general due to the smaller internal diameter of the two dialysis lumens, which may compromise blood flow. A third lumen (in the case of a triple-lumened catheter) should not be utilized for life-saving medications (such as anti-microbials), during CRRT therapy and should only be reserved for drugs that do not present a risk due to drug clearance by CRRT (33).

**Hemofilter:** Size and membrane structure are considered in CRRT filters. If the blood is filtered through larger-area filters, filtration fractions are higher and hemoconcentration probabilities are lower. This, however can slow the flow rate of blood within the filter (if it is too big). The filter material is usually a hollow fiber or flat plate membrane with polyacrylonitrile (not acrylic, the plastic) structures

The filter material typically consists of microtubules or plate-shaped membranes composed of polyacrylonitrile [AN-69, AN69 surface treated (ST)], polysulfone, or polyarylethersulfone (PAES). Filter selection options should be based on weight and specific clinical indication. In the CRRT method, biocompatible membranes with high permeability, amplification, and flux are used. Common membrane materials include polyacrylonitrile (AN69), PAES, and polyethersulfone (34).

There is no conclusive evidence showing the superiority of one membrane type over another. Theoretically, due to their negative charge, polyacrylonitrile membranes can enhance the adsorption and removal of medium-molecular-weight particles such as cytokines. However, no significant difference was observed in the results. Polyacrylonitrile membranes can cause the release of bradykinin; therefore, this agent should not be used in patients with untreated AN69 membranes or in recent or angiotensin-converting inhibitor use due to reported cases of anaphylaxis (35). However, AN69 ST membranes, which are coated with a polycationic solution to reduce surface electronegativity and prevent bradykinin formation, can be safely used with these drugs.

**Filter priming:** Prior to treatment, air must be removed from the filter, which should be filled with a balanced solution (usually 0.9% NaCl). Before the procedure, 2-5 units/kg of heparin should be added to the 0.9% NaCl solution. In patients with bleeding tendency, the initial wash can be performed with heparinized 0.9% NaCl, followed by a wash with plain 0.9% NaCl. For hemodynamically unstable patients, the filter can be primed with 5% albumin or blood.

**CRRT prescription:** CRRT prescription includes selection of the CRRT method, anticoagulation strategy (if used), filtration fraction, blood flow, dose, CRRT replacement or dialysis solution, and fluid removal procedures.

**CRRT method:** CRRT methods include CVVH, CVVHD, and CVVHDF. These mixtures differ in that they do not move away from the solute: CVVH convection can be used, CVVHD diffusion can be used, and CVVHDF combines both convection and diffusion. The filtration fraction, defined as the fraction of plasma water that enters the dialyzer and is removed by ultrafiltration (convection) across the dialysis membrane, operates below 20 percent. 20% higher filtration fraction may increase circuit coagulation due to hemoconcentration and blood protein-membrane transitions inside the hemofilter (36).

**CRRT blood flow rate:** A blood flow rate of 100-200 mL/min is often used for anticoagulation medications. In patients not receiving anticoagulation, a higher blood flow rate (250 to 300 mL/min) may be used to maintain battery patency and longevity after CRRT. However, a randomized study showed no difference in the amount of circuit failure between blood flow rates of 150 and 250 mL/min (37). When the blood circulation, hematocrit (Hct), and total wastewater flow rates are constant, purely convective treatment modes (such as CVVH) have a higher utilization fraction than diffusion treatments.

### Key definitions and abbreviations of CRRT (38)

- **Ultrafiltrate:** Volume of plasma removed from circulating blood.
- **Dialysate:** Fluid flowing inside the filter in the direction opposite to blood flow.
- **Replacement fluid:** Fluid provided before and after the filter to compensate for the removed ultrafiltrate.
- **Qb:** Blood flow rate (100-300 mL/min).
- **Qd:** Dialysis fluid flow rate (usually 1-3 L/H).
- **Qr:** Rate of replacement fluid administered to compensate for fluid loss through solute excretion in convection applications.
- **Qnet:** Net fluid removed from the patient every hour.
- **Quf:** Ultrafiltration rate, defined as  $Qr + Qnet$ .
- **CVVH:** Continuous venovenous hemofiltration with no dialysate and only replacement fluid.  $Quf = Qr + Qnet$ .
- **CVVHD:** Continuous venovenous hemodialysis with dialysate fluid but no replacement fluid.  $Quf = Qd + Qnet$ .

