CRRT in a Sick Child

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11.1 Scenario

A 30 kg child with leukemia develops septic shock with multi-organ system failure including the need for intubation, vasopressor support for hemodynamic compromise, as well as progressive oliguria with both solute and fluid retention. Current ventilator settings include a FIO_2 delivery of 70%, a PEEP of 10. Blood pressure is currently 98/45 with 1 mic/kg/min of norepinephrine adjustment to keep at systolic >110 mmHg. The child is febrile with a temperature of 39 °C. Fluid overload calculations reveal that the child is 15% above dry weight with insufficient urine output to allow for adequate room for medications, nutrition, and overall medical care. Labs reveal a BUN of 69 mg/dL, a cr of 2.3 mg/dL, and a K of 5.9 meq/dL.

Questions are:

1. What is the optimal way to deliver renal support?
2. What is the impact of renal support on medical (and vasopressor) clearance?
3. What is the optimal location of vascular access?
4. What is the optimal prescription?
5. How much fluid can be removed safely?

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11.2 Background

The use of continuous renal replacement therapy (CRRT) has become commonplace over the last two decades in children who require renal replacement therapy (RRT). CRRT is often used in an intensive care setting in patients who have hemodynamic compromise, hypermetabolic syndrome, fluid overload, or ongoing need for fluid management [1]. CRRT can be used as a standard or in conjunction with extracorporeal membrane oxygenation (ECMO) if needed. The purpose of this section is to describe the technical aspects of CRRT in a critically ill child.

11.3 Definition

The definition of CRRT is any form of RRT that is used 24 h a day. In theory then that would include both extracorporeal therapies that are commonly used called CRRT but also could include PD. For the purpose of this discussion, we will limit ourselves to CRRT.

CRRT can be performed as continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemofiltration with dialysis (CVVHD), or a combination of continuous veno-venous hemofiltration with dialysis (CVVHD).

CVVH is using a convective form of dialysis, whereas CVVHD is using a diffusive form of dialysis with CVVHD as a combination of both.

Convection occurs by mass transport. This is essentially a concept of placing a physiologic fluid into a vascular space and forcing across a membrane mass solute for improved clearance.

Diffusion is commonly used in CVVHD, peritoneal dialysis, hemodialysis, as well as slow low-efficiency dialysis (SLED).

Historically, programs that have been ICU initiated commonly use convective clearance, whereas programs that are nephrology initiated often use diffusion clearance.

The question is always is one superior to the other.

If one looks at a paper by Maxvold et al., a perspective study was done looking at small-molecular-weight clearance (urea) and looking at clearance by CVVH versus CVVHD [2]. Using identical blood flow rates, surface areas of membranes, as well as fluid exposure, one identified in that paper that there is no difference in solute clearance. One though has to look at the concept of the sieving coefficient. The sieving coefficient is that which decides the rate at which something comes across a membrane. Things that are a small molecular weight and low protein-bound (e.g., urea, citrate) have a sieving coefficient of 1 in both convection and diffusion. Essentially that means they come across the membrane at roughly a one-to-one relationship.

Things that are a large molecular weight and highly protein-bound (e.g., vancomycin, molecular weight of around 1450 kDa, and a protein-bound of 75%) have a superior clearance on convection (sieving coefficient of 0.84) versus diffusion (sieving coefficient of 0.74) (Fig. 11.1).

Solute (MW)	Convective Coefficient	Diffusion Coefficient
Urea (60)	1.01 ± 0.05	1.01 ± 0.07
Creatinine (113)	1.00 ± 0.09	1.01 ± 0.06
Uric Acid (168)	1.01 ± 0.04	0.97 ± 0.04*
Vancomycin (1448)	0.84 ± 0.10	0.74 ± 0.04**
Calcium (protein bound)	0.67 ± 0.1	0.61 ± 0.07
Cytokines (large)	adsorbed	minimal clearance

*P<0.05 **P<0.01

Fig. 11.1 Examples of sieving coefficients

Experience would suggest that in highly cytokine inflammatory patients, such as stem cell transplants and septic patients, there may be an advantage of doing convection over diffusion. This was identified by Flores et al. in a retrospective data base analysis of patients with stem cell transplants. Looking at roughly 51 patients with stem cell transplants who underwent CVVH or CVVHD, the patients who underwent CVVH had a superior survival rate over CVVHD. This data may be the style of practice or may be that of outcome [3].

