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Continuous Renal Replacement Therapy in Critically Ill Children

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ABSTRACT

Continuous renal replacement therapy is an extracorporeal blood purification therapy that aims to support kidney and other organ functions over an extended period. The high-quality continuous renal replacement therapy requires understanding basic mechanisms of clearance, factors influencing these processes, and the appropriate selection of treatment candidates. This article reviews the different aspects of continuous renal replacement therapy in critically ill pediatric patients.

Keywords: Sepsis, respiratory failure, extracorporeal treatment

CONTINOUS RENAL REPLACEMENT THERAPY

Approximately 20% of critically ill children may experience various degrees of multiple organ dysfunction.[1] Multiple organ dysfunction syndrome encompasses failure of organ systems such as respiratory, renal, neurological, hepatic, and cardiovascular systems. Of these, renal dysfunction has been shown to be one of the most common and strongest predictors of mortality within pediatric intensive care unit (PICU). Recent epidemiological data suggest that renal dysfunction among pediatric patients may be as high as 30% and associated with a mortality of nearly 15% within a PICU.[2-4] To prevent further complications and reduce mortality associated with renal and other organ dysfunctions, many of these children will require extracorporeal technologies such as continuous renal replacement therapy (CRRT).

Continuous renal replacement therapy has become the mainstay of renal replacement therapy (RRT) in PICUs over the past 3 decades.[5] Advances in technology, equipment, and patient care-related guidelines have resulted in CRRT being the preferred technique to manage critically ill children with acute kidney injury and fluid overload. Furthermore, CRRT is used for cardiac, liver, and pulmonary support and in septic patients.

Despite the evolving sophistication of this therapy in the PICU setting, there remains wide practice variation in this application.

INDICATION

Continuous renal replacement therapy is considered by many clinicians for the management of critically ill patients and is a suggested modality of RRT in hemodynamically unstable patients with acute kidney injury (AKI). In the literature, the most clinical indication for CRRT in children is severe AKI complicated with the concomitant requirement of fluid administration and/or metabolic disturbances.[6] Continuous renal replacement therapy is indicated in patients with (a) hemodynamic instability/shock, (b) diuretic-resistant fluid overload, (c) severe metabolic acidosis, and (d) refractory hyperkalemia. Continuous renal replacement therapy has also been considered in drug toxicity, in the prevention of radiocontrast-induced nephropathy, and in inborn errors of metabolic diseases.

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Furthermore, CRRT is now applied to support different organs apart from the kidney in a myriad of clinical conditions such as sepsis, acute liver failure, acute respiratory distress syndrome (ARDS), and cardiogenic shock.[5]

In sepsis, the removal of damage-associated molecular patterns and cytokines might reduce the burden of the disease. For decades, cytokines were the targets of CRRT. They were cytotoxic, and justifying their removal was elaborated by theories like peak concentration,[6] threshold immunomodulation,[7] and late mediator delivery.[8] All those theories advocating a higher convection dose have been shown ineffective in randomized controlled trials.[9] Increasing the filter porosity has also been demonstrated to be insufficient.[10] Nonselective adsorption by membranes has also never shown to be efficient.[11] The discovery of a new technology leading to sorbent went to uncover some very important steps.[12] A sorbent able to eliminate leukocytes and monocytes did show promising findings for the future of blood purification in sepsis.

Liver damage leads to an increased release of damage-associated molecular patterns and systemic pathogen-associated molecular patterns, as the damaged liver fails to remove endotoxin lipopolysaccharide from the portal blood, leading to the activation of the innate immune system through toll-like receptors, and can then rapidly progress to multiple organ failure. In addition, liver damage leads both to reduction in synthetic function and metabolism, leading to increased systemic ammonia concentrations, and alterations of neurotransmitters. Continuous renal replacement therapy offers a treatment that can remove water-soluble products of metabolism like ammonia and inflammatory molecules and effectively reduce bilirubin and bile acids concentrations.

ARDS allows the application of protective ventilation by correcting fluid overload in cardiogenic shock and cardiac surgery in which shifts in fluid balance are poorly tolerated. In patients with heart decompensation, ultrafiltration is better than diuretics.[13] Continuous renal replacement therapy might mitigate further myocardial damage by correcting fluid overload. Further indications would be ammonia-producing inborn error of metabolism (IEM) or patients with intoxications.[14,15]

The selection of treatment candidates for extended indications of CRRT should be tailored to individual patients' treatment requirements.

