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Continuous Renal Replacement Therapy (CRRT) Protocol in Critically Ill Children

Kritik Hasta Çocuklarda Sürekli Renal Destek Tedavi (CRRT) Protokolü

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Introduction

Continuous renal replacement therapy (CRRT) has seen a rising utilization in critically ill children in recent years, owing to technological advancements and the emergence of user-friendly devices.[1,2] However, survival in children receiving CRRT does not increase in parallel with advances in technology. We believe that implementing protocol-based practices will make an important contribution to increasing survival in children receiving CRRT. For this reason, our CRRT Working Group has prepared the protocol below to guide your practices by updating it in line with new data.

1. Definition of Continuous Renal Replacement Therapies and Methods Used

Continuous renal replacement therapies are extracorporeal support systems in which solute and/or water clearance is achieved in the time desired by the clinician using dialysis (diffusion-based solute removal) and/or filtration (convection-based water and solute removal) methods.[3]

Terminology

1. Route; vascular access is necessary for blood flow to reach the extracorporeal system

Venovenous route - This is a vascular access method that does not require arterial access. Two separate catheters are placed in two veins or a double-lumen catheter in a single vein. Blood is directed to the extracorporeal system using a pump.

Advantage - No arterial intervention is required. Fast and predictable blood flow is provided.

Disadvantage - A pump is required to access the extracorporeal system. Air embolism, thrombosis, or stenosis of the venous system may develop.

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2. Working principle; clearance is achieved by diffusion in hemodialysis and convection in hemofiltration.

Clearance is the rate at which solute is removed from the body. Clearance is indicated by the letter "K". Solute clearance is the volume of the desired substance removed from the blood in one unit of time.

K = Removal rate (excreted solute concentration-solute blood concentration)/solute blood concentration

$K = V \times CU_F/C_\beta$

CU_F/C_β = for many solutes the sieving coefficient is assumed to be 1

V = Effluent rate [dialysis rate + ultrafiltration (UF) rate]

Diffusion - Solutes move across a semipermeable membrane due to a concentration difference. Solutes are removed by moving from the high-concentration area to the low-concentration area. Small molecular weight (<1000 Dalton) solutes are removed from the membrane by this method.

Dialysate fluid - This is the fluid that provides the diffusion gradient. Dialysate fluid and blood currents are reversed to increase the concentration difference between compartments.

Convection - A system in which solutes are removed by solvent flow through a semipermeable membrane by creating a hydrostatic pressure difference. In this approach, solutes of varying sizes, ranging from small to medium molecular weights, are extracted from the membrane using water as the carrier within the plasma.

Replacement fluid - It is the solution used to replace the excess plasma removed to prevent hypovolemia in the patient while convection-based water filtration is provided.

Adsorption - The mechanism by which solutes, especially medium to large solutes, are excreted from the body by adhering to the surface of a semipermeable membrane.

Hemodialysis (HD) - A renal replacement method that provides diffusion-based clearance. Small molecular weight solutes are cleared.

Hemofiltration (HF) - A renal replacement method that provides convection-based clearance. Convective transport of small and medium molecular weight solutes in the same direction as water is provided. Solute removal capacity is lower than diffusion-based renal replacement methods.

Hemodiafiltration (HDF) - It is a renal replacement method in which diffusion and convection clearance are used together.

Ultrafiltration (UF) - Removal of water from a semipermeable membrane by creating a pressure gradient (hydrostatic, osmotic, or oncotic).

Filtration fraction (FF) - It is the ratio of the UF rate to the blood flow rate.

3. Treatment methods; today, blood flow is delivered to the filter using roller pumps, single venous access (continuous venovenous = CVV) using a double-lumen dialysis catheter is sufficient.

Slow continuous ultrafiltration (SCUF) - A treatment in which water is removed slowly and over a long period from the patient's blood through a filter. It is used for fluid overload indications when UF is the goal.

Continuous venovenous hemofiltration (CVVH) - This treatment method involves the removal of significant amounts of water through a filter, along with residual substances, achieved by creating transmembrane pressure. As large quantities of water are extracted through the membrane, small to medium molecular weight solutes are concurrently carried along (convection). Hypovolemia in the patient during hemofiltration is prevented with replacement fluid. Replacement fluid can be added to the system before (predilution) and/or after (post-dilution) filtering. In predilution, the diluted blood interacts with the membrane, diminishing the likelihood of filter clotting. With post-dilution, as the quantity of blood in contact with the filter increases, clearance is enhanced. Nevertheless, insufficient blood flow rates can lead to a high filter fraction, increasing the risk of filter blockage.

Continuous venovenous hemodialysis (CVVHD) - A treatment method in which the clearance of small molecular weight solutes is achieved through concentration gradient (diffusion). The factor that provides the concentration gradient is the dialysis solution that moves around the membrane in the opposite direction to the blood flow.

Continuous venovenous hemodiafiltration (CVVHDF) - It is a treatment method in which clearance by diffusion and convection are used together. Dialysate is used for diffusion and replacement fluids are used for convection.

2. Selection of Continuous Renal Replacement Method

Currently, insufficient data is showing that any method is superior.[3-5] Things to consider when choosing a treatment method:

1. Accessibility to the method
2. Experience of the clinician
3. Clinical diagnosis and hemodynamic status of the patient
4. Vascular access
5. Targeting fluid and/or solute removal

The selection of a continuous renal replacement method should not be generalized; rather, it should be based on individual patient characteristics and needs. If addressing fluid overload is the primary concern, hemofiltration should be favored in CRRT applications. Conversely, if the focus is on

solute clearance (such as ammonia, lactate, urea, etc.), HD would be the preferable choice. High-flow HF or HDF may be preferred in patients with multiple organ failure and patients requiring more clearance. Table 1 shows the treatment methods recommended for use in various diseases.

3. Indications for Continuous Renal Replacement Therapy

Indications for renal replacement therapy (RRT) in acute kidney injury (AKI) and general indications:[6-10]

1. For cases where fluid overload remains unresponsive to medical therapy, including conditions like hypertension, congestive heart failure, pulmonary edema, and fluid-induced respiratory failure that do not respond to diuretics, particularly when the cumulative fluid load exceeds 10%, hemofiltration should be considered as a preferred option within the CRRT approach.

2. Hyperkalemia refractory to medical treatment

3. Severe azotemia and symptomatic uremia (presence of encephalopathy)

4. Severe metabolic acidosis

5. Uncontrollable and progressive hypo- or hypernatremia

6. Hyperphosphatemia

7. Tumor lysis syndrome, Crush syndrome

8. Providing the necessary UF to maintain enteral and parenteral nutrition, treatments, blood product replacements

9. Sepsis, septic shock, and multiple organ failure

10. Cardiogenic shock after cardiac surgery

11. Liver failure

12. Urea cycle defects, hyperammonemia, and organic acidemias

13. Removal of toxins and poisons that may be dialyzed, drug overdose

14. Hyperthermia

Advantages of CRRT over other RRTs:

1. CRRT is an effective method for reducing or preventing fluid overload in critically ill children due to its slow and continuous fluid removal capability. While intermittent hemodialysis (IHD) can achieve the UF target rapidly, CRRT aids in maintaining cardiovascular balance by distributing UF over an extended period. CRRT preparations should be initiated when the fluid overload unresponsive to diuretic treatments surpasses 5% of body weight, while the commencement of CRRT itself is recommended when the fluid overload exceeds 10%.[11]

2. It is useful in maintaining metabolic balance by continuous removal of harmful particles. Although IHD is more effective in solute removal, CRRT is useful in preventing fluctuating courses due to its continuity.[4,5]

3. In patients with impaired renal function and decreased urine output, CRRT removes the daily required amount of fluid and enables the use of drugs, nutrition, and blood products without fluid overload. A balanced fluid balance can be achieved with CRRT compared to IHD.

Table 2 presents a summary of the advantages and disadvantages of selecting CRRT over peritoneal dialysis (PD) and IHD among renal replacement systems.

4. Vascular Access

The hemodialysis catheter should be inserted with ultrasonography guidance by teams experienced in vascular access. An insufficient diameter and improper placement of the central catheter are among the most crucial factors contributing to the shortened lifespan of the filter (Table 3). The right internal jugular vein should be preferred as the site of the central venous double-lumen dialysis catheter.

If vascular access cannot be obtained from the right internal jugular vein, the next preferable option is the left internal jugular vein, followed by the femoral vein. The subclavian vein should only be considered if vascular access cannot be

Table 1. CRRT methods that can be preferred according to diseases

Underlying disease	Method
Acute or chronic kidney failure	CVVHD
Sepsis	CVVH
Fluid overload	CVVH
Multiple organ failure	CVVH
Multiple organ failure after bone marrow transplantation	CVVH
Liver failure	CVVH/CVVHDF
Inborn error of metabolism	CVVHD/CVVHDF
Tumor lysis syndrome	CVVHD
Poisonings	CVVHD-albumin should be added to the dialysis solution

CVVH: Continuous venovenous hemofiltration, CVVHD: Continuous venovenous hemodialysis, CVVHDF: Continuous venovenous hemodiafiltration

obtained in both the jugular and femoral regions. The site should be chosen according to the patient's condition.[12] Three-way dialysis catheters are also accessible in our country. While the femoral vein can be utilized for vascular access in patients with bleeding risk, it is preferable to avoid placing the dialysis catheter in the femoral region for patients with increased intra-abdominal pressure. Additionally, the size of the dialysis catheter should be determined based on the child's weight (Table 3). Nevertheless, it is advisable to prioritize the placement of the catheter with the largest diameter that is suitable for the patient's weight.

5. Filter Selection

Size and membrane structure should be considered when choosing a filter for CRRT.[13,14]

1. Filters with large surface areas have a high FF and a low probability of hemoconcentration. The selection of an excessively large filter causes a decrease in the blood flow rate in the filter. If the total volume of the filter and set exceeds 10% of the child's blood volume, "blood priming" should be conducted, as outlined in Appendix 1 of the blood-washing (priming) protocol.

2. The filter material comprises microtubules or plate-like membranes made of polyacrylonitrile nitrate (AN-69, AN69 ST), polysulfone (PS), or polyarylethersulfone (PAES). Filter selection should be based on the patient's weight and the indication for the procedure. Table 4 provides an overview of commonly used devices and filters available in our country.

6. Filling the Filter (Priming)

Before commencing the treatment, it's essential to purge the air from the filter and fill it with a balanced solution. Often, 0.9% NaCl is utilized for filter filling. Before the procedure, it is common practice to add 2-5 units of heparin per mL of 0.9% NaCl. For patients prone to bleeding, the initial flush can be conducted using 0.9% NaCl with added heparin, while subsequent flushes can be performed with 0.9% NaCl without added heparin.

