CHAPTER 201

Technical Aspects of Pediatric Continuous Renal Replacement Therapy

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OBJECTIVES

This chapter will:

1. Outline the basic principles of continuous renal replacement therapy as they apply in pediatric patients.
2. Delineate the particular aspects of pediatric continuous renal replacement therapy that differ from adult continuous renal replacement therapy in terms of prescription, thermic control, access, and anticoagulation.
3. Review the concept of the blood priming–bradykinin-release phenomenon and its importance in infant continuous renal replacement therapy using polyacrylonitrile membranes.
4. Describe the methods and techniques available to avoid the bradykinin-release phenomenon.

Critically ill children with acute oliguric renal failure are a challenging group of patients to manage. These patients often are suited poorly to hemodialysis and peritoneal dialysis because of the tenuous nature of their hemodynamic and pulmonary status. Hemodialysis may remove fluid too quickly for the child to tolerate, and peritoneal dialysis may interfere with ventilation or venous return and is relatively inefficient for fluid and solute removal. Continuous renal replacement therapy (CRRT), by virtue of its continuous nature and the fine control of fluid balance it permits, often is suited ideally to management of the critically ill child who requires fluid or solute removal.

The basic principles of CRRT are similar for adults and for children. Applying these modalities in children, however, requires recognition of the unique technical aspects of pediatric CRRT, including weight-based fluid calculations for solutions, anticoagulation, blood flow, extracorporeal blood volume, blood priming, temperature control, access options, filter size, and properties.

Historically, arteriovenous modalities of CRRT were the standard methods used in practice.[1] Although this technique offers the advantage of simplicity, it poses considerable challenges for use in the pediatric population. The lower mean arterial blood pressure and higher hematocrit in children, as well as the higher resistance and flow limitations of smaller-diameter catheters, have limited the practical application of this technique in children. Another disadvantage of arteriovenous techniques is the requirement for venous and arterial access and the potential risk of limb ischemia from the arterial line.[2] The development of precision-volumetric fluid pumps with air leak detectors and pressure monitors, as well as pediatric-specific dialysis catheters, has made venovenous techniques preferable to arteriovenous methods. As a result, CRRT has become not only feasible but practicable in infants and children. In the past decade, more pediatric-appropriate–sized devices are emerging into the clinical setting. This includes specific pediatric renal

replacement platforms, such as the Newcastle Infant Dialysis Ultrafiltration System (NIDUS) and the Cardiac and Renal Pediatric Dialysis Emergency (CARPEDIEM), as well as filters, such as HF20 and UF500.[3–6]

PRESCRIPTION

The CRRT prescription in the pediatric patient follows the same principles as those in an adult patient, but with dosing based on weight or body surface area. The flow rate of dialysate (Q_d) or filter replacement fluid (Q_f) can be referred to as the *dialysis dose*. The optimal dialysis dose is not known, but Goldstein et al. provided preliminary and limited data consistent with the dialysis dose discussed by Ronco et al. of 2000 mL/hr/1.73 m^2 (35 mL/kg/hr).[7] Higher-dose CRRT (8000 mL/hr/1.73 m^2) may play a role in treatment of the child with hyperammonemia (values >400 umol/L). The maximum dialysis dose may be limited by the total ultrafiltration rate allowed by the filter. A higher dialysis dose also affects removal of medications, nutrition, and electrolytes, such as phosphorus.[8] In most children, a comparable dialysis dose rate of 2 to 4 L/hr/1.73 m^2 is readily achievable.