VASCULAR ACCESS

The performance and delivery of CRRT depend on an efficient vascular access. The vascular access is essential in achieving an adequate blood flow rate, which reduces the chances of extracorporeal clot formation and interruption of CRRT treatment and optimizes the delivered dose. Catheters are the mainstay of vascular access in performing CRRT. Proper management of catheters is crucial in achieving adequate blood flow rate and avoiding mechanical problems.

The commonly used access for CRRT is a short-term hemodialysis catheter (STDC) inserted into one of the central veins. Tunneled dialysis catheters can also be utilized and have been suggested to be the first choice in select and longer-care patients, as they may have improved delivery metrics and fewer complications.[16] However, these results have not yet been validated in a randomized controlled study.

The most important factor ensuring low resistance during high blood flow rate is the catheter diameter and location of the tip (Table 1). The catheter should be long enough so that the tip resides in the superior vena cava near the caval atrial junction when using the upper body approach or the inferior vena cava when using the femoral approach. A single randomized comparison in great thoracic veins with confirmation of atrial tip placement versus superior vena cava tip positioning demonstrated the superiority of longer (atrial) catheters. Importantly, this study reported no difference in the incidence of atrial or ventricular arrhythmias between 2 catheter lengths.[17] Only one study in a pediatric population reported catheter size comparisons in relation to filter life demonstrating only a weak signal.[18] However, the effect is likely greater given the report of a sub-analysis of the large RENAL data set demonstrating achievement of increased renal dose with larger catheters.[19]

The right internal jugular (IJ) insertion site over the femoral site was supported by a prospective cohort study in critically ill adult patients.[20] However, other studies including larger randomized controlled trials have provided contrasting data.[21,22] The author recommends that each center identify its own "best practices" by monitoring internal data. At the institution of this article's author, the right IJ outperforms the femoral. The subclavian veins can also be utilized for CRRT; STDCs placed via this site are effective and have the least complications.[23,24] However, because they are more frequently associated with subclavian stenosis and require more advanced insertion skills by trainees, most physicians only utilize them when the other sites are not available.

Manufacturers have experimented with different shapes of the proximal section of STDCs and tips. The proximal sections can be divided into straight, curved extensions, or precurved STDCs. A prospective follow-up cohort study found that precurved STDCs were associated with better patency and lower infection rates than straight catheters with curved extensions.[25]

Table 1. Appropriate Catheter Sizes and Locations Based on the Patients' Weight

Patient's Weight	Catheter Size (Double Lumen)	Location (Venous)
Neonatal	6.5-7 French	Right internal jugular/femoral/left internal jugular/subclavian/umbilical
3-6 kg	7 French	Right internal jugular/femoral/left internal jugular/subclavian
6-15 kg	8 French	Right internal jugular/femoral/left internal jugular/subclavian
15-30 kg	9 French	Right internal jugular/femoral/left internal jugular/subclavian
>30 kg	10-12.5 French	Right internal jugular/femoral/left internal jugular/subclavian

MODALITIES

Continuous renal replacement therapy can be performed in one or more of the following 4 modalities (a) slow continuous ultrafiltration (SCUF), (b) continuous veno-venous dialysis (CVVHD), (c) continuous veno-venous hemofiltration (CVVH), and (d) continuous veno-venous hemodiafiltration (CVVHDF). Continuous renal replacement therapy is based on 4 main physiologic principles. These are (a) diffusion, (b) ultrafiltration, (c) convection, and (d) adsorption.

Diffusion is the primary mechanism of transport with CVVHD. Typically, dialysate is given counter-current to the blood flow allowing for a sustained solute gradient for more efficient clearance. Solutes equilibrate across the semipermeable membrane. The mechanism of using dialysate is hemodialysis (HD), CVVHD, and peritoneal dialysis (PD).

The use of CVVH is known as convective clearance. Convection sweeps solutes along with the fluid independent of their concentration gradient. The concept of convection is that, by mass transport, the solute is forced across the membrane by solvent. A physiologic, sterile solution is introduced in the vascular space in the circuit, and a pressure gradient is generated, promoting solvent flow through the membrane. During CVVH, membranes are utilized without countercurrent dialysate fluid. Continuous veno-venous hemofiltration can allow a greater removal of middle-size molecules with putative pro-inflammatory effects such as cytokines. The use of convection and diffusion together results in the concept of CVVHDF.