In patients with hemodynamic instability, the filter can be filled with 5% albumin or blood. There are different opinions about when to prime the filter with blood. It is recommended to prime the filter with blood if the patient weighs <5-6 kg, if the patient weighs 10-11 kg and is hemodynamically unstable, or if the filter volume is >10% of the patient's weight. Another perspective suggests that the filter should always be primed with blood if the patient weighs less than 10 kg. For patients weighing more than 10 kg, the decision should be made based on the clinical circumstances. The blood priming protocol is shown in Appendix 1.[15,16]

Table 2. Comparison of renal replacement therapy methods

	CRRT	Peritoneal dialysis	Intermittent hemodialysis
Continuous treatment can be done	Yes	Yes	No
Risk of hemodynamic instability	Low	Low	High
Ease of application	Difficult	Easy	Difficult
Ability to achieve fluid balance	Yes	Variable	Yes
Metabolic control	Yes	Variable	Yes
Optimal nutrition	Yes	No	No
Anticoagulation	Yes	No	Yes
Stable intracranial pressure	Yes	Variable	Variable
Need for vascular access	Yes	No	Yes
Continuous detoxification	Yes	Variable	No
Cost	The most expensive	Cheaper	Expensive
Abdominal surgery and V-P shunt	Yes	No	Yes

CRRT: Continuous renal replacement therapy

Table 3. Temporary hemodialysis catheter sizes that can be used according to the patient's weight

Patient's weight	Catheter diameter (double lumen)	Preferred site (vein)
Newborn	6.5-7 French	Internal vein/femoral/subclavian
3-6 kg	7 French	Internal jugular/femoral/subclavian
6-15 kg	8 French	Internal jugular/femoral/subclavian
15-30 kg	9 French	Internal jugular/femoral/subclavian
>30 kg	10-12.5 French	Internal jugular/femoral/subclavian

Table 4. Frequently used devices and filters in our country

Firm	Weight (kg)	Hemofilter name	Membrane type/structure	Membrane surface area (m^2)	Filter and set total 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
Carpediem	>2.5	HCD 0075	PS	0.075	27
	>2.5	HCD 015	PS	0.15	33
	>2.5	HCD 025	PS	0.25	41

AN69: Acrylonitrile, MT: Microtubule, PAES: Polyaryletersulfone, PS: Polysulfone. *Pay attention to "Bradykinin release syndrome" in patients who need to fill the filter with blood (priming), have acidosis or are taking ACE inhibitors (see bradykinin release syndrome prevention protocol (Appendix 2)

7. Adjustment of Treatment Doses

Blood Flow Rate

In patients undergoing CRRT, it is crucial to adjust the blood flow rate (BFR) appropriately to ensure sufficient clearance.[17,18] The BRF is determined based on body weight and typically remains constant regardless of the method applied. It is depicted in Table 5.

Table 5. Blood flow rates according to body weight in CRRT

Patient (kg)	Blood flow rate (mL/kg/min)
3-6	8-12
6-15	5-8
15-30	4-6
>30	2-4

Dialysate Rate

In CRRT methods operating on the diffusion principle (such as CVVHD and CVVHDF), dialysate is utilized to establish a concentration gradient on both sides of the membrane, enhancing solute transfer through rapid dialysate flow. The dialysate rate is determined accordingly. The dialysate rate is often sufficient when set at 2000 mL/1.73 m^2/h or 20-30 mL/kg/h. As an expert opinion, we recommend that the dialysis rate should be based on the patient's weight in kilograms to avoid administering higher dialysis rates than necessary, particularly in infants weighing less than 10 kilograms.

Example: If the patient is 0.6 m^2, dialysis rate=2000 X 0.6/1.73=693 ≈ 690 mL/hour

In certain special cases such as poisoning and metabolic comas with hyperammonemia, the dialysis rate can be escalated to as high as 8000 mL/1.73 m^2/h (equivalent to 40-60 mL/kg/h) to guarantee adequate clearance.[19-22] In patients undergoing continuous dialysis for intoxication (such as CVVHD or CVVHDF), adding albumin (at a concentration of 2-4 g/dL) to the dialysis solution can enhance efficiency. It's important to recognize that patients undergoing high-flow HD are prone to electrolyte imbalances. Therefore, close monitoring is essential, and if there is no immediate necessity, medium-flow HF should be considered instead.[23,24] Especially in patients weighing less than 10 kg, severe electrolyte imbalances may occur during high-flow hemofiltration. Therefore, special attention and caution should be exercised in these cases.[25,26]

Ultrafiltration Rate

Two critical features of CRRTs contribute to highly efficient fluid removal:

a) The utilization of highly permeable membranes

b) The continuous nature of the technique.

With CRRT, there is indeed potential for the removal of a considerable amount of fluid. However, the amount of fluid that can be removed is not unlimited. It is contingent upon factors such as pump speed, the duration of treatment, patient tolerance, and the gradual decline in filter efficiency over time. In pediatric intensive care units (PICUs), the target UF rate should be 1-2 mL/kg/hour. Blood and blood products should be removed at twice the rate of administration. The UF rate can be augmented in hemodynamically stable patients

where fluid overload is the primary concern. In such instances, it is calculated using the formula: hourly fluid outflow rate + hourly net fluid balance = urine output rate (plus any other losses) + UF rate.

Example: If the net UF rate is targeted at 2 mL/kg/hour in a 30 kg child, and the patient receives 80 mL of fluid per hour, with a urine output of 1 mL/kg/hour, then the UF rate can be calculated as follows:

UF rate = Fluid intake - Urine output

= (80 mL/hour) + (30 kg x 2 mL/kg/hour) - (30 kg x 1 mL/kg/hour)

= 80 mL/hour + 60 mL/hour - 30 mL/hour

= 110 mL/hour

Therefore, the UF rate will be 110 mL/hour.

In PICUs, it's possible to remove more fluid than the targeted amount based on determined hemodynamic parameters. However, it's essential to monitor and regulate this process to prevent the FF from exceeding 0.35-0.4.

FF= UF rate/plasma flow rate

Plasma flow rate= [BFR x (1-hematocrit)]

Example: Let's consider a patient weighing 10 kg, with a BFR set at 60 mL/min and a hematocrit level of 30%. In this case, the maximum UF rate can be determined as follows:

1. Calculate the plasma flow rate:

Plasma flow rate = BFR × (1 - hematocrit)

= 60 mL/min × (1-0.3)

= 60 mL/min × 0.7

= 42 mL/min

= 42 mL/min × 60 min/hour

= 2520 mL/hour

2. Determine the maximum UF rate using the FF constraint:

FF = UF rate/Plasma flow rate

0.35 = UF rate/2520 mL/hour

Solve for UF rate:

UF rate = 0.35×2520 mL/hour

≈882 mL/hour

So, the UF rate can be up to approximately 882 mL/hour, which is approximately 80 mL/kg/hour for a 10 kg patient.

Fluid Balance Management During Continuous Renal Replacement Therapy

Accurate calculation of a patient's CRRT-related and daily fluid management data is essential for maintaining a clear fluid balance. This is typically achieved using a monitoring form, where device settings and planned hourly fluid balance are recorded. In the intensive care unit (ICU), the fluid requirements of patients are often not static and should be evaluated at frequent intervals.

Daily oral and/or intravenous fluid intake of patients may exceed normal levels, and additional fluid infusions may be necessary based on clinical indications. For instance, if 600 mL of fresh frozen plasma needs to be administered two hours before an invasive procedure, adjustments to the fluid balance plan should be made. This change should be documented, including the rationale behind it and the duration for which it will be continued.

Furthermore, it's recommended to divide all fluid balance goals for the patient into 12-hour time intervals and diligently record them. This approach allows for better monitoring and adjustment of fluid management strategies according to the patient's evolving clinical condition.

Practical Advice

Training of nurses and doctors is important to achieve the goals. CRRT instructions should be legible and include the name, signature, and contact number of the relevant physician. The fluid balance should be recorded hourly, and the final balance should be created by calculating additional fluid in and out. This documentation can be computerized or added to the bedside form by the nurse (Figure 1).

Expected Outcome, Potential Problems, Points to Consider and Benefits

Systematic fluid administration instructions, administration, and monitoring of fluids during CRRT ensure that the patient receives the planned treatment efficiently and safely. This approach minimizes errors (persistent fluid overload or dangerous intravenous volume depletion). The most frequently observed problem is usually associated with downtime[27] (filter blockage, or system self-rotation during being out of the unit for surgery or radiologic imaging - Appendix 2.[16] In the presence of these conditions, fluid withdrawal cannot be accomplished as previously planned. If the patient loses five hours, this will significantly hinder achieving the planned fluid removal target. In such a situation, nurses and physicians should be vigilant about the consequences, and appropriate arrangements should be made accordingly. Safe compensation for fluid removal spread over 12 or 24 hours should be ensured, and the hourly net UF rate should be increased. It is necessary to be very careful in patients whose fluid removal may be problematic and to evaluate the patient's fluid balance at frequent intervals.

Another problem encountered is frequent interruption of therapy due to device alarms. In some agitated patients, patients with a femoral catheter who flexes their leg frequently, and patients with a subclavian catheter who sit upright in bed or move, machine alarms are triggered frequently. In addition,

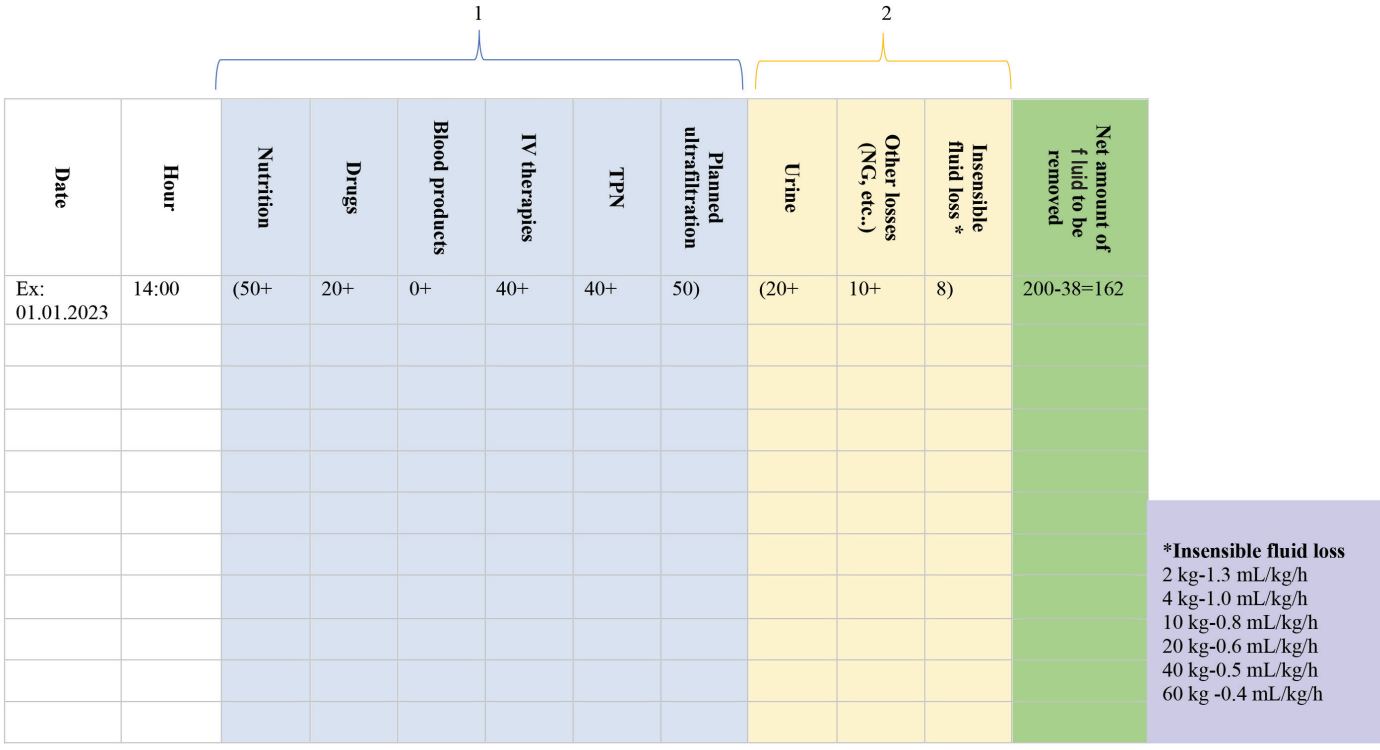

Figure 1. Ultrafiltration chart in CRRT: The total amount of fluids to be extracted equals the sum of fluids in column number 1 minus the sum of fluids in column number 2

other alarms activated during processes such as changing fluid bags or retrieving the waste bag also cause pauses. These can lead to a loss of 5-10 minutes per hour and, when calculated for the day, can add up to a significant loss of time and hinder the achievement of the goal. It is usually possible to overcome the problem by carefully planning a higher fluid removal target than the initial target. Most modern devices allow the user to check how much fluid has been removed in a given period. Frequent checks should be performed to obtain accurate fluid loss data to be used in the patient's fluid balance calculations. Finally, device-induced fluid removal errors may lead to the development of circulatory imbalance.[28]

Replacement Fluid Rate

In CRRT methods working on the principle of convection, small and medium molecular weight solutes are pushed to the opposite side of the membrane by creating transmembrane pressure. A high filtration rate increases the amount of convection but creates a risk of hypotension. Therefore, the UF volume should be partially replaced by using a replacement solution.