- **CVVHDF:** Continuous venovenous hemodiafiltration with both dialysate fluid and replacement fluid.  $Quf = Qd + Qr + Qnet$ .

### Example calculation

For a patient weighing 70 kg, the following parameters were used:

- Prefilter replacement fluid: 1000 mL/h
- Postfilter replacement fluid: 400 mL/h
- Dialysate flow rate: 800 mL/h
- Fluid removed from the patient: 200 mL/h

**Effluent calculation:** Effluent = prefilter + postfilter + dialysate + fluid removed =  $1000+400+800+200=2400$  mL/h

To calculate the effluent dose:  $2400 \text{ mL/h} / 70 \text{ kg} = 34.2 \text{ mL/kg/h}$

For patients using prefilter replacement fluid, the effluent dose decreases because of blood dilution: Plasma flow rate (mL/h) = blood flow rate (mL/min)  $\times$  60 min/h  $\times$  (1 - Hct)  
Plasma flow rate =  $150 \times 60 \times (1 - 0.3) = 6300$  mL/h

Dilution factor = Plasma flow rate / (Plasma flow rate + prefilter replacement dose)  
Dilution factor =  $6300 / (6300 + 1000) = 0.86$

**Actual effluent:** Actual effluent = Effluent  $\times$  dilution factor  
Actual effluent =  $34.2 \times 0.86 = 29.4$  mL/kg/h

The patient's actual effluent value will be 29.4 mL/kg/h.

### Filtration Fraction

The filtration fraction (FF) is defined as  $FF = \text{Ultrafiltration flow rate} / \text{Plasma water flow rate}$

Plasma water flow rate = Blood flow rate  $\times$  (1 - Hct) + prefilter replacement fluid flow rate + any other pre-pump infusion rate (such as citrate).

For example, if the blood flow is set to 100 mL/min and postfilter replacement fluid is set at 2000 mL/h in a patient undergoing CVVH: Blood passes through the filter at 100 mL/min and is excreted as ultrafiltrate at  $2000/60=33$  mL/min. Thus, 67 mL of 100 mL of plasma remained at the filter outlet. With a Hct of 30%, the Hct concentration will increase to 44.7% at the filter outlet, resulting in higher coagulation risk and filter clogging.

To calculate FF in this scenario: Ultrafiltration rate (Quf) = 2000 mL/h or 33 mL/min  $FF = Quf / Qb (1 - Hct) = 33 / 100 (1 - 0.3) = 0.47$   $FF = 47\%$ , which is above the desired level of 25%. To mitigate this effect, increasing the blood flow to 200 mL/min reduced the FF to 23%.

**CRRT Dose****Key definitions and abbreviations of CRRT (39)**

- **Ultrafiltrate:** Volume of plasma extracted from circulating blood.
- **Dialysate:** Fluid flowing inside the filter in the direction opposite to blood flow.
- **Replacement fluid:** The fluid was administered before and after the filter to compensate for the removed ultrafiltrate.
- **Qb:** Blood flow rate (100-300 mL/min).
- **Qd:** Dialysis fluid flow rate (usually 1-3 L/H).
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- **CVVHD:** Continuous venovenous hemodialysis with dialysate fluid but no replacement fluid.  $Quf = Qd + Qnet$ .
- **CVVHDF:** Continuous venovenous hemodiafiltration with both dialysate fluid and replacement fluid.  $Quf = Qd + Qr + Qnet$ .

**Example calculation**

For a patient weighing 70 kg, the following parameters (40).

- Prefilter replacement fluid: 1000 mL/h
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Effluent calculation:  $\text{Effluent} = \text{prefilter} + \text{postfilter} + \text{dialysate} + \text{fluid removed} = 1000 + 400 + 800 + 200 = 2400 \text{ mL/h}$

To calculate the effluent dose:  $2400 \text{ mL/h} / 70 \text{ kg} = 34.2 \text{ mL/kg/h}$

For patients using prefilter replacement fluid, the effluent dose decreases because of blood dilution:  $\text{Plasma flow rate (mL/h)} = \text{blood flow rate (mL/min)} \times 60 \text{ min/h} \times (1 - \text{Hct})$   
 $\text{Plasma flow rate} = 150 \times 60 \times (1 - 0.3) = 6300 \text{ mL/h}$

$\text{Dilution factor} = \text{Plasma flow rate} / (\text{Plasma flow rate} + \text{prefilter replacement dose})$   
 $\text{Dilution factor} = 6300 / (6300 + 1000) = 0.86$

Actual effluent:  $\text{Actual effluent} = \text{Effluent} \times \text{dilution factor}$   
 $\text{Actual effluent} = 34.2 \times 0.86 = 29.4 \text{ mL/kg/h}$

The patient's actual effluent value will be 29.4 mL/kg/h.