Slow Continuous Ultrafiltration

The objective is to achieve volume control in patients with severe, diuretic-resistant volume overload. This procedure is designed to remove patient fluids almost exclusively using semipermeable membranes and ultrafiltration without fluid replacement. Blood is pumped through the fibers of filter at a pressure higher than that of surrounding the fibers. The hydrostatic pressure gradient between the blood compartment of the filter and the filtrate compartment is the transmembrane pressure, which determines the rate of fluid removal.

It is used for patients with refractory fluid overload (FO) who may not tolerate rapid fluid removal. It is classically utilized in hemodynamically unstable, fluid-overloaded congestive heart failure patients. It cannot correct electrolyte or acid–base abnormalities.

Continuous Veno-Venous Hemofiltration

Continuous veno-venous hemofiltration uses convection to remove solutes through large volume ultrafiltration. Replacement fluids play an integral part in the delivery of CVVH (and CVVHDF). The replacement fluid can be infused pre-filter (pre-dilution), post-filter (post-dilution), or both. There are advantages and disadvantages of each approach. The post-dilution mode theoretically provides the most efficient way to achieve solute removal. In this mode, the concentrations of solute in the blood delivered to the filter are the same as plasma concentrations. However, post-dilution hemofiltration is limited inherently by the attainable blood flow rate and the associated filtration fraction (FF) maximum. Post-dilution allows more effective larger molecule solute clearance but can lead to more filter clotting due to hemoconcentration.

From a mass transfer perspective, the use of pre-dilution has several potential advantages over post-dilution. Hematocrit and blood total protein concentration are reduced significantly before the entry of blood into the filter. This reduces the risk of fouling and clotting, resulting in improved mass transfer. Pre-dilution also favorably affects mass transfer because of augmented flow in the blood compartment. Finally, pre-dilution also may enhance mass transfer for some compounds by creating concentration gradients that induce solute movement out of red blood cells. However, because the clearance of solutes is dependent on their concentration in the filter, the major drawback of pre-dilution CVVH is the low efficiency related to dilution.

Continuous Veno-Venous Hemodialysis

The primary mechanism of solute removal in CVVHD is diffusion. During CVVHD, blood and dialysate solution circulate countercurrent. A countercurrent configuration provides better stability and control of hydrodynamic conditions. It maintains an average concentration gradient between plasma and dialysate throughout the filter. This modality allows the effective removal of small-molecular weight solutes and crystalloids.

Comparisons of CVVHD and CVVH using similar membranes have shown little difference in solute clearance for small- and middle-molecular weight solutes. Continuous veno-venous dialysis is slightly more efficient than pre-dilution CVVH at eliminating small-molecular weight solutes but similar in efficiency to post-dilution CVVH. However, β2-microglobulin is cleared more effectively with CVVH due to convections' greater clearance of higher-molecular-weight solutes.[26,27]

Continuous Veno-Venous High-Flux Dialysis

Continuous veno-venous high-flux hemodialysis is a CVVHD treatment utilizing a high-flux membrane. Due to the high-flux properties of the membrane, a convective component of solute clearance is achieved even if replacement fluid is not infused.

A variant of CVVHD involves the use of a large-pore filter (rather than a standard high-flux filter) to extend the solute removal spectrum of CVVHD to approximate what can be achieved with CVVH. The average pre-size of this type of "super high-flux" membrane allows passage of appreciable amounts of albumin, and its use cannot be recommended in the CVVH mode. These filters can achieve substantial removal of myoglobin or cytokines, although the clinical implications remain to be determined.

Continuous Veno-Venous Hemodiafiltration

Continuous veno-venous hemodiafiltration combines HD and HF, where mechanisms of solute removal include diffusion and convection. The resulting solute clearance is the sum of diffusive and convective clearance. This modality requires replacement and dialysate fluids. Replacement fluid is infused pre- and/or post-filter, and dialysate flows countercurrent into the dialysate compartment. It permits achieving a larger diffusive plus convective clearance without having to incur the problems associated with an excessively high FF.