Different formulas have been proposed for the calculation of replacement fluid rates in different sources. The replacement fluid rate can be determined as 2000 mL/1.73 m^2/hour. Another recommendation is to set the replacement fluid rate as 30 mL/kg/hour for mid-flow filtration and 40-90 mL/kg/hour for high-flow filtration. Medium-flow filtration is frequently applied. In the application where dialysis and filtration are performed together (CVVHDF), the effluent flow rate consists of the sum of dialysate and replacement fluids.

Example: If the dialysate and replacement rates are 2000 mL/1.73 m^2/hour, the effluent flow rate is 4000 mL/1.73 m^2/hour.

Experimental studies have shown positive effects of high-flow CRRT on shock, immunoparalysis, and apoptosis.[29,30] High-flow CRRT has been recommended for use in pediatric patients with cancer-related ARDS and sepsis. However, in a later prospective study conducted in pediatric patients, no effect of increasing the CRRT dose on the outcome was found.[31-35] Therefore, the determination of filtration dose in CRRT should be patient-specific.[36] In patients on CRRT due to metabolic disease, the replacement fluid rate should be adjusted to keep ammonia or lactate levels within normal limits.

Replacement solution can be administered prefilter (pre-dilutional) and postfilter (post-dilutional). The benefits of using pre-dilutional replacement fluid are (a) increased urea clearance and (b) prolonged filter life. However, when pre-dilutional replacement is used, the concentrations of many solutes reaching the filter will decrease, and the clearance coefficients will decrease. In new technology devices, predilution and post-dilution can be performed simultaneously.

There is insufficient evidence, but it is recommended to set 1/3 of the total replacement fluid rate as pre-dilutional and 2/3 as pos-dilutional. The use of the replacement solution before and/or after filtering should be decided according to the individual characteristics of the patient.

Anticoagulation Selection and Dosage

CRRT in children is performed using relatively lower BFRs and small-diameter catheters compared to adults, the possibility of clotting in the circuit is high and anticoagulation should be applied.[37] However, non-anticoagulation factors must be optimized for adequate filter life. Ten basic recommendations in order of importance to prolong filter life are listed below:[38]

1. Correct circuit preparation

- Adequate flushing

- Not using bicarbonate-based solution during priming

- Adding heparin to the priming fluid

2. Ideal location of the catheter

- Right internal jugular

- Femoral

3. Checking vascular access and confirming adequate blood flow through both lumens

4. BFR appropriate for the patient's weight

5. Use of biocompatible membrane

6. Use of bicarbonate-based solutions

7. Adding predilution replacement fluid

8. Use of diffusive clearance

9. Adjusting the air-retaining column

10. Adding post-dilution replacement solution

11. Training at regular intervals

12. Fast response to alarms

Anticoagulation can be done using different methods. Citrate and heparin are the most used anticoagulants in modern practice. In addition, the proportion of centers performing prostacyclin anticoagulation has been increasing in recent years.

Heparin is infused into the circuit before the blood enters the filter, intending to achieve prolonged activated partial thromboplastin time (aPTT) and activated clotting time (ACT) within the filter. Heparin anticoagulation is easy to administer but there is a risk of bleeding. The heparin protocol is shown in Appendix 3.

Regional anticoagulation is provided with citrate. Citrate is infused into the circuit before the blood enters the filter and calcium is infused before the blood leaves the filter and returns to the patient. The amount of citrate is adjusted to chelate calcium in the blood. The amount of calcium to be infused after the filter should be adjusted according to the citrate dose and citrate should not enter the systemic circulation. Patients using citrate anticoagulation require a separate, preferably central route for calcium infusion and a calcium-free dialysis solution. The basic rationale for citrate anticoagulation is to maintain a citrate concentration of 2.5-3 mmol per liter in the solution-independent extracorporeal circuit. The formulation to be used for this is:

Citrate dose = $Q_{citrate}$ x $C_{citrate}$/BFR

$Q_{citrate}$; citrate blood flow rate

$C_{citrate}$; citrate concentration of the solution

BFR; blood flow rate

Using the formulation, the citrate rate can be adjusted according to the targeted citrate concentration in the extracorporeal circuit based on the citrate solution content and BFR in our unit. The net citrate load that the patient must metabolize depends on the citrate dose, BFR, and total effluent rate. For instance, in citrate treatment at a concentration of 3.0 mmol/L - for regional 18/0 - the citrate replacement solution rate varies. It's 1200 mL/hour when the blood flow rate is 120 mL/min, 1500 mL/hour when the blood flow rate is 150 mL/min, and 1800 mL/hour when the blood flow rate is 180 mL/min. Consequently, the net citrate load to be metabolized increases as the blood flow rate rises. The effects of blood flow rate and total effluent rates on citrate load are shown in Table 6.

The citrate protocol is shown in Appendix 4.

Table 6. Effects of blood flow rate and total effluent rate on metabolic citrate load

Blood flow rate	Citrate solution rate required to keep citrate dose constant	Effluent rate (dialysis + filtration)	Metabolic citrate load
↑	↑	-	↑
-	-	↓	↑
↑	↑	↓	↑
↓	↓	-	↓
-	-	↑	↓
↓	↓	↑	↓

Citrate is metabolized in the mitochondria of the liver, kidney, and skeletal muscles. Citrate anticoagulation works well for most patients, but it is contraindicated in certain patient groups where citrate cannot be efficiently metabolized to bicarbonate. Patients who may have problems with citrate metabolism are those with mitochondriopathy or mitochondrial dysfunction (usually mild hyperlactatemia up to 4 mmol/L is not a problem). Citrate should be used with caution in patients with severe circulatory failure, liver failure, and in infants (<2 years).[39] If lactate levels are ≥4 mmol/L in patients with circulatory failure, there is an increased risk of citrate accumulation (known as the citrate lock phenomenon), and citrate use should be approached with caution. Similarly, it has been shown that the risk of citrate accumulation is high if the lactate level is ≥4 mmol/L or prothrombin activity is below 25% in patients with hepatic dysfunction or failure.[40]

Citrate may lead to citrate lock phenomenon (excessive citrate binds free calcium, total calcium/ionized calcium ratio becomes >2.5, ionized calcium level decreases, metabolic acidosis and hypercalcemia may be observed), hypomagnesemia, metabolic alkalosis, or acidosis.

In patients who develop citrate lock phenomenon, citrate anticoagulation should be discontinued if the problem persists despite protocol adjustments (reducing blood flow and citrate rates, increasing dialysis and/or replacement rates, and/or using calcium-free replacement solution).

In a pediatric CRRT study comparing prospective heparin and citrate anticoagulation, it was demonstrated that the duration of CRRT circuit usage was prolonged, and there was a low probability of bleeding in patients treated with citrate.[41,42]

Epoprostenol (Prostacyclin): Epoprostenol has been increasingly utilized for anticoagulation in patients undergoing CRRT in recent years.[43] Epoprostenol may be administered to patients for whom citrate anticoagulation is not advisable or in the presence of any of the following circumstances:

1. The patient has a heparin allergy or heparin-induced thrombocytopenia syndrome

2. There is antithrombin III deficiency

3. The filter clogging occurs twice within 24 hours with heparin treatment

Epoprostenol is applied at 5 nanograms/kg/min (2-8 nanograms/kg/min) before the filter. Once diluted, epoprostenol can remain stable at room temperature for 24 hours. It should be administered using a filter from a separate central venous catheter.

In scenarios 1 and 2 as described above, epoprostenol can be initially employed as the sole agent for anticoagulation. However, in scenario number three, it is advised to combine a heparin infusion at a rate of 5 U/kg/hour with epoprostenol.

In patients at risk of bleeding, characterized by a platelet count less than 50,000/mm^3, a prothrombin time (PT) >25 seconds, or aPTT >60 seconds, anticoagulation may pose a risk. In such instances, several measures can be undertaken:

1. Insertion of a large-diameter catheter to mitigate the risk of clotting.

2. Maintaining a high BFR.

3. Infusing 0.9% NaCl into the circuit before the filter, may offer benefits. Implementing a triple tap on the arterial line before the filter and applying a 100 mL/hour infusion of 0.9% NaCl. When patients are anticoagulated with sodium chloride, it's crucial to consider the infusion rate of 0.9% NaCl when calculating the UF rate.

8. Solution Selection

If CRRT systems operate on the principle of diffusion (CVVHD), dialysate is utilized. Conversely, if they function on the principle of convection (CVVH), replacement fluid is employed. In cases where both methods are to be combined (CVVHDF), both dialysis and replacement solutions are utilized. Solutions utilized in CRRT facilitate solute transfer, aid in correcting metabolic disorders, and play a crucial role in providing renal support. Solutions used in CRRT should ideally possess the following characteristics:

(a) Physiological: Mimicking the composition of bodily fluids to maintain electrolyte balance and osmolarity.

(b) Inexpensive: Cost-effective to ensure affordability and accessibility.

(c) Easy to administer: Simple to prepare and administer to facilitate efficient treatment delivery.

(d) Easy to store: Stable under appropriate storage conditions to maintain efficacy.

(e) Accessible: Readily available to ensure uninterrupted therapy.

Preference should be given to commercially produced solutions, which typically contain sodium, buffer, calcium, and magnesium in concentrations resembling plasma levels. Solutions employing bicarbonate as a buffer are preferable.

In cases where citrate anticoagulation is planned, dialysate and replacement solutions should not contain calcium.

Adding Electrolytes to Solutions

In long-term CRRT applications, phosphorus can either be incorporated into the solutions or administered separately through additional vascular access.[44,45] If phosphorus supplementation is chosen to be included in CRRT solutions, it is crucial to maintain the total phosphorus concentration within the solutions below 2 mmol/L. In cases where potassium addition is required, the total potassium concentration in CRRT solutions should not exceed 4.5 mmol/L.[44] In patients

with elevated levels of potassium and phosphorus, it is advisable not to add additional potassium and phosphorus to the solutions used in CRRT.

For patients diagnosed with tumor lysis syndrome, if blood biochemistry reveals potassium levels below 4 mmol/L, potassium chloride may be introduced into the solutions, with careful attention to maintaining the total potassium concentration within the solutions below 4.5 mmol/L. However, it's important to note that phosphate should not be included in solutions for patients with tumor lysis syndrome.

In patients with congenital metabolic disease or systemic inflammatory response syndrome, potassium chloride can be added up to 3 mmol/L and potassium phosphate up to 1.5 mmol/L as needed. However, it is crucial to ensure that the total potassium concentration in the solutions does not exceed 4.5 mmol/L.[44]

The solutions available in our country and their contents are presented in Table 7. Figure 2 shows an example CRRT algorithm in children.