Regarding the modality of treatment, continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD) have been described with comparable solute clearances. Although CVVHD is primarily a diffusion-based therapy, some degree of convection will be present because of the prescribed net fluid balance and ongoing removal of intravenous fluids from the patient. Goldstein et al. described a mean contribution by convective clearance of 17% to the total dose of dialysis in patients on CVVHD.[9] Net patient fluid removal usually is between 0.5 and 2.0 mL/kg/hr, depending on patient volume status and hemodynamics. This rate is a direct extrapolation from work on hemodialysis by Donckerwolcke and Bunchman, who demonstrated this to be a safe and effective ultrafiltration rate in pediatric hemodialysis.[10] In the severely edematous and hemodynamically marginal patient, increasing pressor support to optimize mean arterial blood pressure may allow for more aggressive ultrafiltration in the initial 24 to 48 hours of CRRT, resulting in improved cardiac and pulmonary function as volume overload is reduced. The advancement in technology has allowed for improvement in the accuracy of fluid removal. A prospective study assessing the accuracy of a volumetric-based fluid measurement in CRRT using pediatric patients treated for an accumulated duration of 318 hours. They demonstrated that measured ultrafiltration (UF), using an independent scale, was different than the reported UF by the software/CRRT platform per patient over 48 to 112 hours per patient was −8 +/−1.7 mL/hr to 10 +/−1.8 mL/hr.[11] A key consideration is to consider the rapidity of fluid removal. Too rapid a fluid removal in the face of fluid overload (which may have taken days to achieve) may be a risk factor for extending real injury. It should be titrated to minimize the possibility of further extending renal injury by reducing effective circulating volume. Many leading centers are developing strategies and protocols to effect this very important component of the prescription.

BLOOD PRIMING

As in infant hemodialysis, the relationship of the patient's blood volume to the extracorporeal volume of the CRRT circuit must be taken into consideration. Patients weighing less than 10 kg have blood volumes of approximately 80 mL/kg, whereas larger children have blood volumes closer to 70 mL/kg. If the circuit volume is in excess of 10% of the patient's total blood volume, blood priming often becomes necessary.

Blood priming has its own set of potential problems. Banked blood has an inherently low pH and low ionized calcium concentration related to the presence of anticoagulant. In addition, high potassium content develops during prolonged storage. Another concern is that this low pH potentiates the bradykinin release when an AN-69 membrane is used. This unphysiologic blood prime potentially may cause further hemodynamic instability in the child during initiation of CRRT. A couple of different approaches can be used to prevent a serious decrease in the patient's hematocrit while avoiding hemodynamic instability.

One approach involves *direct transfusion of blood* into the patient at the time of dialysis initiation. The packed red cells obtained from most blood banks possess a high hematocrit of approximately 50% to 60% and should be reconstituted to a hematocrit of 30% to 35% with 0.9% saline or 5% albumin, to minimize risk of clotting the circuit. The blood can be infused directly through the venous port of the dialysis catheter. This infusion should occur simultaneously with initiation of CRRT, the circuitry for which has been primed with 0.9% normal saline. As the patient's blood infuses into the circuit from the arterial port, the primed saline is drained into a collection bag that has been connected temporarily to the venous end of the filter system. Once blood has reached the venous collection bag, then the CRRT machine is paused temporarily. The collection bag then is removed, and the venous end of the filter system is connected to the venous port of the dialysis catheter. Sodium bicarbonate boluses can be used to help minimize cardiac instability secondary to a "membrane reaction" during the initiation of CRRT.[12]

Another approach involves the *zero balance ultrafiltration* ("Z-BUF") technique.[13] The CRRT machine is primed according to the manufacturer's recommendations. Banked blood, diluted to an approximate hematocrit of 30% to 35% with 5% albumin, then is used to prime the circuit. Before the circuit is connected to the patient, the arterial and venous ends of the circuit are connected to each other, and the circuit is hemofiltered or dialyzed on itself using a physiologic solution of electrolytes such as Normocarb. Calcium chloride is added to the solution to improve the ionized calcium of the prime. The blood flow rate is set to 100 mL/min, and the circuit is then ultrafiltered at a rate of 2 L/hr for 15 to 20 minutes while a neutral circuit volume (zero balance) is maintained. Hemofiltration or hemodialysis of the circuit seems to be equally effective at normalizing pH and electrolyte content of the prime. This technique also may help blunt the initial bradykinin-type reaction seen with initiation of CRRT. Careful monitoring of the pressures in the circuit is essential. Once the blood has circulated for the allotted time, the machine is placed in pause, and the arterial and venous lines are connected to the patient. The circuit flow then is resumed.