There is a lack of solid evidence showing the superiority of any CRRT modality on mortality, dialysis dependence, or hospital length of stay. The choice of modality is dependent upon the clinical scenario presented and should be tailored to individual patients' treatment requirements. Data by Maxvold et al[28] indicated that for small-molecular-weight membranes, the convection and diffusion are identical for solute clearance. Experience in sepsis as well as cytokine responses identified that convection may be superior to diffusion in patients highly inflamed. The clearance of cytokines is nonspecific, and circulating inhibitory cytokines are nonspecific and circulating inhibitory cytokines are reduced, potentially minimizing the effects of proinflammatory cytokine removal.

In conclusion, the process of choosing an appropriate CRRT modality for critically ill pediatric patients must be incorporated into the considerations of multiple aspects of the care. Patients' hemodynamic status, coexisting medical conditions, local expertise, and the availability of resources must be taken into consideration when selecting modalities of CRRT. In children, the modality of choice appears to be center dependent without significant clinical differences, and in the only available report on the pediatric population, 21% of patients received CVVH, 48% received CVVHD, and 30% received CVVHDF.[6]

APPLICATIONS OF CONTINUOUS RENAL REPLACEMENT THERAPY

The most common cause of AKI in an intensive care unit setting is sepsis. In this setting, convective clearance may have superiority over diffusion. Data to date have not suggested CRRT to be either superior or inferior to any other mode of RRT for AKI. The comparisons of PD versus HD versus CRRT have never been investigated in a prospective manner. Therefore, the use of modality is based on the center's experiences.

Problems with ammonia-producing IEM arise from the unknown generation rate of ammonia; therefore, CRRT may not give adequate clearance, making HS superior. Hemodialysis is superior to CRRT because it is the largest source of solute clearance over a set time frame and can be used as sequential therapy with CRRT to mitigate complications of elevated ammonia levels prior to control ammonia generation.

In cases of intoxication, HS is clearly superior to CRRT because of the large volume of dialysate moving across the membrane, but in patients who are hemodynamically unstable, CRRT may be necessary. As IEM, the use of sequential therapy of HD followed by CRRT for intoxications maximizes rapid clearance and minims rebound.

To date, there are no prospective data on children with any other form of RRT. Knowing the benefits and risks of each modality is important. Table 2 compares CRRT to other forms of RRT. The choice of modality is dependent upon the clinical scenario presented and should be tailored to individual patients' treatment requirements.

TIMING OF INITIATION

The timing of CRRT initiation has been discussed over the decades. The actual initiation timing of CRRT in clinical work varies a lot, as it is greatly affected by the subjective judgment of physicians and the distraction of medical resources. However, there is still no consensus on whether earlier CRRT initiation can benefit the patients with AKI.

Table 2. Comparison of RRT Modalities

Modality	CRRT	HD	PD
Clearance	Diffusion and/or convection	Diffusion	Diffusion and convection
Systemic anticoagulation	Heparin or citrate	Heparin or none	None
Thermic control	Yes	Yes	Partial
Ultrafiltration control	Yes	Yes	Partial
Solutions	Industry made	Online production	Industry made
Drug clearance	Continuous	Intermittent	Continuous
Nutritional clearance	Continuous	Intermittent	Continuous
Solute clearance	2	1	3
UF with hemodynamic stability	1	3	2

CRRT, continuous renal replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy, UF, ultrafiltration.

Earlier initiation of CRRT might provide better control of acid–base and electrolyte balance. Moreover, it can be more helpful in maintaining hemodynamic stability and reducing the risks of their potential complications of AKI.[29] While early initiation of CRRT can also increase the unnecessary financial burden of patients with AKI, it can increase the risk of coagulatio n-anticoagulant disorder and even delay recovery function, which may negatively affect the prognosis of patients.[30] On the contrary, late initiation of CRRT may provide more time to the patients with AKI for hemodynamic optimization before CRRT or even avoid the need for CRRT and its associated complications.[31]