Cardio-renal Pediatric Emergency Dialysis Device

The cardio-renal pediatric emergency dialysis device (CARPEDIEM) is the first CRRT device produced specifically for pediatric patients weighing between 2.5 and 10 kg.[46] When utilizing this device, double-lumen catheters ranging from 4Fr to 7Fr are preferred for vascular access. Its advantages include an extracorporeal set volume of 27 mL and a variety of surface area options for the dialysis membranes, ranging from 0.075 m^2 to 0.25 m^2. Additionally, other benefits of the device include the ability to adjust the BFR within the range of 5-50 mL/min, its compatibility with low prime volume, and low pump flow rate requirements. In CRRT applications with the CARPEDIEM device, only heparin is utilized for anticoagulation.

Table 7. Solutions and their ingredients available in our country

Product	Volume (L)	Na (mmol/L)	K (mmol/L)	Ca (mmol/L)	Inorganic phosphate (mmol/L)	Mg (mmol/L)	Cl (mmol/L)	HCO_3 (mmol/L)	Glucose (mmol/L)	Lactate (mmol/L)
Multibic- 0[#]	5	140	0	1.5	0	0.5	109	35	5.55	0
Multibic- 2[#]	5	140	2.0	1.5	0	0.5	111	35	5.55	0
Multibic- 3[#]	5	140	3.0	1.5	0	0.5	112	35	5.55	0
Multibic- 4[#]	5	140	4.0	1.5	0	0.5	113	35	5.55	0
MultiPlus-dialysate with phosphate	5	140	2.0	1.5	1.0	0.75	109.7	35	5.55	0
Ci-Ca Dialysate K2	5	133	2.0	0	0	0.75	116.5	20	5.55	0
Ci-Ca Dialysate K4	5	133	4.0	0	0	0.75	118.5	20	5.55	0
Ci-Ca Dialysate K2 Plus	5	133	2.0	0	1.25	1	115.75	20	5.55	0
Ci-Ca Dialysate K4 Plus	5	133	4.0	0	1.25	1	117.75	20	5.55	0
Dialisan[&]	5	140	2.0	1.75	0	0.50	111.5	32	6.1	3
Prism0cal[+]	5	140	0	0	0	0.5	106	32	0	3
Prism0calB22[+]	5	140	0	0	0	0.75	130.5	22	6.1	3
HDF SM 35[%]	5	140	1.5	1.75	0	0.5	11.5	35	3	0.61
MD042*	2	140	2.5	1.5	0	0.75	115	32	5.55	0
Sodium citrate 4%[^]	Citrate 136 mmol/L, bag volume 1 and 1.5 L									
Prismocitrate 10/2	Citrate 10 mmol/L, citric acid 2 mmol/L, Na 136 mmol/L, Cl- 106 mmol/L									
Prismocitrate 18/0	Citrate 18 mmol/L, citric acid 0 mmol/L, Na 140 mmol/L, Cl- 86 mmol/L									

[#]: It has received FDA approval as a dialysis and replacement solution, [%]: It has received CE approval as a dialysis and replacement solution in Europe, [&]: It has received FDA approval only as a dialysis solution, but it is also used as a replacement fluid in practical application, [^]: Citrate solution. If citrate anticoagulation is to be applied, there should be no calcium in the dialysate solution. Ci-Ca Dialysate solutions are used together with citrate anticoagulation, [+]: Prism0cal and Prism0cal B22 solutions are dialysate solutions used during anticoagulation with Prismocitrate solutions. Since PrismOcal B22 solution contains 4 mmol/L potassium, additional potassium is not added to this solution. Solutions no. 1-9, 15 have been made available by Fresenius, solutions no. 10, 11, 12, 16, 17 have been made available by Baxter, and solution no. 13 has been made available by Medica. Solution number 14 has been made available for use abroad by Meditronic.
*: It is offered for use as the dialysate solution of the cardio-renal pediatric emergency dialysis device (CARPEDIEM), CARPEDIEM: Cardio-renal pediatric emergency dialysis device

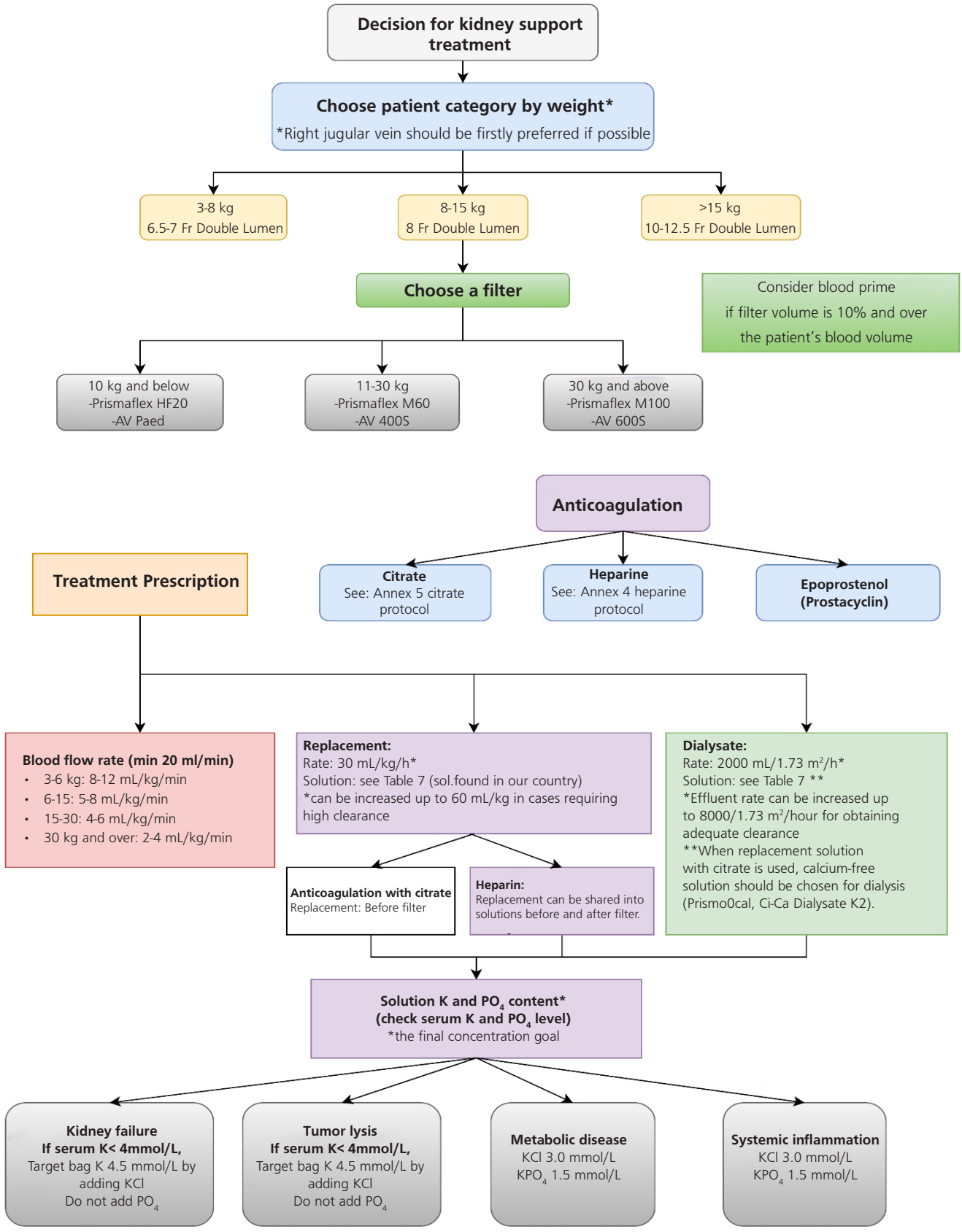

Figure 2. Sample CRRT algorithm in children

Since the data on clearance in CRRT applications with the CARPADIEM device is limited, it is not recommended to be used in cases where rapid clearance is desired, such as hyperammonemia and leucine toxicity.

9. Nutrition

Malnutrition is frequently observed in patients with AKI. This condition arises due to various factors including malabsorption, increased protein degradation, insulin resistance, and impaired hormonal regulation. In patients undergoing CRRT, essential nutrients such as amino acids, carnitine, trace elements, glucose, and water-soluble vitamins are removed. Moreover, beyond these losses, CRRT may serve as a significant yet overlooked source of exogenous energy.

There are no specific guidelines for the nutrition of patients undergoing CRRT in the PICU.

Energy Requirements in Patients Receiving Continuous Renal Replacement Therapy

It has been shown that intensive parenteral hyperalimentation has a positive effect on the prognosis in patients diagnosed with AKI who receive CRRT.[47] The daily calorie requirement of these patients is 25-35 kcal/kg (60-70% from carbohydrates and 30-40% from lipids). It should be noted that hypothermia due to inadequate heating of fluids during CRRT can significantly increase the caloric requirement.

However, CRRT can serve as a significant yet often overlooked source of exogenous energy. It's estimated that 35-45% of the dextrose in dialysis solutions is absorbed during CRRT. Additionally, lactate present in lactate-based solutions can serve as an additional energy source, providing approximately 3.62 kcal/g. Lactate in CRRT solutions may correspond to a caloric intake of approximately 500 kcal/day, which should be considered when calculating the patient's energy balance. Daily calories gained from lactate-based dialysis solutions can vary widely, ranging from 120 to 2300 calories, depending on factors such as blood flow and UF rates.

Another source of calories in CRRT patients is citrate. Once citrate enters the mitochondria via the Na/citrate transporter, it undergoes rapid metabolism in the citric acid cycle, providing approximately 0.59 kcal/mmol of energy. The caloric gain from citrate can be calculated by multiplying the citrate load by the citrate bioenergetic equivalent of 0.59/mmol.

The citrate load can be calculated using the formula (mmol/min) = [(flow rate x 1000) x citrate dose) x (1-(filtration fraction/100)]. Here, the flow rate represents the effluent flow in mL/min, the citrate dose is in mmol/L, and the filtration fraction is expressed as a percentage.

Daily energy gain from citrate can be determined by multiplying the citrate load (mmol/min) by 60 and then multiplying the hourly value by the number of hours citrate anticoagulation is administered.

Amino Acid Requirement in Patients Receiving Continuous Renal Replacement Therapy

ASPEN's recommendation for protein requirements in critically ill pediatric patients according to age groups: 0-2 years: 2-3 gr/kg/day, 2-13 years: 1.5-2 gr/kg/day, 13-18 years: 1.5 gr/kg/day.[48] During CRRT, there is significant nitrogen loss, primarily in the form of amino acids. To counteract these losses, it is recommended to increase the intake of amino acids in the diet by 10-20%. Specifically, glutamine should constitute approximately 25% of the amino acid losses. This adjustment helps maintain nitrogen balance and supports proper protein metabolism during CRRT.

Lipid Requirement in Patients Receiving Continuous Renal Replacement Therapy

In AKI, hepatic lipase and lipolysis activities are negatively affected and the triglyceride content of lipoproteins increases and HDL level decreases. With the deterioration in lipid metabolism, lipid clearance, especially triglycerides, decreases by nearly 50%. Hypertriglyceridemia and hyperglycemia are common, especially in patients receiving parenteral nutrition. The lipid levels of patients should be monitored. L-carnitine is lost at a considerable rate during CRRT, and its deficiency contributes to lipid accumulation in critically ill patients. It is important to be mindful that carnitine deficiency may develop, especially in patients who receive CRRT for an extended period (≥3 weeks). Since the metabolism of medium-chain fatty acids does not require carnitine, their use can compensate for L-carnitine deficiency.