A third option, which lessens the membrane hypersensitivity reaction, uses a different membrane, such as a polyarylethersulfone membrane. The larger HF 1000 can be used in small infants but requires careful attention to relative volume of circuit/filter compared with patient blood volume. The bradykinin-release phenomenon can be avoided with this filter, but potential complications of acidotic, hypocalcemic, and hyperkalemic blood products of the blood prime still must be addressed at the time of

startup. The use of an HF20 filter, which requires less, if any, blood prime at the time of startup of CRRT, minimizes these blood volume priming issues.[5]

TEMPERATURE CONTROL

Infants and small children have large body surface area-to-weight ratios. This feature, coupled with the significant amount of blood volume that resides in the extracorporeal circuit at any given time, places these small patients at substantial risk for the development of hypothermia. Simple techniques such as use of radiant warmers may help but often are not enough to maintain body temperature. With the new dialysis machines, line warmers may be available for purchase, such as the Prismaflow II (Gambro Renal Products, Lakewood, CO) or AstoFlo Plus (Stihler Electronic, Stuttgart, Germany). Other warming techniques have been adapted, such as heating pads, forced air warmers, or nondialysis blood line warmers. The drawback with these techniques is that they can excessively trigger the machine's alarm, resulting in inefficient dialysis. More importantly, these techniques can affect the CRRT machine's internal volumetric sensors and result in either too little or too much fluid removal from the patient as the dialysis machine attempts to maintain the programmed total fluid removal goal.

BLOOD FLOW

Blood flow rates for CRRT in children are related to patient size, which will dictate the size of the catheter used, but also are influenced by the vascular access pressures. Poiseuille's law,

$$Q = \frac{\pi r^4 P}{8\eta L}$$

describes the determinants of flow for newtonian fluids and provides the basis for understanding the potential limitations to blood flow in the pediatric CRRT circuit. The hematocrit in infants and particularly newborns is higher than in older children, which increases the viscosity (h), which will in turn resist flow. The ideal access for optimal flow is a short, large-bore catheter.[14] The catheter diameter size that can be used in young children is by far the greatest limitation to blood flow. A typical blood flow prescription for CVVHD is a rate of 3 to 5 mL/kg/min,[15] with higher blood flow rates (6 to 10 mL/kg/min) preferred in patients for whom anticoagulation is contraindicated or to optimize access pressures in the machine. Blood flow rates range from 10 to 50 mL/min in the infant weighing less than 5 kg, 30 to 85 mL/min in the child weighing 5 to 15 kg, 50 to 125 mL/min in the child weighing 16 to 25 kg, and often 100 to 250 mL/minute in the larger child.

ACCESS

The primary goal of vascular access for CRRT is to have adequate flow to provide optimal therapy with minimal interruption. A free-flowing catheter allows for more efficient hemofiltration and less tendency for circuit loss resulting from clotting. In general, a larger lumen size catheter is associated with longer filter life. The use of a catheter greater than 7-French had a 51% to 60% filter survival at 60 hours.[16] However, infants have small vessels, limiting catheter options. Westrope et al. published their use of either 5-Fr or 6.5-Fr double-lumen cannula catheters for access for 139 circuits with a median duration of 43 hours per circuit.[17] El Masri et al. published a small case series using 4-Fr single-lumen catheters. The mean circuit life was 55.2+/−30 hours.[18] In general, maintenance of a venous access pressure less than 200 mm Hg is desirable. Although recirculation is a common consideration with hemodialysis, it is less of an issue with continuous modalities. Dual-lumen catheters are sufficient for CRRT, but with the increased use of citrate anticoagulation, an additional separate central line port for calcium infusion may be necessary. A triple-lumen pediatric dialysis catheter to accommodate the extra port is available, but such catheters are limited to larger French sizes so as not to compromise blood flow by decreasing lumen size. The alternative is to establish a second central access, or calcium can be "Y-ed" into the return line of a double-lumen dialysis catheter. The latter is a less desirable solution because of the increased risk of clotting in the return port.