Gaundry et al[32] enrolled 620 patients and randomized them into early and late initiations. There were no mortality differences at 60-day mortality. Barbar et al enrolled 488 patients and randomized them into early and late stages with a cut-off time after randomization of 12 hours. Similarly, no mortality benefit was found in the early group.[33] However, Zarkbock et al[34] included 231 patients and they defined early strategy as an initiation of CRRT within 8 hours from the diagnosis of AKI and late strategy as initiation within 12 hours from diagnosis and found that early initiation had beneficial effects in 28-, 60-, and 90- day mortalities and RRT dependency after therapy. Liu et al did a meta-analysis and the results of 18 studies with 3914 patients were combined and found that the early initiation of CRRT could improve the status of the patients with AKI in terms of renal recovery after CRRT (RR 1.21, 95%CI 1.01-1.45). Furthermore, the subgroup analysis showed a significant benefit for the earlier stage of AKI CRRT initiation.[35] The Cochrane Database of Systematic Reviews studied the timing effect of RRT initiation for AKI on death and recovery of renal function. This review, which included 5 randomized studies enrolling 1084 adults, concluded that early RRT may reduce the risk of

death and may improve the recovery of kidney function in critically ill patients.[36]

No clear cut-off values for CRRT initiation are currently available for pediatric patients. The US multicenter, prospective, pediatric CRRT registry confirmed that FO independently increases mortality. However, the studies failed to define a target FO% for CRRT initiation. It has been suggested that CRRT should be started rapidly in oligo-anuric pediatric patients before a FO threshold of 10-20% is reached.[37]

The time to initiate CRRT should be based on the risk–benefit ratio, which is particularly challenging in critically ill children. However, early CRRT can provide a favorable influence on short-term mortality and renal recovery after CRRT.

DOSES

Solute transport during extracorporeal treatments strictly depends on the operating conditions, including blood flow rate, dialysate, net ultrafiltration, and replacement flow rates. 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 CVVH modalities) and ultrafiltrate and dialysate (in CVVHD and CVVHDF modalities). The effluent flow rate is expressed as milliliters of blood per kg of patient body weight per hour of CRRT (mL/kg/h).

In 2000, Ronco et al[38] have shown that a higher delivered dose (35 mL/kg/h and 45 mL/kg/h) using post-dilution hemofiltration is superior to 25 mL/kg/h in improving the survival rate in adult patients (15%-20% reduction in mortality). However, 3 major multicentric randomized controlled trials showed that increasing dose intensity does not deliver clinical benefits to critically ill adult patients with severe AKI.[39-41] Furthermore, Van Wert et al[42] assessed 12 studies with 3999 adult patients and showed no benefit of intensive CRRT regarding survival or dialysis dependence.

The recommended effluent dose of CRRT should be kept between 20 mL/kg/h and 25 mL/kg/h. However, it is important to differentiate between prescribed and delivered doses. Interruption of CRRT treatment can have a substantial impact on the actual delivered dose. 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.

Short-lived filters due to clotting are associated with blood loss, inadequate clearance due to frequent interruption of treatment, and increased costs. The major causes of short-lived filters are inappropriate prescribed dose of anticoagulation, slow or inadequate blood flow rate, and/or high FF. The blood flow rate should prescribe according to the weight of the child: neonates −8 to 12 mL/kg/min, children −4 to 8 mL/kg/min, older children −2 to 4 mL/kg/min. The FF is defined as the ratio between the ultrafiltration flow rate and blood flow rate. Filtration fraction should keep between 25% and 30%. Higher FF corresponds to higher post-filter hematocrit, which will tend to degrade the life of the filter and promote clot formation.

Table 3. The Machines and Filters Which are Available in Turkey

Company	Weight (kg)	Hemofilter Name	Membrane Type	Membrane Surface Area (m^2)	Filter Setting Volume (mL)
Fresenius	3-10	AV Paed	PS / MT	0.2	72
	10-30	AV 400S	PS/MT	0.75	135
	>30	AV 600S	PS/MT	1.4	246
	>30	AV 1000S	PS/MT	1.8	276
Baxter	8-15	Prismaflex HF20	PAES/MT	0.2	58
	>30	Prismaflex HF1000	PAES/MT	1.15	165
	>30	Prismaflex HF1400	PAES/MT	1.4	186
	15-30	Prismaflex M60	AN69/MT*	0.6	93
	>30	Prismaflex M100	AN69/MT*	0.9	153
	>30	Prismaflex M150	AN69/MT*	1.5	189
Medica	0-10	D050	MS/Memb.	0.06	45
	10-20	D150	MS/Memb.	0.25	59
	10-20	DP03HE	MS/Memb.	0.3	61
	>20	DP07HE	MS/Memb.	0.7	89
	Erişkin	DP09HE	MS/Memb.	0.9	127
	Erişkin	DP12HE	MS/Memb.	1.2	145
	Erişkin	DP15HE	MS/Memb.	1.5	157
	>20	DP60HE	MS/Memb.	0.6	79
	Erişkin	DP120HE	MS/Memb.	1.2	139
	Erişkin	DP150HE	MS/Memb.	1.5	157
	Erişkin	DP190HE	MS/Memb.	1.9	185
	Erişkin	DP230HE	MS/Memb.	2.3	203