Trace Element Requirements in Patients Receiving Continuous Renal Replacement Therapy

Trace element deficiencies may develop in patients undergoing CRRT, but the necessity of their replacement is controversial. The general opinion is that micronutrients should be replaced. Although the optimal dose for multicomponent trace element preparations in pediatric patients undergoing CRRT has not yet been determined, the standard daily doses recommended for parenteral nutrition, excluding selenium, are thought to be sufficient. Selenium is the element most lost during CRRT, and 100 micrograms/day intravenously is recommended in adults.[49]

Vitamin Requirements in Patients Receiving Continuous Renal Replacement Therapy

The risk of water-soluble vitamin deficiency is high in patients receiving CRRT with high clearance/high flow or for a long time. Although there are no specified dosage recommendations for

children, ESPEN recommends 100 mg of thiamine (vitamin B1), 2 mg of vitamin B2, 20 mg of vitamin B3, 10 mg of vitamin B5, 100 mg of vitamin B6, 200 µg biotin (vitamin B7), 1 mg in adult patients undergoing CRRT. It recommends giving mg folic acid, 4 µg vitamin B12, and 250 mg vitamin C supplements.[49] Although the elimination levels of fat-soluble vitamins are lower, they are recommended to be supplemented during the CRRT process, except for vitamin A. Vitamin E and vitamin K supplements should be provided during CRRT. During CRRT in children, it is recommended to continue vitamin support at recommended daily standard doses and to monitor blood levels of water-soluble vitamins and trace elements in long-term applications.

10. Continuous Renal Replacement Therapy in Patients Undergoing Extracorporeal Membrane Oxygenation

The prevalence of combined CRRT and Extracorporeal Membrane Oxygenation (ECMO) applications in critically ill pediatric patients is on the rise. Patients undergoing ECMO monitoring face a heightened risk of AKI and fluid overload. AKI affliction occurs in approximately 70-80% of ECMO-receiving patients.[50] Given the nature of ECMO support, patients may necessitate substantial fluid resuscitation and considerable volumes of blood products.

If AKI develops in patients monitored on ECMO, PD, IHD, and CRRT can be applied. Although each method has advantages and disadvantages, CRRT is the frequently preferred method in ECMO patients. For this, a separate vascular line can be used or the CRRT circuit can be integrated into the system using existing ECMO cannulas. The development of AKI during ECMO is an independent risk factor for mortality and failure to wean from ECMO. However, if there is no underlying primary kidney disease, renal recovery is seen in over 90% of surviving patients after ECMO and the need for chronic RRT is low.

Indications for Combination of ECMO and CRRT

Indications for starting RRT in ECMO patients are similar to patients not on ECMO. In the study conducted by the kidney interventions during the membrane oxygenation study group in neonatal and pediatric intensive care patients in 2020, it was shown that the primary indication was the treatment or prevention of fluid overload.[51] Reasons for performing CRRT in ECMO patients, in order of frequency:

1. Fluid overload (43%)
2. AKI (35%)
3. Preventing fluid overload (16%)
4. Electrolyte disorders (4%)
5. Others (2%)

Advantages of ECMO-CRRT Combination

The concurrent utilization of ECMO and CRRT offers notable advantages in enhancing tissue and organ oxygenation as well as perfusion. By rectifying hypoxia through ECMO support, lactic acidosis can be mitigated, potentially expediting renal recovery. Introducing CRRT, particularly with bicarbonate-based solutions, alongside ECMO in hemodynamically unstable patients, serves to forestall fluid overload, promote favorable fluid balance, and ameliorate cardiac and pulmonary functions. This combined approach facilitates the prompt correction of severe lactic acidosis and its metabolic ramifications, thereby averting hypocalcemia. Moreover, CRRT's maintenance of fluid balance ensures adequate nourishment for the patient, obviating restrictions on medication and blood product administration. Furthermore, this strategy reduces inflammatory cytokine levels, dampening the systemic inflammatory response syndrome instigated by ECMO. The ECMO-CRRT synergy proves beneficial in addressing electrolyte imbalances and mitigating kidney damage attributable to ECMO.

Timing of Initiating CRRT in ECMO Patients

Although there is no clear data for the timing of CRRT, literature information has shown that fluid overload negatively affects the prognosis in ECMO patients. It has been found that early initiation of CRRT in patients on ECMO support has a positive effect on the outcome.[50] CRRT decision should be made based on the cumulative fluid load and fluid status of the patient, whose fluid status is evaluated daily.

A Combination of CRRT and ECMO

There are several ways to perform CRRT in a patient using ECMO support. The first way is to use separate vascular access and circuits for CRRT and ECMO. The other option is to connect the CRRT device to the ECMO circuit.

1. CRRT with Separate Vascular Pathway

This option requires additional vascular access and is generally preferred if CRRT is already used before ECMO. The application of this method is no different from CRRT applications in patients not on ECMO.

However, when the indication for CRRT is placed while the patient is on ECMO, the placement of a new large-lumen catheter in the patient receiving high-dose anticoagulants increases the risk of complications. Multiple vascular access sites may be required to perform ECMO, limiting the number of access sites available to establish the CRRT circuit. In these cases, CRRT should be integrated into the ECMO circuit.

2. Combining Two Independent Extracorporeal Circuits

There are various methods for integrating the CRRT circuit with the ECMO circuit. Typically, the CRRT device is linked to the venous line of the ECMO circuit, with options to position the input to the CRRT circuit either before or after the oxygenator or centrifugal pump. Similarly, the outlet line of the CRRT can be connected before the centrifugal pump or between the centrifugal pump and the membrane oxygenator. Each connection method depicted in Figures 3 to 7 offers distinct advantages and disadvantages.

However, in our country, leading ECMO centers with extensive experience recommend connecting both the inlet and outlet of CRRT to the venous line before the centrifugal pump. This particular configuration may be favored due to its perceived advantages in terms of circuit simplicity, ease of monitoring, and potentially lower risk of hemolysis or clotting issues.

When the ECMO circuit and CRRT are combined, the blood flows of both systems may interact with each other. The combination of the two circuits can cause some technical problems, most of which are related to the CRRT device inlet and outlet pressure alarms. Pressure levels of different segments of the ECMO circuit may not be compatible with CRRT device pressure alarm limits. CRRT devices are designed to provide connection in the range of 0-20 mmHg, compatible with central venous pressure. While the pressures of the ECMO circuit before the centrifugal pump are significantly negative compared to these values, the pressures between the pump and the oxygenator are significantly positive. Detecting pressure outside the alarm limits in the CRRT device may stop the CRRT device. If the output line of the CRRT machine is connected to the ECMO circuit before the centrifugal pump,

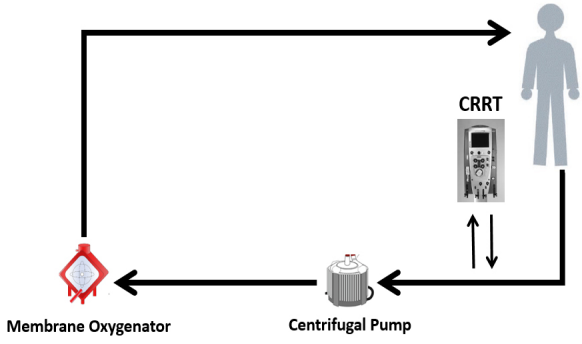

Figure 3. The inlet and outlet of the CRRT are on the venous line before the centrifugal pump
CRRT: Continuous renal replacement therapy

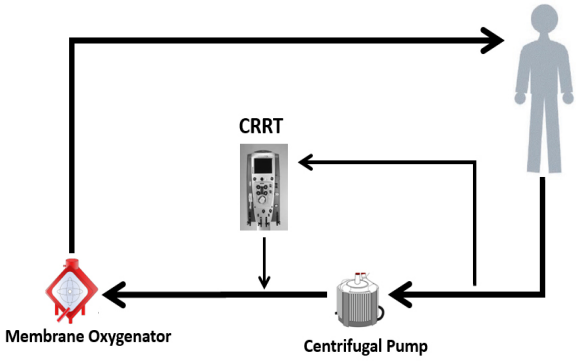

Figure 4. CRRT inlet on the venous line before the centrifugal pump, CRRT outlet after the centrifugal pump
CRRT: Continuous renal replacement therapy

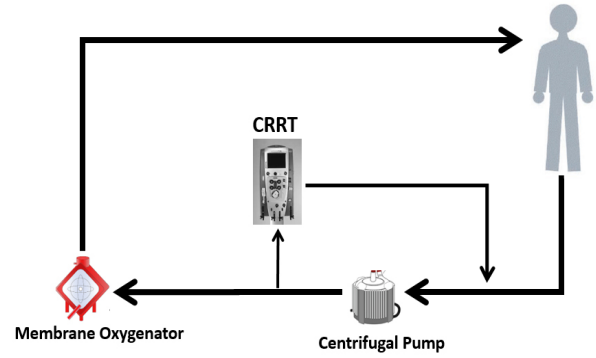

Figure 5. The inlet of the CRRT is after the centrifugal pump, and the outlet is on the venous line before the centrifugal pump
CRRT: Continuous renal replacement therapy

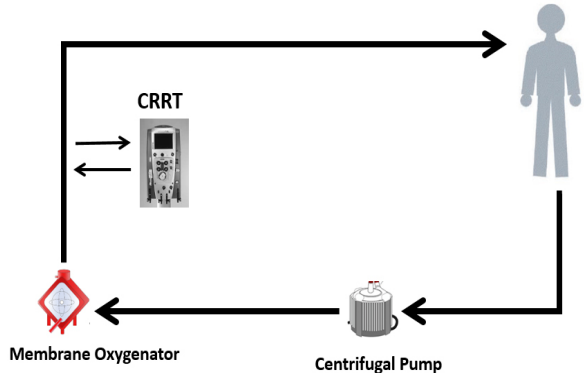

Figure 6. The inlet and outlet of the CRRT are after the oxygenator
CRRT: Continuous renal replacement therapy

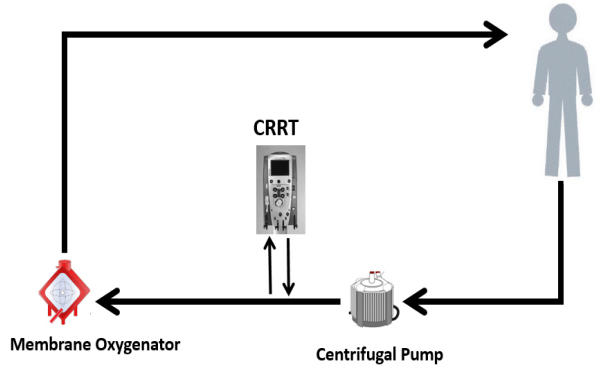

Figure 7. The inlet of the CRRT is after the centrifugal pump, and the outlet is before the oxygenator
CRRT: Continuous renal replacement therapy

blood from the CRRT returns to the negative pressure portion of the ECMO circuit. This creates a low return pressure alarm on the CRRT machine and may automatically shut down over time. Ignoring the limits may lead to excessive negative pressures, causing hemolysis and microembolization. Patients with severe hypoxemia often require high blood flow, thus ECMO pump speeds above 3000 rpm. This leads to excessive negative pressures, especially in patients with borderline ECMO input flow. To prevent this situation, it would be appropriate to convert the return pressure towards 0 or positive by placing small clamps on the venous line going from the CRRT machine to the ECMO set.

Incorporating the CRRT circuit into the ECMO circuit has advantages.

1. Cost-effectiveness
2. Easy circuit installation
3. Working with lower blood volume
4. Easy management
5. Low resource usage
6. No need for additional vascular access and no complications related to catheter placement
7. When the CRRT device is placed before the oxygenator, possible embolism due to air and blood clots is retained by the oxygenator.

Anticoagulation

Anticoagulation is administered via two distinct methods: citrate and heparin. As systemic heparinization is standard practice during ECMO, additional routine anticoagulation for the CRRT circuit is typically unnecessary. However, in exceptional circumstances such as instances of excessive bleeding during ECMO, aiming for low ACT targets, or temporary cessation of heparin, it becomes crucial to implement regional anticoagulation with CRRT citrate. This approach ensures appropriate anticoagulation within the CRRT circuit while minimizing systemic implications and complications associated with systemic anticoagulation.