Access can be placed in the internal jugular, subclavian, or femoral vessels, with the choice based on patient size, local anatomy, hemostasis considerations, and operator comfort. Many nephrologists avoid the use of subclavian catheters with the corresponding risk of subclavian artery stenosis, because subsequent development of end-stage renal disease, as occurs in some patients, may necessitate creation of a fistula later. Any subtle kinking of the catheter between the first rib and the clavicle may affect access pressure and blood flow. The advantage of the internal jugular catheter is that it is independent of the patient's motion and appears to give adequate blood flow with minimal resistance. The internal jugular vein location is associated with longer filter life.[16,17] The disadvantages of the internal jugular catheter are the potential for pneumothorax or hemothorax and the risk of inadvertent carotid artery puncture at the time of placement. These risks may be minimized by the use of ultrasound imaging during venipuncture. The femoral line may carry a lower risk of complications at the time of placement and afford easier hemostasis compared with a "high line." However, the disadvantages are greater risk of infection; the potential for catheter kinking with flow problems in an awake, uncooperative patient; and the risk of thrombosis of the vein, complicating future renal transplantation.

Table 201.1 lists appropriate catheters for pediatric patients based on size.

SOLUTIONS

The type of modality to be used, diffusive or convective, must be considered in choosing the type of dialysis solution for CRRT. At present, the use of countercurrent dialysis solution versus filter replacement fluid or both is based on the local standard of care. The replacement and dialysis solutions used by adults also can be used by the pediatric population. Alternatively, pharmacy-prepared bicarbonate-based customized solutions may be used. The use of bicarbonate concentrations of 25 mEq/L in customized solutions will help maintain acid-base balance in most clinical situations. If acidosis must be treated aggressively, then a separate sodium bicarbonate drip (150 mEq/L) can be infused into the patient at 40 to 80 mL/m^2/hr. These custom solutions may be phosphorus based or calcium based. If calcium-depleted

TABLE 201.1

Suggested Vascular Access Devices for Use in Continuous Renal Replacement Therapy in Pediatric Patients

PATIENT SIZE	CATHETER SIZE	SITE OF INSERTION
Neonate	Single-lumen 5 Fr	Femoral artery or vein
	Dual-lumen 7.0 Fr	Internal/external jugular, subclavian, or femoral vein
3–6 kg	Dual-lumen 7.0 Fr	Internal/external jugular, subclavian, or femoral vein
	Triple-lumen 7.0 Fr	Internal/external jugular, subclavian, or femoral vein
6–30 kg	Dual-lumen 8.0 Fr	Internal/external jugular, subclavian, or femoral vein
>15 kg	Dual-lumen 9.0 Fr	Internal/external jugular, subclavian, or femoral vein
>30 kg	Dual-lumen 10.0 Fr	Internal/external jugular, subclavian, or femoral vein
>30 kg	Triple-lumen 12 Fr	Internal/external jugular, subclavian, or femoral vein

solutions are used, calcium must be infused into the patient. When phosphorus-depleted solutions are used, phosphorus must be given as a continuous infusion, starting at 0.5 to 2 mmol/kg per 24 hours. As an alternative, phosphate-based solutions can be used to minimize the loss of phosphorus. Most programs now use commercially available solutions that are approved by regulatory bodies. The use of custom solutions carries the risk of mixing errors and should be discouraged as standard practice.[19]

ANTICOAGULATION

Activation of the clotting cascade occurs in CRRT circuits as a result of contact of the circulating blood with artificial surfaces. A low blood flow rate, turbulent blood flow, and high hematocrit exacerbate this effect. Various methods of anticoagulation have been suggested for CRRT. Historically, either anticoagulation for CRRT was heparin based, or no anticoagulation was given, with use of intermittent NS flushes to maintain patency of the filter; however, multiple approaches now have been proposed and well established. Beyond using no anticoagulation with intermittent normal saline flushes, the two most common methods include heparin and citrate. Adult studies support a longer filter life span with use of citrate rather than heparin. Pediatric studies have demonstrated improved survival or indifference in filter life span between citrate and heparin.[20–22] Citrate anticoagulation has gained acceptance owing to its ease of administration and favorable patient side effect profile compared with heparin.[20,23] The individual circumstances of the patient dictate the anticoagulation regimen to be used.