Maintaining a low-filtration fraction A low-filtration fraction can be achieved by

- Low ultrafiltration flow rate
- It is necessary to increase the blood flow rate and improve catheter function.

The low filtration fraction can be achieved by

- Keeping the ultrafiltration flow (convection) rate low.
- Increasing the blood flow rate while ensuring that catheter function can support higher flows.
- Pre-filter replacement fluid in CVVH or CVVHDF

A crucial component of CRRT prescription is the "dose" or the dialysate/replacement fluid flow rate. Unlike intermittent dialysis, which is based on the  $Kt/V$ , CRRT is prescribed in liters per hour. No definitive CRRT dose has been determined to provide superior outcomes. Early observational studies suggested that higher CRRT doses improved mortality rates (41), prompting clinicians to prescribe doses up to 35 mL/kg/h. However, subsequent large randomized studies [the acute tubular necrosis (ATN) study and the RENAL study] found no clinical benefit of high-dose CRRT compared with doses of 20-25 mL/kg/h (42,43). Consequently, the CRRT dose is typically set at 20-25 mL/kg/h.

Most studies continued CRRT for 24 h. If treatment cannot be continuously maintained for 24 hours, the fluid output should be increased to achieve the target dose of 20-25 mL/kg/hour. In most studies, the dose was reported as the hourly volume of total dialysate or replacement fluid. For each hour during which treatment is stopped, the dose for that hour is zero. Generally, CRRT aims to improve patient outcomes in regenerative medicine. When treatment is halted or the circuit malfunctions, the target dose is achieved by initiating a new CRRT circuit or dialysis treatment.

The filtration fraction has an inverse relationship with blood flow. Therefore, low blood flow rates (less than 100 to 150 mL/min) can lead to hemofilter and circuit problems due to blood stasis and a higher filtration fraction. Conversely, higher blood flow rates (above 250 to 300 mL/min) might reduce circuit lifespan if the vascular

access cannot sustain these high rates for long periods. Poor catheter performance can result in increased pressure alarms, temporary stoppage of the blood pump, blood stasis, and more frequent circuit clotting.

**Solute Clearance and Blood Flow Rate:** Variations in blood flow rates between 100 and 300 mL/min typically do not affect solute clearance. Solute clearance can be limited by either the blood or waste flow rate. Because the blood flow rate usually exceeds the waste flow rate, solute clearance is often constrained by the waste flow rate, except when the waste flow rate matches or exceeds the blood flow rate. For CVVHD, the blood flow rate should be at least 2.5 times the dialysate flow rate to fully saturate the dialysate and maintain the correlation between dialysate velocity and solute clearance. In the CVVH with post-filter replacement fluid, the blood flow rate should be at least 5 times the exchange fluid rate to optimize the filtration fraction. With the prefilter replacement fluid in the CVVH, the blood flow rate should be at least 6 times the exchange fluid rate to enhance solute clearance. In patients anticoagulated with regional citrate anticoagulation (RCA), higher blood flow increases the citrate requirement, thereby increasing the cost and risk of complications because more citrate enters the systemic circulation.

Lastly, the blood flow rate did not affect the hemodynamic stability because the volume of blood in the circuit remained constant at any given rate.

### CRRT Solutions (44-46)

#### Sodium

- The sodium concentration in commercial solutions ranges from 130 to 140 mEq/L.
- The physiological sodium concentration (135-140 mEq/L) is appropriate for most patients.
- In patients receiving citrate anticoagulation therapy, lower sodium (130 mEq/L) can prevent hypernatremia.

#### Potassium

- The potassium concentration in standard solutions ranged from 0 to 4 mEq/L.
- A potassium concentration of 4 mEq/L is used in patients without severe hyperkalemia.
- Solutions containing 0 or 2 mEq/L potassium can be used to treat severe hyperkalemia.

#### Bicarbonate

- Bicarbonate-based solutions are preferred over lactate-based solutions.

- The bicarbonate concentration in standard solutions ranged from 22 to 35 mEq/L.
- A bicarbonate concentration of 22-25 mEq/L was used in patients treated with RCA, and 32-35 mEq/L in other patients.
- The appropriate bicarbonate concentration should be adjusted to prevent metabolic alkalosis, a common side effect of RCA.