Bivalirudin serves as an alternative option for anticoagulation management in patients undergoing ECMO. This medication operates by inhibiting thrombin activity. Notably, bivalirudin offers several advantages over other anticoagulants. It boasts a lower propensity for side effects associated with heparin usage, such as heparin-induced thrombocytopenia (HIT). Moreover, it can be effectively employed in cases of heparin-related thrombocytopenia (HIT), as well as instances of heparin resistance and non-HIT-related thrombocytopenia. Bivalirudin exhibits a relatively short half-life, lasting approximately 25 minutes.[52] It binds directly to thrombin, acts independently of the antithrombin level, and does not induce the formation of antibodies against platelets.[53] Its disadvantage is that there are no antidotes that can reverse its effects. Approximately 20% of bivalirudin excretion occurs via renal elimination, with the remainder being metabolized by proteolytic enzymes. While various sources suggest a broad starting dose range, the average recommended dosage falls between 0.045 and 0.48 mg/kg/min. Notably, there is typically no requirement for an initial bolus dose when initiating bivalirudin therapy.[54] Close monitoring of patients undergoing bivalirudin therapy is essential. Regular assessment of parameters such as ACT, aPTT, thromboelastography (TEG) or rotational thromboelastometry (ROTEM), and platelet counts is imperative. This vigilant monitoring plays a crucial role in fine-tuning bivalirudin dosage and evaluating the efficacy of anticoagulation.

Antibiotic Dosage in CRRT and ECMO

Limited data exist regarding the separate impacts of ECMO and CRRT on antibiotic pharmacokinetics. Individuals undergoing treatment on extracorporeal circuits frequently exhibit alterations in volume of distribution and clearance rates, which can vary considerably. Clinical investigations have revealed notable modifications in pharmacokinetics, potentially resulting in inappropriate dosing practices, including both suboptimal and excessive dosages of medications. Guidelines for medication dosing should take into account the specific mode of RRT, the dosage administered, BFRs, filter material composition, and surface area of the filter.

11. Complications That May Occur During Continuous Renal Replacement Treatment

While CRRT is recognized as an effective intervention for managing acute renal failure in critically ill patients, its implementation poses challenges, particularly in infants and children. The complexity of CRRT administration in pediatric populations often leads to an increased risk of complications.[26,55-57]

CRRT-related complications are shown in Table 8.

In general, complications associated with CRRT can be categorized as mechanical, hemodynamic, metabolic, nutritional, and pharmacological complications. Knowing CRRT systems, possible complications, and causes of alarms minimizes side effects.

A. Mechanical complications: Under this category, we encounter complications related to vascular access and extracorporeal circuits.

Vascular Complications and Alarms

Complications of vascular access include vascular damage and infection. It has been reported that it develops in 5-19% of its patients. Arterial interference, hematoma, hemothorax, and pneumothorax are the most common vascular problems.

Table 8. Complications associated with CRRT
A. Mechanical complications
Catheter-related complications Bleeding Infection Venous thrombosis Venous stenosis Traumatic arteriovenous fistula Pneumothorax Hemothorax Air embolism Organ injury Extracorporeal circuit-related complications Allergic reaction to hemodialyzer/hemofilter Circuit thrombosis Hemolysis Air embolism
B. Hemodynamic complications
Hypothermia
Hypotension
C. Metabolic complications
Acid base disorders Electrolyte disorders Hypophosphatemia Hypokalemia Hypocalcemia Hypomagnesemia Hyponatremia
D. Nutritional complications
E. Pharmacological complications
CRRT: Continuous renal replecement therapy

Arteriovenous fistula, aneurysm, thrombus formation, and retroperitoneal bleeding have been reported. Vascular complications are more common in patients <10 kg and in infancy.

Vascular spasms may develop due to a high blood flow rate at the beginning of the procedure, movement of the catheter in the opposite direction on the vessel wall, or the catheter being longer than necessary.

A low arterial pressure alarm is a mechanical complication during CRRT that indicates a mechanical problem with blood flow. It is caused by a physical obstruction such as a clamp remaining closed, bending in the catheter or tubes, or a clot in the system. In addition, it should be considered that the pump speed is high compared to the catheter size, the catheter pulls against the vessel wall and causes flow obstruction. In pediatric patients, it means that the pump speed is higher than the central venous pressure or right atrium blood volume.

A low venous pressure alarm occurs when the system cannot detect venous flow or there is positive pressure in the return line of the circuit. In the presence of this problem, it should be considered that the system is disconnected from the venous line, there is an obstruction between the filter and the venous pressure sensor, or the pump speed is not at a level to create the necessary positive pressure in the venous catheter. The transmembrane pressure alarm reflects changes in membrane pressure between the blood and ultrafiltrate compartments. It is an indication that the filter is clogged. In some systems, this alarm is also activated when the clamp on the UF line is left closed incorrectly.

Excessive Ultrafiltration

It has been shown to develop in 30% of patients undergoing CRRT. The patient's fluid balance should be closely monitored (see monitoring of fluid balance).

Balance, Bag Volume, or Weighing Alarm

Ultrafiltrate is activated when replacement fluid or dialysate falls outside the target volume. The main reasons for the alarm to occur are replacement or dialysate solutions remaining clamped or scales moving while the process is in progress.

Infection

It is the most serious complication that may develop during CRRT application. It can develop in 50% of patients receiving CRRT and results in death in 70%.

Filter Clogging

Thrombosis is the most important cause of loss of vascular access. Hypotension and hypovolemia are common, especially in infants. Hypotension, hypovolemia, and low UF rate increase the likelihood of filter clogging.

To minimize possible complications, the pressures in the device should be closely monitored and the procedure should be terminated in case of an increase in pressure. Pressure upper limits:

1. Pre-filter pressure >270 mmHg
2. Transmembrane pressure >250 mmHg
3. Filter life >72 hours

Membrane Reaction

Patients with severe metabolic acidosis prior to undergoing CRRT may encounter a sudden release of bradykinin when their blood interacts with the membrane. This can manifest clinically with symptoms ranging from vomiting to life-threatening anaphylaxis. In high-risk patients, it is recommended to prime the filter with blood before initiating the procedure. This precautionary measure helps mitigate the risk of adverse reactions associated with bradykinin release (see Appendix 5).

B. Hemodynamic Complications

Hypothermia

Hypothermia is a frequent complication during CRRT since the patient's blood is circulated outside the body and exposed to

cold dialysate or replacement solution. Prolonged hypothermia is undesirable as it can result in energy depletion, heightened oxygen demand due to shivering, vasoconstriction, impaired leukocyte function, and coagulopathy. If relying solely on the integrated heating system within the CRRT machine proves insufficient, supplementary external heating should be administered to maintain the patient's body temperature at 37 °C.

Hypotension

Hypotension is one of the important complications seen during the initiation of CRRT, especially in pediatric patients. The solution may be to start with a low blood flow rate and gradually increase the blood flow rate according to the patient's tolerance.

C. Metabolic Complications

Metabolic complications associated with CRRT include acid-base abnormalities, electrolyte disturbances, and hypoglycemia.

Correction of Metabolic and Electrolyte Disorders That May Occur During CRRT

Additional recommendations regarding these complications are also described in the section on adding electrolytes to CRRT solutions (see solution). Situations that need to be taken into consideration and examples of additional applications that can be applied are summarized below:[44]

- Azotemia; increase dialysis/replacement rate

- Hyponatremia; add 70 mL of 3% hypertonic saline to a 5-liter bag

- Hypernatremia; start intravenous infusion of 5% dextrose 0.45% saline

- Metabolic acidosis; start a bicarbonate infusion or replace the replacement solution with a solution containing 3 ampoules of sodium bicarbonate added to 5% dextrose or add 20 mL of bicarbonate per liter to the dialysis solution.

- Metabolic alkalosis; replace the replacement solution with isotonic fluid to which potassium chloride has been added.

- Hypercalcemia; increase the rate of replacement or dialysate fluid.

- Hypocalcemia; add 24 g of calcium gluconate into 1000 mL of isotonic and infuse at 5 mg/kg/hour, aiming for Cai to be 1.1-1.3 mmol/L.

- Hypophosphatemia; start phosphorus infusion, check phosphorus level every 2-4 hours.

- Hypokalemia; give potassium infusion.

- Hyperkalemia; administer potassium-free fluid or increase the rate of dialysis/replacement solution.

D. Nutritional Complications: Described in the nutrition section (see nutrition).

E. Pharmacological Complications: Adjusting the dosage of antimicrobial drugs in critically ill patients undergoing CRRT presents a significant challenge. Most antimicrobials have a molecular weight below 1500 daltons, and their blood levels can fluctuate with convective treatments, leading to increased clearance. For drugs that are highly protein-bound and have a large volume of distribution, such as amphotericin and macrolides, clearance may be reduced. Conversely, water-soluble antimicrobials with a low volume of distribution, such as aminoglycosides and β-lactam antibiotics, are easily cleared via CRRT.

Although guidelines offer recommendations for adjusting antimicrobial dosages, these recommendations are not foolproof due to the multitude of variables influencing clearance. Therefore, a personalized approach to dose adjustment should be adopted, based on therapeutic levels if available, to ensure optimal treatment outcomes.

12. Follow-up of the Patient on Continuous Renal Replacement Therapy

The cornerstone of effective and uninterrupted CRRT in pediatric intensive care relies on comprehensive training of the medical staff. This training should encompass both didactic components (covering reasons for implementation, treatment modalities, patient scenarios, and documentation) and practical simulations (including proficiency assessments, machine setup, and troubleshooting). Regular bedside visits for CRRT supervision and periodic proficiency checks are essential for identifying and rectifying any potential deficiencies in practice.[58,59]

Patients undergoing CRRT necessitate meticulous monitoring to uphold hemodynamic equilibrium, ensure the smooth operation of the system, and promptly address any arising issues. Ideally, daily weighing should be conducted, and vital signs ought to be recorded hourly. Regular physical examinations, focusing on fluid status and detection of bleeding complications, should be performed in 6 to 8-hour intervals.

Adjustments to ultrafiltration, dialysate, and replacement fluid volumes should be made as necessary throughout treatment, considering sensitive losses when calculating fluid status. This comprehensive monitoring regimen is crucial for optimizing patient care and treatment outcomes during CRRT.

Electrolytes (glucose, Na, K, Cl, bicarbonate, Ca), blood urea nitrogen, and creatinine levels should be assessed every 6-8 hours. Magnesium, phosphorus, and blood count should be checked every 12-24 hours. For patients receiving heparin, aPTT or ACT should be monitored. In cases where

citrate is administered, ionized calcium levels and blood gas parameters should be monitored and documented according to the protocol.

Hypothermia is a common occurrence, particularly during high-flow CRRT procedures. If feasible, this issue can be addressed by incorporating a heater into the system or implementing active external heating measures. Additionally, inlet pressure, return pressure, and filter pressure should be monitored hourly and documented using the standardized form (Figure 8).

During CRRT, the patient should be monitored by an intensive care nurse with experience in monitoring CRRT patients, if possible. The responsibilities of the health care providers are as follows:

a) The entry site of the catheter must be regularly assessed and documented. Additionally, the nurse should promptly notify the physician of any signs of bleeding, infection, or other potential issues. This proactive communication ensures timely intervention and optimal management of the patient's condition.

b) Hourly monitoring of fluid intake and output is essential for the patient, who should actively participate in maintaining fluid balance.

c) The nurse is responsible for monitoring and documenting the continuation of CRRT according to the prescribed renal replacement therapy doses.

d) Throughout CRRT, it is essential to regularly monitor and document the patient's vital signs. The caregiver must ensure that alarm limits are appropriately set on the monitoring equipment.

e) It is imperative for nurses to remain vigilant and responsive to potential alarms during CRRT. They should actively engage in addressing alarm triggers and swiftly undertake necessary interventions, such as altering solutions, emptying waste bags, or preparing heparin syringes. This proactive approach is crucial for ensuring the safety and efficacy of CRRT procedures.

f) The nurse should also monitor complications that may not be directly related to CRRT, such as bleeding, convulsions, and hypothermia.