The use of no anticoagulation has been shown repeatedly to be associated with a shorter circuit life.[20,24] This approach typically is used in a patient with fulminant disseminated intravascular coagulation (DIC). However, DIC may deplete anticoagulant factors as well, leading to a hypercoagulable state, which would benefit from regional anticoagulation to prevent the CRRT system from clotting. In addition, the use of fresh frozen plasma (FFP) in patients with underlying coagulopathies associated with liver failure is associated with a shorter filter life.[25]

Heparin is one option for anticoagulation. Heparin is infused in the CRRT system at a prefilter point and is used to anticoagulate the system. Anticoagulation is optimized by measuring a postfilter partial thromboplastin time (PTT) or an activated clotting time (ACT). Heparin monitoring targets an ACT between 180 and 220 seconds or the PTT between 1.5 and 2 times normal. This usually is accomplished by initially giving a 20- to 30-unit/kg bolus followed by a continuous intravenous infusion of 10 to 20 units/kg/hr of heparin. The advantage of heparin is its familiarity to medical personnel. The disadvantage of heparin is systemic anticoagulation with increased risk for bleeding. An additional risk is that of heparin-induced thrombocytopenia (HIT), which can increase the potential for bleeding and thrombosis. In many patients with multiorgan system failure (MOSF) necessitating renal replacement therapy, systemic heparinization may be a detriment and should be avoided.

Citrate anticoagulation has been used by adult programs since the 1990s and subsequently has been adopted by pediatric programs. Infusing citrate prefilter starting at 1.5 times the blood flow rate allows for regional anticoagulation of the CRRT system. Coagulation is a calcium-dependent process; therefore binding calcium minimizes clot formation in the circuit. Hypocalcemia is avoided by infusing calcium back into the patient through a central venous access separate from the CRRT system access. Citrate anticoagulation can be conceptualized as two processes. The first process is management of the citrate anticoagulant infusion in the circuit to target a postfilter ionized calcium between 0.25 and 0.40 mmol/L. The second process is the infusion of calcium chloride back into the patient, titrated to achieve a serum ionized calcium level between 1.10 and 1.30 mmol/L. Although many protocols exist, either a 4% trisodium citrate (TSC) solution or an ACD-A (Baxter Healthcare, Deerfield, IL) solution is available. An equimolar amount of Anticoagulant Citrate Dextrose Solution, Solution A (ACD-A) has a lower amount of citrate (67% TSC and 33% citric acid) compared with 4% TSC, resulting in a lower risk of metabolic acidosis and a lesser sodium load.

Side effects are more frequent in pediatric patients, necessitating close monitoring for development of increased anion gap metabolic acidosis, metabolic alkalosis, citrate toxicity, hypocalcemia, hyperglycemia, and hypernatremia. The metabolic acidosis and alkalosis often are related to citrate metabolism by the liver. Under normal circumstances, 1 mmol of citrate is metabolized into 3 mmol of bicarbonate, potentially resulting in a metabolic alkalosis. This complication used to be more common with use of higher-concentration bicarbonate-based replacement and dialysis solutions. Recently, the concentration of bicarbonate in these solutions has been decreased. Metabolic alkalosis can be corrected readily by decreasing the citrate infusion rate, increasing the dialysate rate to increase the clearance of citrate, or infusing saline as a filter replacement fluid (e.g., 0.9% NS, pH 5.4 to 5.8, infusing at 25% citrate rate in mL/hr) back to the patient. If the patient is on total parenteral nutrition, the chloride-to-acetate ratio also can be adjusted to help avoid alkalosis. Anion gap metabolic acidosis from citrate is rare and generally occurs only in the setting of extreme liver failure, in which citrate cannot be metabolized. The clearance rate of citrate (sieving coefficient of 0.88 to 1.00) is related to the clearance properties of the hemofilter (either convective or diffusive) and hepatic metabolism.[26]