11.4 Equipment

Equipment for CRRT would include the machine, vascular access, solutions, as well as anticoagulation protocols.

Over the last few decades, many machines have come and gone. The standard machines are made by the Baxter, B. Braun, and Bellco, as well as the machines in the Asian and Eastern European area. Newcomers to the areas that are currently in clinical trials include the CARPEDIEM in Italy as well as the NIDUS in the UK [4, 5].

The commonality of these present machines is that they have blood flow rate controllers, dialysate flow rate controllers, convective flow rate controllers, as well as heating sources.

All machines currently used throughout the world have an error rate of ultrafiltration; therefore there needs to be a very close attention to detail of the volume status.

Access for CVVH or CVVHD is important. Work by Hackbarth et al. has demonstrated the optimal location and size of access based on the age and size of the patient [6]. In their clinical observation in greater than 300 children, a right IJ vein is superior to any other location for consistent flow rates. They also demonstrated that the largest vascular access with the shortest length of the access would give superior flow rate and low resistance with less clotting sources (Fig. 11.2).

Solutions in CRRT have changed dramatically over the last two and a half decades. In North America prior to the year 2000, lactate-based solutions were

PATIENT SIZE	CATHETER SIZE & SOURCE	SITE OF INSERTION
NEONATE	Dual-Lumen 7.0 French (COOK/MEDCOMP)	Femoral vein
3-6 KG	Dual-Lumen 7.0 French (COOK/MEDCOMP)	Internal/External-Jugular, Subclavian or Femoral vein
6-30 KG	Dual-Lumen 8.0 French (KENDALL/ARROW)	Internal/External-Jugular, Subclavian or Femoral vein
>15-KG	Dual-Lumen 9.0 French (MEDCOMP)	Internal/External-Jugular, Subclavian or Femoral vein
>30 KG	Dual-Lumen 10.0 French (KENDALL, ARROW)	Internal/External-Jugular, Subclavian or Femoral vein
>30 KG	Triple-Lumen 12 French (KENDALL/ ARROW)	Internal/External-Jugular, Subclavian or Femoral vein

Fig. 11.2 Suggestions of vascular access for size of child

commonly used. Lactate-based solutions would deliver lactate to the patient, and it would be hard to discriminate whether the lactate in the blood was related to the patient or the machine. Since 2000 work by Normocarb Dialysis Solutions Inc., which is no longer on the market, as well as other companies all now have bicarbonate-based replacement solutions for convection and dialysis solutions for diffusion.

FDA will identify that convective solutions are considered a drug and can be placed in the vascular space but that diffusive solutions are considered a device and should only be placed in the extravascular space. Many programs will utilize a single solution for convection and use it also for diffusion which is within the constraints and law of the FDA.

Anticoagulation protocols have commonly been based around heparin. This is because heparin is being used commonly throughout the world for dialysis. Heparin-based protocols have a common source of a bolus, and then it continues the infusion of heparin targeting a clotting time or an activated clotting time of roughly twice normal at bedside. Other programs do not have the ability to do ACT at bedside; therefore they often will send it to the lab for a much slower turnaround time but targeting a partial thromboplastic time or a PTT of nearly twice normal.

In the latter part of the 1980s and early 1990s, Mehta and Ward identified the concept of citrate anticoagulation [7]. Work done by our group has identified in 2000 that citrate anticoagulation can be used easily in pediatrics [8]. Citrate utilizes calcium chelation, and by dropping the calcium out of the blood, it will actually have a low clotting circuit. Citrate has to occur by putting the citrate in post-patient prefilter, but the patient needs calcium back independent of the dialysis or the CRRT line in order to recover any complications from hypocalcemia.