Patient's Name-Surname: **Method:** **Date:**

Hour	Blood flow rate mL/min	Dialysis rate mL/h	Replacement rate mL/h	Fluid intake/h	Ca rate mL/h	Citrate/ Heparin rate	aPTT/ ACT	PostF Cai	PreF Cai	UF rate /h	Amount of urine/h	Net amount of fluid drawn	Arrival pressure	Return pressure	Filter pressure
09:00															
10:00															
11:00															
12:00															
13:00															
14:00															
15:00															
16:00															
17:00															
18:00															
19:00															
20:00															
21:00															

Heparin titration protocol

ACT level(sec)	PTT level (sec)	Heparin dose
180-220	60-80	No change
>220	>80	Stop heparin for an hour
<180	<60	Start by reducing the dose by 10% after one hour.

Citrate – calcium infusion rate according to PreFCai level

Prefilter-Cai level (mmol/L) *	Calcium infusion rate regulation	
	>20kg	<20kg
>1.3	Rate 5 ml/hour ↓	Rate 2.5 ml/hr ↓
1.1-1.3	No change	
0.9-1.1	Rate 5ml/hour ↑	Rate 2.5 ml/hr ↑
<0.9	Rate 10ml/hour ↑	Rate 5 ml/hr ↑

Citrate-calcium infusion rate according to postFCai level

Post-filter Cai level (mmol/L) *	Citrate infusion rate regulation	
	>20 kg	<20kg
<0.35	Citrate rate 10% ↓	Citrate rate 5% ↓
0.35-0.5	No change	
0.5-0.6	Citrate rate 10% ↑	Citrate rate 5%↑
>0.6	Citrate rate 20% ↑	Citrate rate 10%↑

*: It should be taken from the blue port located at the outlet of the dialysis membrane.

Figure 8. CRRT follow-up chart

g) Any fluctuations in arterial, venous pressure, transmembrane, and dialysate pressures, possibly arising from thrombosis within the set, filter, or catheter, as well as blood flow-related issues, should be closely monitored. Any detected abnormalities should be promptly communicated to the attending physician for early resolution.

h) At the end of the treatment, the catheter lumens should be filled with heparin solution at a concentration appropriate to the patient's age, ensuring readiness for the next treatment. Heparinized fluid should be administered in an amount equal to the volume of the catheter lumen, and a notation should be made on the catheter indicating that it has been filled with heparinized fluid.) Must ensure that the catheter entry site dressing is done appropriately and regularly.

Device Alarms and Clinical Trouble Prevention and Troubleshooting in CRRT Tracking

On CRRT machines, alarms are colored according to the urgency of the situation:

Green: Machine operation is OK

Orange: The pumps are working, but there is a situation that is not urgent but needs to be corrected, for example, the waste bag is full, the dialysate/replacement bag is empty.

Red: This is an emergency alarm situation where the pumps will halt until the issue is rectified. Failure to address the problem promptly may result in filter coagulation. Examples of issues triggering this alarm include air in the return line, blood leakage, excessive negative inlet pressure, or excessively high return pressure.

Below, the main CRRT machine alarms, prevention, and troubleshooting methods are summarized (Table 9).

Clinical Troubleshooting

The venous catheter or patient-related inlet/return pressure alarms:

- Please ensure that the patient's position, entry, and return lines are checked thoroughly for any signs of pinching or twisting around the patient or clamps.

- Temporarily decreasing blood flow can help alleviate pressure on the vessel wall.

- Aspirate and rinse the lumens to inspect for any clots. Aspirated blood can be sprayed onto gauze to assess for clot presence.

- In instances of negative arrival pressures, consider rotating the temporary dialysis catheter 180 degrees around its axis. This procedure should be carried out by a skilled CRRT nurse in collaboration with the PICU physician.

- If blood supply remains poor despite previous measures, the final option is to replace the inflow-return lumens. However,

Table 9. Clinical problem prevention and resolution in CRRT monitoring

Clinical problem/alarm	Prevention	Troubleshooting
Inlet pressure is too negative and/or return pressure too positive	-Use appropriate size catheter -Adjust the blood flow rate appropriately -Make sure the clamps are opened after each procedure.	-Check patient position -Temporarily reduce blood flow rate -Check/flush catheter lumens for clots -Change input-return lumens
Trans membrane pressure and filter pressure rising	-Use an appropriate dosage of anticoagulant -Adjust blood flow rate, UF rate appropriately -Keep filtration fraction <25%	-If TMP >300 despite appropriate settings and anticoagulation, consider set replacement -Check the return pressure, if it is high, troubleshoot. -Check replacement fluid speed, reduce speed if too high -Consider additional factors such as sepsis, lipid and/or propofol infusion
Loss/gain fluid limit reached	-Use the "change bags" button when changing dialysate/ replacement/waste bags -When the bags are tied, make sure the safety valves are broken properly and the clamps are opened. -Make sure the bags are not touched from the bottom or sides.	-Change set
There's air on the set	-Check the set for air after prime -Make sure all connections in the set are made correctly -Check that the fluid/blood level in the air chamber is at the appropriate height.	-Fill the air chamber with liquid by pressing and holding the "up arrow" button. -Replace the set if there is still air in the return line to the patient.
Blood leak detected	-Clean the blood detector compartment before set installation	-Change the set
Bag volume and/or weighing alarm	- Make sure the safety valves are broken properly when the bags are tied - Make sure the clamps are open after each procedure. - Make sure nothing touches the bags from the bottom or sides	- Check the set for errors in the prevention section

it's essential to acknowledge that this manipulation carries a risk of recirculation, estimated at approximately 25%, which could consequently reduce clearances by around 10%.

Filter alarms [trans membrane pressure (TMP) and filter pressure rising]:

Extending filter life can be attained through several measures including using properly sized catheters and sets, adjusting blood flow rates based on the patient's weight, maintaining the filtration fraction below 25%, optimizing anticoagulation levels, and promptly addressing alarms-particularly those flagged as red. Typically, normal filter pressure ranges between 100 to 250 mmHg.

The maximum filter pressure is +450 mmHg. Nevertheless, when the pressure reaches 300 mmHg, the device will trigger a TMP high alarm, indicating significant clotting. At this point, there's a risk that blood may be returned to the patient before clotting is complete, necessitating consideration for filter replacement.

- If the filter pressure remains static while TMP increases, this could indicate adsorption, such as in cases of sepsis or accumulation of fat particles from infusions like propofol or lipids. In such scenarios, careful monitoring and appropriate interventions are essential.

- An increase in return pressure correlates with an increase in TMP, indicating a need to inspect the return path. It's crucial to investigate and address any issues in the return path promptly.

- High-flow replacement, especially post-dilution, can elevate TMP. In such cases, it's advisable to consider reducing the replacement rush rate to alleviate the TMP increase.

- If there is a sudden increase in both filter and TMP, it may be prudent to consider discontinuing the treatment.

Table 10. Determination of heparin concentration

Weight of the patient (kg)	Heparin concentration (U/mL)
<10 kg	40
11-25 kg	100
16-60 kg	250
>60 kg	500

Table 11. Heparin titration protocol

ACT level (sec)	PTT level (sec)	Heparin dosage
180-220	60-80	No change
>220	>80	Stop heparin for an hour. Start by reducing the dose by 10% after one hour
<180	<60	Increase the dose by 10%

ACT: Activated clotting time, PTT: Partial thromboplastin time

Table 12. Citrate solutions and their ingredients commonly used in the world

Content (mmol/L)	Acid-Citrate-Dextrose A	4% sodium citrate	Prismocitrate 18/0
Citric acid	38	0	0
Citrate	75	136	18
Sodium	225	408	140
Dextrose	124	0	0

Blood Leak Detected

This protocol is solely applicable in the event of a sudden rupture in the filter, permitting blood passage into the filtrate. Replacement of the entire circuit becomes imperative. While

Table 13. Solutions that do not contain calcium

Solution	Volume (L)	Sodium (mmol/L)	Potassium (mmol/L)	Calcium (mmol/L)	Magnesium (mmol/L)	Chloride (mmol/L)	Bicarbonate (mmol/L)
Prismocal	5	140	0	0	0.5	106	32
Prismocal B22	5	140	4	0	0.75	130.5	22
Ci-Ca Dialysate K2	5	133	2	0	0.75	116.5	20
Ci-Ca Dialysate K4	5	133	4	0	0.75	118.5	20

Table 14. Adjustment of citrate-calcium infusion rate according to the patient's ionized calcium level

Ionized calcium level of the patient (mmol/L) *	Calcium infusion rate regulation	
	>20 kg	<20 kg
>1.3	Rate 5 mL/hour ↓	Rate 2.5 mL/hour ↓
1.1-1.3	No change	No change
0.9-1.1	Rate 5 mL/hour ↑	Rate 2.5 mL/hour ↑
<0.9	Rate 10 mL/hour ↑	Rate 5 mL/hour ↑

*: Blood sample should be taken from the draw line (red port) or from the peripheral vene

Table 15. Citrate-calcium infusion rate adjustment according to the ionized calcium level of the filter

Post-filter Cai (mmol/L) *	Citrate infusion rate regulation	
	>20 kg	<20 kg
<0.35	Citrate rate 10% ↓	Citrate rate 5% ↓
0.35-0.5	No change	No change
0.5-0.6	Citrate rate 10% ↑	Citrate rate 5% ↑
>0.6	Citrate rate 20% ↑	Citrate rate 10% ↑

*: Blood sample should be taken from the blue port located at the outlet of the dialysis membrane

Table 16. Management of metabolic complications that may develop with citrate use

	Citrate accumulation	Excess citrate use	Insufficient citrate use
Mechanism	Presence of high amounts of citrate-calcium complex in the circulation because of inadequate citrate-bicarbonate conversion	Development of alkalosis because of excessive use of citrate and citrate bicarbonate conversion	Failure to correct acidosis due to acute kidney injury because of insufficient citrate use and citrate bicarbonate conversion
Diagnosis	Metabolic acidosis and total Ca/iCa>2.5	Metabolic alkalosis and total Ca/iCa <2.5	metabolic acidosis and total Ca/iCa<2.5
Management	-Reduce blood flow rate or -Increase dialysate speed or -Consider alternative anticoagulation.	-Reduce blood flow rate or -Increase dialysate speed or -Reduce alkaline buffer concentration in other solutions.	-Increase blood flow rate or -Reduce dialysate speed or -Increase the alkaline buffer concentration in other solutions.

such occurrences are uncommon, if encountered, securely store the ruptured filter in a waste bag for subsequent return to the manufacturer for evaluation.

Anaphylactic Reaction

In rare instances, the patient may experience an anaphylactic reaction to the filter membrane or to the ethylene oxide utilized for filter sterilization. Priming the set with albumin or blood may mitigate this risk. However, if the priming process was conducted more than 30 minutes before patient connection, there's a potential for ethylene oxide accumulation, heightening the risk. In such scenarios, it's imperative to re-prime the set before connecting it to the patient.

- If anaphylaxis develops, it typically manifests with the hallmark symptoms of tachycardia, hypotension, urticarial or maculopapular skin rash, and bronchospasm.