This phenomenon, termed *citrate lock*, becomes apparent when the patient's total calcium (albumin-calcium complex + citrate-calcium complex + ionized calcium = total calcium) rises while the patient's ionized calcium is stable or dropping. Citrate levels can be measured, but results of these tests are not immediately available. A ratio of total calcium to ionized calcium greater than 2.5 supports a diagnosis of citrate lock. If this phenomenon occurs, the citrate infusion is discontinued for 30 minutes and reinitiated at 70% of the previous rate. Citrate can be used in hepatic insufficiency, but the initial rate of citrate infusion should be 50% to 70% of the usual starting rate and monitored in the same fashion as in patients with normal hepatic function. Blood flow also can be decreased, allowing for a proportional decrease in overall citrate infusion.

Hypocalcemia can be a life-threatening event, and judicious monitoring of the patient's ionized calcium concentration is imperative. Hyperglycemia is more frequent in smaller infants because of the glucose in the ACD-A solution (2.45 g/dL), and these patients may require adjustment in the dextrose concentration in the TPN and possibly a concomitant insulin infusion. Hypernatremia can occur but is less common with the use of ACD-A (220 mEq/L) solution compared with the 4% TSC solution (440 mEq/L). Vigilant monitoring of electrolytes can minimize the occurrence of metabolic derangements and allow for timely correction of any developing anomalies.

MEMBRANES

The hemofilters used in pediatric CRRT have chemical properties identical with those used in adults, and size and material options often are limited to those compatible with the CRRT machine being used. The patient's body surface area must be considered in selecting a filter. The biocompatibility of hemofilters and hemodialysis membranes has improved in recent decades. The AN-69 membrane (polyacrylonitrile membrane) is associated with the *bradykinin-release phenomenon*, wherein hypotension develops on initiation of CRRT, primarily in the smaller child.[12,27] The use of a polyarylethersulfone membrane, such as the HF20 (Baxter), or the polysulfone-based UF 500 filter set (Baxter) decreases the body weight threshold for those patients needing a blood prime and eliminates the bradykinin reaction.[5,6]

CONCLUSION

CRRT affords the critically ill pediatric patient an efficient, reliable, and safe form of renal replacement therapy in the setting of appropriate monitoring. CRRT use is expanding within the pediatric critical care community as the technology has become better adapted to the pediatric patient. The proper timing of initiation of therapy, the most appropriate dialysate dose and modality for particular disease processes, and effect on outcome continue to be studied. Once the determinants of survival for critically ill infants and children with acute renal failure and metabolic disorders are better established, it is likely that CRRT will assume a greater role in the overall approach to treatment. The continued cooperation of manufacturers and nephrologists, intensivists, and other members of the healthcare team is mandatory to maximize the usefulness of CRRT in the pediatric patient.

key points

1. Continuous renal replacement therapy, by virtue of its continuous nature and ability to finely control fluid balance, ideally is suited to and the preferred modality for the critically ill child requiring fluid or solute removal.
2. Recognition of the unique technical aspects of pediatric continuous renal replacement therapy, including weight-based fluid calculations for solutions, anticoagulation, blood flow, extracorporeal blood volume, blood priming, temperature control, access options, filter size, and properties, is essential.
3. Patients weighing less than 10 kg have blood volumes of approximately 80 mL/kg, whereas larger children have blood volumes closer to 70 mL/kg. If the circuit volume is in excess of 10% of the patient's total blood volume, blood priming often becomes necessary. The bradykinin-release phenomenon with an AN9 membrane may occur in the face of blood priming and must be anticipated.
4. Infants and small children have large body surface area-to-weight ratios. This, coupled with the significant blood volume residing in the extracorporeal circuit at any given time, places infants and children at substantial risk for developing hypothermia.
5. Vascular access for pediatric continuous renal replacement therapy is the key to successful therapy. Adequate flow rates provide optimal therapy with minimal interruption or coagulation issues and maximal staff satisfaction.

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