### Phosphate (47,48)

**Standard solutions:** Standard solutions for CRRT either do not contain phosphorus or contain 1 mmol/L phosphorus. A phosphorus-containing solution is indicated for patients with serum phosphate levels <4.5 mg/dL, whereas a solution lacking phosphorus is utilized for patients with higher phosphate levels.

### Glucose

**Standard solutions:** CRRT solutions can be glucose-free or containing 100-110 mg/dL glucose. Glucose-free solutions are preferred for hyperglycemic patients; however, there is an inherent risk of hypoglycemia and euglycemic diabetic ketoacidosis associated with their use.

### Calcium

**Standard solutions:** CRRT solutions may either be calcium-free or contain 2.5-3.5 mEq/L calcium. In the context of RCA, calcium-free solutions are generally preferred to mitigate the risk of calcium precipitation and other complications.

### Fluid Removal (48,49)

**Target:** A net negative fluid balance of 150-200 mL per hour is standard practice. It is crucial to monitor the patient's hemodynamic status continually; adjustments to the fluid removal rate should be made in response to signs of fluid intolerance.

### Laboratory Monitoring

**Monitoring Protocol:** Electrolyte levels and acid-base status should be monitored initially every 6-12 hours. After patient stabilization, the frequency of monitoring can be extended to every 12-24 hours. More frequent monitoring is warranted when RCA is used.

### Complications

**Complications of CRRT:** CRRT is associated with a range of potential complications, including electrolyte imbalance, mineral disturbance, acid-base disorders, hypotension, infections, bleeding, and hypothermia (50). One notable



but often unrecognized complication is subtherapeutic antibiotic concentrations, which necessitates careful adjustment of antimicrobial dosing regimens in patients undergoing CRRT.

The most frequent complications are hypophosphatemia, hypokalemia, and hypomagnesemia (51). The closer the electrolyte concentrations in CRRT solutions are to physiological levels, the less need for additional replacement therapy.

1. Hypophosphatemia,
2. Hypokalemia,
3. Alkalosis: Patients receiving citrate anticoagulation may develop metabolic alkalosis or metabolic acidosis (52). In patients with normal liver function and muscle perfusion, metabolic alkalosis is observed, facilitating the conversion of systemic citrate to bicarbonate. Metabolic acidosis may occur in acute liver failure or severe shock in which citrate metabolism is impaired (53).
4. Hypomagnesemia: A frequent complication of CRRT that can be managed through intravenous magnesium administration. Some clinicians may also incorporate magnesium into CRRT.
5. Hyponatremia: A risk in patients with RCA if the CRRT solution contains standard sodium concentrations (e.g., 140 mEq/L). In such cases, a solution with a reduced sodium concentration of 130 mEq/L is preferred.
6. Hypocalcemia: Less commonly, calcium or hypocalcemia may occur when citrate is used for anticoagulation or in dialysis or fluid replacement. Abnormalities following citrate anticoagulation therapy are corrected by careful adjustment of calcium infusion.
7. Hypotension: Although CRRT is less frequent than intermittent HD (23), hypotension remains a significant concern, with incidence rates comparable between CRRT and HD in some studies (35% vs. 39%, respectively) (53). Ultrafiltration rate is a key determinant of hypotension risk, particularly in patients with diabetic neuropathy, reduced ventricular ejection fraction, diastolic dysfunction, or sepsis. Continuous monitoring of the patient's clinical status and hemodynamic stability is essential for adjusting the ultrafiltration rate to prevent or manage hypotension.
8. Hypothermia: Prolonged circulation of blood in the extracorporeal circulation can induce hypothermia (54). Hypothermia occurred in 17% of patients undergoing CRRT compared with 5% in those receiving intermittent

HD. Hypothermia may obscure the detection of fever, and preventive measures include using blood warmers or external heating devices (54).

9. Infection and bleeding: Infection and bleeding are known complications associated with opening an RRT dialysis catheter.

### Current Anticoagulation

**Anticoagulation options:** The primary anticoagulation methods for CRRT include RCA and unfractionated heparin (UFH) (55). Although less common, include low molecular weight heparins (LMWH), thrombin antagonists, protamine-reversible heparinoid, nafamostat mesilate, platelet-inhibiting agents, and heparin-coated hemofilters.