Recent work by Deep et al. identified the use of prostacyclin used predominantly in liver failure patients as another source of anticoagulation [9].

The source of anticoagulation is a style of practice and should best be consistent within the individual program.

11.5 Prescriptions for CRRT

Historically blood flow rates for CRRT have been identified as 3–5 mL/kg/min. This historical data was done in the 1990s. The style of practice at present though suggests that blood flow rate is probably optimally based on the maximum blood flow rate that the vascular access will allow. The only exception to this is in patients with very high osmolar situations where one does not want to dialyze them rapidly in order to bring the osmos down slowly. So we will often begin at 5 mL/kg/min and adjust upward to as high as 8–10 mL/kg/min as long as our arterial access which is our vascular access is −150 or closer to 0 and our return access is +150 or closer to 0. This will give us the flexibility of maximum blood flow with less clotting.

Whether one does dialysis or replacement fluid, two papers should be brought to mind. One is Maxvold's paper that suggests that 2000/1.73 m^2/h will give us optimal clearance per urea, and the other paper is by Ronco et al. in the Lancet that identified 35–45 mL/kg/h on convective solutions [2, 10]. Roughly, Maxvold's 2–2.5 liters/1.73 m^2/hr is similar to Ronco's 40 mL/kg/h of convective clearance.

11.6 Anticoagulation Protocols

As mentioned, heparin is commonly used. Standard protocol would be bolusing the patient with 10–20 units/kg of unfractionated heparin and starting the child on roughly 10–20 units/kg/h of unfractionated heparin. One would then check a post-membrane ACT or activated clotting time to target an ACT of roughly 200, normal being 100. Risk of heparin use would include heparin-induced thrombocytopenia, which is a rare event in children, as well as bleeding in the patient.

Once heparin is discontinued, the half-life is roughly 4 h; therefore procedures need to be thought about in the context of having the patient systemically heparinized. Heparin can also be revered with protamine if necessary by knowing that the protamine has a shorter half-life than the heparin itself.

Citrate anticoagulation has become more common since the early 2000s. Citrate works by chelating the calcium by making the circuit hypocalcemic. Essentially, as

the blood comes out of the patient, the citrate mixes into the blood, and the circuit has a citrated or hypocalcemic circuit. One can then target the ionized calcium of the circuit post-membrane. One then needs to deliver calcium chloride or calcium gluconate back to the patient in order to rescue them from the citrate.

A standard protocol for citrate would be a blood flow rate of 5 mL/kg/min, a dialysate or replacement flow rate of roughly 2.5 L/1.73 msq/h, and a citrate rate of roughly 1.5 times the blood flow rate. Therefore, if the blood flow rate is at 100, the citrate rate goes at 150, and the calcium chloride (8 g/L saline) or calcium gluconate (23 g/L saline) can run at roughly 0.6–0.8 the blood flow rate. So essentially if the blood flow rate is 100, the citrate rate starts at 150 using ACDA, and the calcium replacement is roughly between 60 and 80/h.

One then targets post-membrane ionized calcium of roughly one-third physiologic in patients' ionized calcium back to physiologic. Therefore in our hospital, normal ionized calcium is 1.1–1.3 mmol/L, and one would adjust upward or downward the calcium back to the patient for that target. Using that same data, we would target our post-membrane ionized calcium levels to 0.25–0.5 in order to have a hypocalcemic circuit.

Prostacyclin is commonly used in the liver failure patient at King's Hospital in London. Their protocol is essentially starting the prostacyclin at no greater than 5–6 Ng/kg/h and adjusting upward.

Complications of heparin as mentioned are HIT as well as bleeding. Complications of citrate can be hypocalcemia or metabolic alkalosis secondary to the citrate metabolizing to bicarbonate [11]. Complications of prostacyclin can be vasodilatation and bleeding.

All these protocols need to be watched carefully at bedside in order to assure there are no complications.

11.7 Benefits of CRRT

In a patient who is quite inflamed and who is hyperthermic, CRRT will often allow for extracorporeal cooling as well as for clearance of solute. The standard protocol would allow for the patient to become hemodynamically stable and then slowly take fluid off over time.