AN69, acrylonitrile; Memb, membrane; MS, medisulfone; MT, microtubule; PAES, polyarylethersulfone; PS, polisulfone.

FILTER LIFE

Hemofilter Membrane Characteristics

Hollow fiber membranes appear superior to flat plate membranes. A trend favoring polysulfone membranes ahead of cellulose triacetate in being associated with longer filter life was apparent in one multiple regression analysis,[43] but a newer modified cellulose membrane showed no difference.[44] No significant difference in filter life existed between the non-surface-coated polyacrylnitrile membrane (AN69) and polysulfone membrane.[17] Newer surface-treated (heparin binding and potentially more biocompatible) AN69ST membrane did not show advantage in the filter life over the non-surface-treated AN69.[45] Membrane area was not associated with filter life. The filters and machines which are available in our country are shown in Table 3.[46]

Mode and Dose

The optimum modality of CRRT for filter life was consistent across nearly all studies including 2 randomized trials with CVVHDF.[47,48] Continuous veno-venous hemofiltration is associated with worse filter life in published studies.

Higher CRRT-prescribed ultra-filtration rate and fluid removal rate were not associated with differences in filter life among the retrospective analyses.[49-51] The results of 2 randomized trials of RRT intensity suggested that higher-intensity CRRT may be associated with filter life.[52,53]

Higher blood flow rates have been hypothesized to prolong filter life by minimizing stasis within the blood path, however, results vary across studies. Of the 3 studies, none detected a difference through blood flow.[54-56] In Mottes' study, higher blood flow (hazard ratio (HR) = 0.942, P = .009, I^2 = 25.8%) favored[57] and suggested that each 10 mL/min increase in blood flow equates to a 5.8% increase in filter survival. The blood flow rates based on the patients' weight are shown in Table 4.

Blood Products

Platelet or packed red cell infusion were both associated with a reduction in filter life though platelet infusion did not. Fresh frozen plasma administration was associated with a non-significant increase in the filter failure rate.

Anticoagulation

In order to maintain adequate patency of the extracorporeal circuit and the performance of the filter, anticoagulation is usually needed for CRRT (Table 5). Effective anticoagulation to ensure the circulation of blood is an important measure to ensure the continuous implementation of CRRT. Reasonable anticoagulation should follow the principle of individualization, the correct selection of anticoagulants, and close monitoring.

Table 4. The Dosing for CRRT

Weight (kg)	Blood Flow Rate (mL/kg/day)
3-6	8-12
6-15	5-8
15-30	4-6
>30	2-4
Net ultrafiltration rate (per hour)[1]	1-2 mL per kg
Dialysate rate (per hour)[2]	2000 mL × m^2/1.73m^2
Replacement rate (per hour)	25-30 mL per kg

[1]The net ultrafiltration rate can be regulated according to the hemodynamic and fluid status of the patient.
[2]The dialysate rate can be increased up to 8000 mL × m^2/1.73 m^2 in inborn error of metabolic diseases and intoxications.

Unfractionated heparin (UFH) is the most common anticoagulant in clinical practice. Unfractionated heparin is combined with antithrombin-III to inhibit filter coagulation. Systemic anticoagulation with UFH is of low cost, the activated partial thromboplastin time (aPTT) is easy to monitor and uses protamine as a reversal agent. It is the most widely used anticoagulation method used worldwide. Heparin is infused in the CRRT circuit pre-filter and titrated to achieve a targeted post-filter aPTT 1.5-2 times normal, or an activated clotting time between 180 seconds and 220 seconds. The initial regimen begins with an initial heparin bolus of 20-30 units/kg, followed by a continuous infusion of 5-20 units/kg/h.