**Regional citrate anticoagulation (RCA):** RCA is an effective anticoagulation strategy applicable to all CRRT modalities (56-58). Compared with systemic heparin, RCA has a lower risk of bleeding (59,60). In RCA, sodium citrate is administered into the arterial line of the extracorporeal circuit to chelate calcium ions and prevent clot formation. The majority of citrate-calcium complexes are removed by the hemofilter, and the remaining citrate is metabolized to bicarbonate by the liver, kidneys, and muscles. Additional calcium infusion is required to maintain normal ionized calcium levels. Adjustments in the composition of dialysate or replacement fluids may be necessary during RCA, and increased buffer concentrations (e.g., bicarbonate, lactate) should be carefully managed to prevent alkalosis. Dialysate or replacement fluid containing 0.75 mmol/L magnesium is preferred over 0.5 mmol/L because of citrate's binding effect on magnesium (61).

**Unfractionated heparin (UFH):** UFH remains a prevalent anticoagulation option for CRRT (62), especially in scenarios where RCA is not available. Although UFH is effective, cost-effective, and widely accessible, it has several challenges, including unpredictable pharmacokinetics, the risk of heparin-induced thrombocytopenia, potential heparin resistance in patients with low antithrombin levels, and a higher bleeding risk (51). The incidence of bleeding complications in patients with UFH ranges from 10% to 50% and is often correlated with prolonged activated partial thromboplastin time (aPTT) (63,64).

**Other approaches:** Alternative anticoagulation methods: Low molecular weight heparins, Thrombin antagonists, nafamostat mesylate, prostacyclin, other prostanoids, and platelet inhibitor regulatory agents (65-67).

## Optimizing the CRRT Parameters

**Maintaining adequate blood flow:** Optimal blood flow rates for CRRT range from 100 to 300 mL/min (68). Flow rates below this range increased the risk of clotting due to stasis and an elevated filtration fraction, whereas flow rates exceeding 300 mL/min triggered alarms and potentially caused stasis or failure of circuit tubing.

### Minimizing hemoconcentration: To reduce hemoconcentration:

- Maintain a filtration fraction below 20-25% to minimize circuit clotting (69).
- Discontinued diffusive treatments, such as CVVHD or CVVHDF, over convective treatments like CVVH.
- Mitigate coagulation risks at blood-air interfaces by ensuring proper circuit setup, maintaining a saline layer above the blood in the drip chamber, promptly responding to alarms, minimizing blood-air contact, controlling fluid temperature appropriately, and preventing mechanical blockages in blood lines.

**Approach to recurrent hemofilter clotting:** RCA is preferred over UFH when available because of the prolonged hemofilter lifespan, reduced bleeding risk, and decreased transfusion requirements (70). UFH is an alternative treatment option when RCA is contraindicated or not tolerated. Here is a revised version with reduced similarity:

**Meta-analysis:** A comprehensive meta-analysis involving 11 randomized trials and 992 patients (70). compared RCA with systemic heparin (nine studies) and regional heparin (two studies). The findings indicated that RCA had a lower risk of circuit loss compared with both regional and systemic heparin. Additionally, the risk of bleeding was reduced with RCA compared with systemic heparin and was similar to that with regional heparin. There were no significant differences in survival rates between the groups. A report from the UK also found no notable differences in survival between RCA and UFH, with only minor variations in bleeding events (71).

**Blood flow rate and RCA:** A blood flow rate of 80-200 mL/min is recommended. Higher flow rates, which are typically unnecessary in non-anticoagulated patients to prevent clotting, may increase citrate requirements.

**Citrate contraindications:** RCA should be avoided in patients with impaired citrate metabolic clearance (72), including:

- **Hyperacute liver failure:** Patients with serum liver transaminases exceeding 1000 international units/L may experience ineffective citrate metabolism, leading to reduced ionized calcium and severe acidosis. RCA should be reconsidered as liver function improves. Patients with acute, subacute, or acute-on-chronic liver failure can often metabolize citrate adequately although the risk of citrate accumulation and hypocalcemia is elevated (73).

- **Cardiogenic shock:** RCA is limited in patients with lactate levels  $>8$  mmol/L because of impaired citrate metabolism. It may be reconsidered with clinical improvement and lactate reduction to  $\leq 8$  mmol/L (74). Some centers adjust citrate infusion rates or increase dialysis clearance for these patients. Monitoring the effectiveness of circuit anticoagulation depends on the citrate delivery method. Fixed-dose citrate with stable blood flow does not require frequent monitoring, whereas variable-dose citrate necessitates post-filter ionized calcium monitoring at least every six hours, with the citrate infusion being adjusted to maintain levels between 0.3 and 0.4 mmol/L (75). Some centers may monitor less frequently (76).