- If the circuit is filled with blood, it can mimic and be difficult to distinguish from a transfusion reaction.

- In very mild cases, treatment typically involves administering antihistamines.

- In the majority of cases, hemofiltration will need to be discontinued.

• Blood in the extracorporeal circuit should not be returned to the patient.

• Blood sample should be separated for Igs, IgE, mast cell tryptase.

Drug Clearance

During CRRT, drugs may be filtered out to a degree that could compromise the treatment of underlying conditions, such as sepsis or hypotension. It may be necessary to adjust doses of vasopressors, inotropes, sedative-analgesics, and antibiotics in patients undergoing CRRT. When renewing drug dosages, considerations should include factors like the patient's renal clearance, residual renal function, distribution volumes, molecular weight, and protein binding. Clearance may also be influenced by the location of drug infusion relative to the vascular access of the CRRT circuit. Therefore, careful attention should be paid to the location of drug infusion concerning proximity to CRRT access.

Ethics

Authorship Contributions

Concept: A.Y., M.D., N.A., D.D., Design: A.K., T.D., D.D., Data Collection or Processing: E.A., T.B., Analysis or Interpretation: D.D., Literature Search: A.K., A.Y., E.A., M.D., N.A., T.D., T.B., D.D., Writing: A.K., A.Y., E.A., M.D., N.A., T.D., T.B., D.D.

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Appendix 1. Protocol for Filling the Filter with Blood (Blood Priming) and Preventing Bradykinin Release

1. In cases where the filter volume constitutes 10% or more of the patient's blood volume, filling the filter with blood may be considered to mitigate potential hemodynamic issues at the onset of treatment.

2. If the filter is to be filled with erythrocyte suspension, verify the hematocrit level of the provided suspension, and dilute it accordingly to achieve the target hematocrit level. If the hematocrit level cannot be measured, a ratio of 9 parts erythrocyte suspension to 5 parts isotonic solution can be used.

3. Heat the diluted erythrocyte suspension to 37 °C.

4. Transfer the heated erythrocyte suspension into the total parenteral nutrition bag.

5. Once the standard priming program of the machine is completed, attach a dispensing spike (Braun) to the end of the total parenteral nutrition bag.

6. Add a three-way stopcock to the end of the installed dispensing spike.

7. Connect the arterial end of the extracorporeal circuit to one end of the three-way stopcock.

8. Open the three-way stopcock in the direction that allows blood to fill the circuit. Operate the device in either CVVHD or CVVHDF mode, setting the blood flow rate to 70 mL/min and the dialysis rate to 2000 mL/hour.

9. Operate the device until the blood reaches the waste bag attached to the venous end.

10. Once blood reaches the waste bag, stop the pump to fill the system with blood. However, note that the pH and calcium levels in the filled blood may be very low. Therefore, conducting short-term dialysis on the filled blood helps prevent potential issues arising from acidic blood flowing to the patient (bradykinin release syndrome).

11. Clamp and separate the venous end from the waste bag.

12. Connect the venous end to the empty end of the three-way stopcock previously connected to the arterial end.

13. Close the triple tap at the arterial end to prevent blood from flowing into the circuit.

14. Through the triple tap, allow the blood in the venous pathway of the circuit to pass to the arterial side, thus forming a closed circuit circulating within itself.

15. At this stage, ensure that the venous line is not clamped and verify its integrity.

16. Open the triple tap in the direction that allows blood to fill the circuit. Operate the device in CVVHD or CVVHDF mode, running it for 7.5 minutes* with the blood flow rate set to 70 mL/min and the dialysis rate set to 2000 mL/hour.

17. Upon completion of the procedure, check the pH and calcium levels of the blood inside the filter, which often reach physiological limits.

18. Stop the device, clamp the artery and venous lines, disconnect them from the three-way stopcock, and connect them to the patient.

19. Open the clamps and restart the device, initiating renal replacement therapy by adjusting the target blood flow, replacement, and dialysate rates.

Appendix 2. Returning the set within itself (recirculation=recirculation) protocol

If CRRT needs to be temporarily interrupted, recirculation with blood or saline can be considered to facilitate set reuse. If ***the set has been in use for less than 24 hours*** and is free of clots, it can be preserved by following the steps outlined below during treatment interruption:

Recirculation with saline:

1. Press the "Stop Treatment" button.
2. Select "Refill".
3. Press the "Saline Recirculation" option button.
4. Suspend 1000 mL of 0.9% sodium chloride in the device and attach a distribution spike to the end.
5. Clamp and disconnect the red access line from the patient, connecting it to the distribution spike at the end of the saline bag, then open the clamp.
6. Select the volume of blood to be returned to the patient (equivalent to the volume of the set and accessories) and adjust the return speed.
7. After the patient's blood is returned, clamp and disconnect the blue access line from the patient, connecting it to the distribution spike at the end of the saline bag, then open the clamp.
8. Restart circulation with saline.
9. Solutions are not consumed during recirculation; adjustments are made only to the blood flow rate during this process, which can be tailored according to the specific set used.
10. When the set is to be reused, stop recirculation, reconnect the filter to the patient, and perform a new priming process.
11. With the saline recirculation method, the set can be maintained for **up to 2 hours.**

Recirculation with blood:

1. Press the "Stop Treatment" button.
2. Select "Refill".
3. Press the "Blood Refill" option button.
4. Clamp and disconnect the blue access line from the patient.
5. Create a closed circuit with the blue access line and the red access line through the three-way tap, ensuring circulation within itself.
6. Initiate recirculation with blood.
7. Solutions are not consumed during recirculation; adjustments are made only to the blood flow rate during this process, which can be tailored according to the specific set used.
8. The set can be reconnected to the patient without requiring re-priming in this method.
9. With the blood recirculation method, the set can be maintained for **up to 1 hour.**

Appendix 3. Heparin Protocol

1. Before initiating anticoagulation, it's essential to check the PT/PTT or ACT and platelet count.

2. In patients undergoing ACT monitoring, aPTT should be measured at least once daily.

3. Heparin should not be initiated if the initial ACT level is >200 sec, or aPTT is >60 sec, or PT-INR is >2.5 times the normal value, or the platelet count is <50,000/mm^3.

4. If there is no coagulopathy (ACT<180 sec or aPTT<60 sec), administer 20 units/kg of intravenous heparin.

5. Twenty minutes later, recheck the ACT or aPTT level (sample taken from the blue port after the filter). If ACT <180 sec or PTT <60 sec, repeat the heparin loading dose (maximum 2 times).

6. Target ACT level should be 180-220 seconds, and PTT level should be 60-80 seconds.

7. After the loading dose, start a continuous intravenous infusion of heparin at a rate of 10 units/kg/hour. Maximum heparin concentrations per liter according to age are shown in Table 10.

8. If possible, monitor activated clotting time (ACT) every 20-30 minutes for the first hour.

9. Check ACT or aPTT level one hour after each heparin dose change.

10. Follow the heparin dose adjustment protocol as outlined in Table 11.

11. Once a stable heparin infusion rate is achieved, monitor ACT or aPTT every four hours.

12. Check ACT or aPTT 20 minutes after each circuit change or blood transfusion.

Appendix 4. Citrate Anticoagulation Management

1. The recommended initial citrate dose is 2.5 mmol/L.

2. In certain devices, when dose information (mmol/L) is inputted, the device can automatically determine the citrate flow rate. However, in other devices, the initial citrate flow rate can be calculated manually using the formula:

Citrate dose = $Q_{citrate}$ x $C_{citrate}$/blood flow rate (mL/hour)

Where:

- $Q_{citrate}$ represents the citrate flow rate

- $C_{citrate}$ denotes the citrate concentration of the solution used

The contents of commonly used citrate solutions worldwide are detailed in Table 12. Among these solutions, acid-citrate-dextrose (ACD-A) A solution has been demonstrated by studies to be safe for use in children. While the content of 4% trisodium citrate solution closely resembles that of ACD-A solution, its sodium concentration is elevated. Despite this, it can still be utilized in pediatric patients with careful monitoring. Pediatric studies have been conducted on prismocitrate 18/0 solution. However, the challenge with prismocitrate 10/2 and 18/0 in pediatrics is that their concentrations per liter are low, necessitating high rates to achieve the effective citrate concentration in the extracorporeal circuit.

3. The solution intended for use as the dialyzer (second solution bag) should not contain calcium. However, there is no restriction for the solution designated as replacement (third solution bag) to contain calcium. Solutions devoid of calcium are outlined in Table 13.

4. Calcium infusion should ideally be administered through a separate central venous catheter. If this isn't feasible, a Y connector/triple tap system can be placed on the return line of the dialysis (blue line) to initiate calcium infusion to the patient. Calcium gluconate preparations, available in our country, are commonly used for calcium infusion, containing calcium at a concentration of 232 mmol/L. In pediatric patients, it is often diluted to a 1:1 ratio, resulting in a concentration of 116 mmol/L.

The calcium infusion rate can be calculated using the formula:

Calcium infusion rate = Citrate flow rate ×0.03.

For example, if the blood flow rate of a patient is determined to be 50 mL/minute, and the citrate flow rate is adjusted to provide a citrate dose of 2.5 mmol/liter concentration using 18/0 prismocal solution, the calculated citrate flow rate would be 416 mL/hour. Thus, the calcium infusion rate would be:

Calcium infusion rate =416 mL/hour × 0.03=12.5 mL/hour.

Dosage adjustment recommendations based on ionized calcium levels before (preFCai) and after (postFCai) the filter are provided in Tables 14 and 15, respectively.

5. Magnesium infusion guidelines:

- The magnesium level should be within a normal range (>0.7 mmol/L) before initiating citrate anticoagulation.

- If the magnesium level is low, 0.4 mmol/kg magnesium sulfate ($MgSO_4$) should be infused over 30-60 minutes prior to treatment.

- During citrate anticoagulation, $MgSO_4$ can be administered through a separate central venous catheter at a dose of 0.4 mmol/kg every 6-12 hours.

- Magnesium sulfate should not be infused through the same route as calcium.

- Plasma magnesium levels should be monitored every 12 hours. If the level falls below 0.7 mmol/L, an additional dose of $MgSO_4$ should be administered at a dose of 0.4 mmol/L, and magnesium levels should be checked at intervals of 6-8 hours.

6. Patients receiving citrate anticoagulation should be monitored as follows:

- Check patient and filter ionized calcium levels 30 minutes after the start of dialysis.

- Simultaneously measure ionized calcium levels from the patient and the filter.

- Monitor ionized calcium levels every hour for the first 3 hours and then every 4 hours after achieving balanced levels.

- Urea, creatinine, magnesium, phosphorus, calcium, and sodium levels should be checked at least every 12 hours.

- Management of acid-base imbalances due to citrate is detailed in Table 16.

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Appendix 5. Protocol for the Prevention of Bradykinin Release Syndrome

The steps in Annex-1 of the protocol are followed. However, for patients at risk of bradykinin release syndrome, the filter should fill with erythrocyte suspension diluted with physiological saline to achieve the target hematocrit level.

1. The venous end is clamped and separated from the waste bag.

2. The venous end is connected to the empty end of the three-way tap that was previously connected to the arterial end.

3. The direction of the triple tap at the arterial end is closed to prevent blood from flowing into the circuit.

4. The blood in the venous pathway of the circuit is then passed to the arterial side through the triple tap, creating a closed circuit that circulates within itself.

5. At this stage, the venous line should remain unclamped and checked.

6. The triple tap is opened to allow blood to fill the circuit. The device is operated in CVVHD or CVVHDF mode. The system is run for 7.5 minutes, setting the blood flow rate to 40 mL/min and the dialysis rate to 200 mL/min.

7. At the end of the procedure, the pH and calcium levels of the blood inside the filter should be checked, as they often reach physiological limits.