However, the incidence of adverse reactions is high with the use of UFH. The UFH use is associated with an increased risk of bleeding, heparin-induced thrombocytopenia, and potentially deleterious pro-inflammatory effects because it binds to the lysyl residue of antithrombin and accelerates the interaction between thrombin and antithrombin, thereby inhibiting the anti-inflammatory action of antithrombin and the release of inflammatory mediators.[58]

Regional citrate anticoagulation (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. Citrate is infused into the circuit after the blood leaves the patient but before the blood enters the CRRT filter. This result in chelating the calcium in the blood, therefore making the circuit hypocoagulable. Calcium is then infused back into the patient via a central line independent of the circuit to reverse the anticoagulation and potential hypocalcemia that can occur with the administration of citrate. One molecule of citrate binds 2 calcium anions, forming a citrate complex. About 60% of this complex is lost in dialysate effluent. This kind of anticoagulation, where the anticoagulant does not enter the body, greatly reduces the influence of the anticoagulant

Table 5. Modes of Anticoagulation During Continuous Renal Replacement Therapy

• **Mode**	• **Characteristics**
• No anticoagulation	• No bleeding risk, but increased risk of clotting
• Unfractionated heparin	• Widely available, easy to use, but increased risk of bleeding
• Low molecular weight heparin	• Limited use in patients with acute kidney injury
• Regional citrate anticoagulation	• Highest filter patency, lower risk of bleeding, but requires rigorous protocols and is associated with potential citrate toxicity

on the risk of bleeding. Regional citrate anticoagulation has been associated with significantly less bleeding,[59] less need for blood transfusion,[60] and extended life of extracorporeal circuit.[61]

The operation of this method is complicated. The treatment protocol depends on the citrate solution used. The citrate infusion rate is titrated to target a circuit ionized calcium concentration of 0.25-0.4 mmol/L. Calcium in normal saline solution is concomitantly infused to maintain desired systemic ionized calcium concentration of 1.1-1.3 mmol/L.

Regional citrate anticoagulation requires close monitoring, especially upon initiation of RCA anticoagulation. Disadvantages of RCA are the patient's inability to metabolize citrate (e.g., liver failure) within the systemic circulation, the complexity of citrate protocols, and citrate toxicity. Relative contraindications include patients with acute liver dysfunction or severe cirrhosis.

The Kidney Disease Improving Global Outcome (KDIGO) guidelines suggested using RCA rather than heparin in patients who do not have contraindications for citrate.[62]

Deep et al[63] performed research with prostacyclin-based anticoagulation in children with fulminant hepatic failure. Their institutional data suggest that prostacyclin is superior to other forms of anticoagulation with a circuit life of 1-2 days to avoid the risk of anticoagulation. More data is needed on anticoagulation with prostacyclin.

TIMING OF TERMINATION

Discontinuation of CRRT, as per the KDIGO guidelines, is "when CRRT is no longer required either because intrinsic kidney function has recovered to the point that is adequate to meet patient needs or because CRRT is no longer consistent with the goal 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 CRRT." The clinical indicators for discontinuation of CRRT include off vasoactive, increased urinary output, no more FO. Clinician should consider "filter holiday" if spontaneous urine output is >0.5 mL/kg/h and fluid status and potassium levels are controlled.

CONCLUSION

Critically ill patients with AKI and/or multiorgan failure in PICU require special modalities of therapies to ensure hemodynamic stability, euvolemic status, and acid–base and electrolyte balance, with an aim of speeding up renal recovery and avoiding deleterious consequences. Continuous renal replacement therapy stands as a valuable supportive therapeutic modality for such patients. Advancements in CRRT machine technology have simplified the delivery of this therapy. However, adequate delivery of CRRT and avoiding the pitfalls associated with suboptimal circuit life remain challenging.

A tailored approach to vascular access, doses, modality, anticoagulation, timing of initiation, and termination may increase the efficacy of CRRT. Vascular access should be placed at the highest blood flow location and in order sequence of the right internal jugular vein, femoral vein, left internal vein, and right subclavian vein. The prescribed dose is 20-25 mL/kg/h, but to deliver this dose, higher doses are required. Regional citrate anticoagulation is the recommended method of anticoagulation. Continuous renal replacement therapy management also includes proper timing of initiation and termination. Early start may have better survival and renal recovery rates.

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