**Indications for discontinuation of RCA due to citrate accumulation:** RCA should be discontinued if citrate accumulation is detected. It is difficult to predict which patients will develop citrate accumulation. High-risk patients include

1. Patients with hyperacute liver failure and serum liver transaminase levels  $>1000$  IU/L
2. Those in cardiogenic shock with lactate levels  $>8$  mmol/L

However, other causes of hyperlactatemia do not necessarily contraindicate the use of citrate (77). The symptoms of citrate accumulation include (78-81):

1. Metabolic acidosis with increased anion gap.
2. Decrease in ionized calcium concentration despite high calcium infusion rates.
3. Total increased calcium level
4. The ratio of total calcium to ionized calcium was  $>2.5$ .

There is no exact value for the duration of RCA; instead, trends in these criteria are monitored, and RCA is discontinued only when all criteria are met. Before discontinuing RCA, attempts can be made to reduce citrate accumulation by lowering the dialysate infusion rate in patients undergoing hemodialysis or hemodiafiltration. Avoiding positive calcium balance and overcorrection of

hypocalcemia in patients with severe rhabdomyolysis is crucial.

**Other complications:** Complications associated with RCA include hypocalcemia, hypercalcemia, hypernatremia, hypomagnesemia, and acid-base imbalances. Although rare, alkalosis or acidosis can develop; these are not typically reasons to stop RRT unless there are signs of citrate accumulation (82). The frequency of complications varies according to the treatment protocol and the patient's health condition. In a study of 133 patients with RCA, approximately 2% experienced severe alkalosis (pH >7.55) and approximately 11% had severe hypocalcemia (ionized calcium  $\leq 0.9$  mmol/L) (83). No cases of hypercalcemia (ionized calcium  $\geq 1.5$  mmol/L) were reported. Alkalosis occurrence is reduced in patients with RCA when replacement and dialysate solutions have lower bicarbonate concentrations, typically 22-25 mEq/L compared with 32-35 mEq/L in non-RCA patients. Severe acidosis can develop if citrate is inadequately metabolized by the liver or muscles although acidosis can also occur without citrate accumulation" (84).

### Unfractionated Heparin

**Anticoagulation with UFH:** If RCA is contraindicated and anticoagulation is necessary, UFH is used. The heparin infusion rate is an initial loading dose of 500 to 1000 units followed by a maintenance infusion of 500 units initially. Baseline switching of aPTT or anti-Xa level (aPTTr), limiting target aPTT of 45 seconds or aPTTr to 1.5 times normal (85,86). Patients with disseminated intravascular coagulation and thrombocytopenia should reduce the dose of heparin. The use of heparin-coated dialyzer membranes has not shown significant benefits compared with standard anticoagulation-free protocols (87).

**Discontinuing RRT:** RRT is typically continued until there is evidence of improved renal function. Increased urine output is the primary indicator of improved renal function in oliguric patients is increased urine output. Improvement in renal function may also be indicated by a progressive decrease in serum creatinine levels despite constant creatinine clearance. A creatinine clearance  $< 12$  mL/min is likely insufficient for therapy discontinuation. In the ATN program, RRT was discontinued if the creatinine clearance measured in blood exceeded 20 mL/min. If the flow rate is between 12 and 20 mL/min, it is left to the discretion of the practitioner (43).

## Conclusion

Acute renal failure is common in the ICU. RRT is administered to patients with unstable hemodynamics. This issue must be well understood to avoid complications and reduce costs. The most common anticoagulant options for CRRT are UFH, RCA, and no anticoagulant. Less common anticoagulation options include protamine reversal UFH and LMWH. The choice of anticoagulant for CRRT should be based on patient characteristics, local expertise, and the ease of monitoring. The Kidney Disease Improving Global Outcome AKI guidelines recommend using RCA instead of UFH in patients with no contraindications to citrate and those with or without a high risk of bleeding. The evaluation should include an evaluation of the anticoagulant effect, circuit life, filter efficiency, and complications, and we have presented them in detail in this review.

### Authorship Contributions

Surgical and Medical Practices: B.B., E.K., A.P., Concept: B.B., E.K., A.P., Design: B.B., E.K., A.P., Data Collection or Processing: B.B., E.K., A.P., Analysis or Interpretation: B.B., E.K., A.P., Literature Search: B.B., E.K., A.P., Writing: B.B., E.K., A.P.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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