From the practical setting if one starts someone on CRRT using pressor agents, the goal for the first 4–6 h should not be to take fluid off but to make the patient at lease fluid even. Once hemodynamics are under control, then one can slowly start targeting 1–2 mL/kg/h of net fluid off.

To be practical about this, if one has total IV fluids in roughly 300 mL/h that would include the calcium, the TPN, the meds, as well as the citrate in a 20 kg child, then your goal for the first 3–4 h is to have your net fluid removal at 300 to keep the child even. After a few hours of hemodynamic stability and if necessary turning up the norepinephrine or vasopressor agents, one can slowly start taking off 20–40 mL or roughly 1–2 mL/kg/h net fluid removal from that patient.

The temptation is to try to get off all the fluid in the first 24 h that one has accumulated over 5 days, but one has to understand that fluid will come off slowly and it is really based on hemodynamic situations.

It is important to have a high level of communication on medications and nutrition on patients on continuous dialysis. It is important to understand how much potassium is in the foods or in the TPN and how much potassium is in the dialysate and replacement in order to ensure there is no hyper or hypokalemia.

Many protocols have a phosphorous-free solution; therefore it is important to maximize phosphorous in TPN in order to prevent problems with hypophosphatemia.

11.8 Complications of CRRT

The first complication one has to think about is membrane reactions [12]. In the Baxter M60 and M100 series, this membrane does not react well to acidotic plasma. Blood bank blood has a pH of roughly 6.2–6.4. Therefore if one does a blood prime with this membrane because of a small child and a large extracorporeal circuit, then one will actually induce anaphylaxis as the blood goes back into the patient. Protocols by Brophy et al. as well as Hackbarth et al. have mitigated these side effects. Brophy protocol uses blood transfusions into the patient with a saline prime and this dump of a saline prime in order to maintain euvolemia and avoid having the acidotic plasma into the patient. That protocol still requires 3–4 meq/kg as initial bolus of bicarb to the patient to offset the metabolic acidosis.

Hackbarth's paper identifies dialyzing the blood containing circuit from a blood bank in order to pH normalize and cytokine normalize the patient. This protocol takes about an hour [13]. If one uses the Hackbarth's protocol, one realizes that citrate will be dialyzed off because of the sieving coefficient of 1 and heparin must be added to that circuit in order to avoid clotting.

Other complications are thermic control. In children less than 25 kg, hypothermia is a relatively common even and needs to be paid attention to in patients on extracorporeal therapy. In larger children thermic normalization may occur masking that of a fever. Therefore one will lose the normal findings of thermic changes if one is looking for fever. Many programs will do daily blood cultures routinely on patients on CRRT because of this mask effect.

Nutrition is lost during CRRT. In Maxvold's paper in 2000 in Critical Care Medicine, she pointed out that roughly 30% of amino acids are lost in CRRT [2]. In further workup by Zappitelli both as part of a consortium study and individual study, he pointed out that many programs do not target their protein to more than 2 g/kg/day and one probably needs to target to 4 g/kg/day on CRRT [14]. Further things that Zappitelli has identified are that water-soluble vitamins are easily cleared on CRRT and need to be given back to the patient.

Vasopressor agents are typically low protein-bound and low molecular weight; therefore they are cleared easily. Therefore epinephrine, norepinephrine, dopamine, and dobutamine are commonly cleared and may need to be adjusted upward in

patients as one initiates CRRT. It is not an unusual finding though that after a few hours of CRRT these vasopressor agents can be slowly turned down because of hemodynamic stability.

In summary, CRRT has become now the standard of care for renal replacement therapy in ICU patients with critical illness. In patients with sepsis, in patients with fluid overload, and in patients who are hypermetabolic, it is a common practice that can be done easily at bedside.

Programs have gone through learning curves but have markedly improved the outcome with the use of this therapy. Further, industry is improving access, solutions, protocols, as well as machinery to work with medical systems in order to overall improve healthcare.

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