CHAPTER 209

Techniques and Machines for Pediatric Renal Replacement Therapy

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OBJECTIVES

This chapter will:

1. Describe the current modalities currently available for pediatric continuous renal replacement therapy, giving context to the differences and indications for peritoneal dialysis and extracorporeal dialysis.
2. Present some general rules to follow to rationally prescribe acute dialysis in children, considering that very little literature is available in this field.
3. Provide some recent updates on recent pediatric monitors described for the specific care of children with severe acute kidney injury.

Typically, pediatric continuous renal replacement therapy (pCRRT) is prescribed according to local expertise and without the use of any specific recommendation. The prospective pCRRT (ppCRRT) is the main source of observational information on pCRRT practice (in the United States), and it is the only reliable published experience derived from hundreds of treated children.[1] The ppCRRT Registry was founded in 2001 and enrolled 13 pediatric centers in the United States. Comprehensive data on 344 patients with ages ranging from 1 day to 25 years and weights from 1.3 kg to 160 kg are currently available. Eleven different primary diagnoses were described in the registry, including sepsis, stem cell transplantation, cardiac disease, liver disease, and oncologic diagnoses.[1] The mortality of these patients

is globally around 42%, but it significantly increases in patients with multiple organ dysfunction syndrome and fluid overload and those weighing less than 10 kg or receiving stem cell transplantation.[1] The registry also focused on several technical aspects such as position and size of dialysis catheters, the association with filter lifespan, or anticoagulation. However, several issues remain controversial: (1) optimal timing of pCRRT is a matter of ongoing debate (although it is clear that it should be considered before fluid is accumulated in children); (2) the dose and level of adequate dialytic delivery in children (including the significant differences present between neonates and older children); (3) long-term outcomes of children with acute kidney injury (AKI) undergoing continuous renal replacement therapy (CRRT) require urgent analysis because it is emerging that patients surviving CRRT often have reduced renal reserve and do not achieve restoration of premorbid renal function.

MODALITIES

Peritoneal dialysis (PD) and CRRT are the modalities most frequently used in infants, so far. PD generally is applied in neonates, unless specific contraindications are present (i.e., peritonitis, abdominal masses, or bleeding).[7] PD uses peritoneum as a semipermeable membrane to achieve solute diffusion and plasma water ultrafiltration. Dialysate is infused through an abdominal catheter, and after a period of so-called "dwell time," waste solution is drained from the abdomen. Typically, to avoid excessive intraabdominal pressure rise during dialysis, especially in high-risk patients (i.e., after cardiac surgery), a "low-flow" prescription of 10 mL/kg dialysate is delivered.[8] This is also useful to prevent hemodynamic instability secondary to reduced venous return by inferior vena cava compression. Dwell times may vary from 10 to 30 minutes according to the needed dose. As a general rule, dialysate tonicity (provided by glucose concentration, 1.36% to 2.5%) is responsible for peritoneal net ultrafiltration. PD is simple and safe, it can be administered without dedicated technology, and a steep learning curve is not needed; it typically is administered by ICU nurses without specific expertise with dialysis. Nonetheless, PD is certainly limited by a lack of efficiency; water removal appears to be particularly difficult in selected patients, which is a major issue in severely overloaded patients. Other important flaws of PD use are the possibility of interstitial fluid accumulation in case of suboptimal dialysate drainage, hyperglycemia, and risk of peritoneal infection. PD obviously is contraindicated in patients with recent abdominal surgery or abdominal bleeding.[7] As a matter of fact, PD frequently is applied to post–cardiac surgery patients, and its main advantage is to be started in a very early phase of oligoanuria or fluid retention. PD recently has been shown to be associated with improved survival in a large cohort of post–cardiac surgery neonates if started in the first 24 postoperative hours when compared with patients who received PD after the second postoperative day.[9]

As an alternative to PD, extracorporeal dialysis in children can be conducted with intermittent hemodialysis and CRRT. These theoretically can be delivered as hemofiltration, hemodialysis, or hemodiafiltration.[10] The choice of dialysis modality may be influenced by several factors, including local expertise and preferences, the required dialytic targets, and the clinical picture of the treated baby. Intermittent dialysis may not be well tolerated in hemodynamically unstable critically ill infants because of its rapid rate of solute clearance and net fluid removal. These children generally are treated by CRRT that reasonably provides effective fluid and solute elimination added to proinflammatory mediators' removal. Circuits with reduced priming volume together with monitors providing an extremely accurate fluid balance are still not commercially available.[10] Current literature, however, focused on the possibility of treating patients' fluid overload at dialysis start. It is more than clear that at the time of dialysis initiation, survivors tend to have less fluid overload than nonsurvivors, especially in the setting of multiple organ dysfunction syndrome (MODS).[11] Differently from the adult patients in whom dialysis dose may play a key role, adequate water content in small children is the main independent predictor of outcome.

With regard to the CRRT modality, the solute clearance in three modes of CRRT at the low blood flow rates typically used in pediatric patients were compared: postdilution continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD) gave nearly equivalent clearances.[12] At the low blood flow rates used in pediatric patients, which raise concerns about high filtration fractions during postdilution CVVH causing excessive hemoconcentration and filter clotting, CVVHD appeared to be the optimal modality for maximizing clearance of small solutes during CRRT. Nevertheless, the advantages of hemofiltration with respect to hemodialysis should be taken into consideration; medium and higher molecular weight solutes are significantly better removed by convective modalities.[13] In light of these thoughts, predilution hemofiltration may be the preferred modality in pediatric patients.

PRESCRIPTION

It may seem easy to understand that children should be considered a peculiar cohort of patients undergoing CRRT.[14] In fact, not only the (multidimensional) prescription will have to be adapted to pediatric patients' clinical picture but also to different physiologic conditions existing at different pediatric ages.[15] Far beyond the scope of this chapter, children deeply change their body composition from birth to the adult age; essentially, together with babies' growth, total body water (TBW) (roughly, urea volume of distribution) is progressively reduced, muscle mass increased, and many organs (including heart, lungs, and kidneys) require several days to achieve full maturity and adults' normal function.[15] In this light it has been speculated that children (especially infants and neonates) may require a relatively higher dialytic dose with respect to adult patients.[14] In other words, it is clinically plausible that the dose of a continuous therapy in a pediatric patient should be proportioned inversely to his or her age. To administer, for example, 35 mL/kg/hr (the high range efficiency currently recommended in adults) in a 3-kg neonate with a TBW of 2.4 L for 24 hours would result in a Kt/V of 1.05 (whereas this implies a value of 1.2 in an adult patient).[14] The adequate pediatric dialytic efficacy has not been established, so far, but some authors have proposed to index pediatric CRRT (pCRRT) prescription on body surface area (BSA) instead of on body weight. The proposed pediatric dose of 2 L/hr/1.73 m^2 would correspond to about 35 mL/kg/hr in an adult patient, weighing 70 kg and with a BSA of 2 m^2 (www.pcrrt.com).[16] Interestingly, though, the efficacy of this prescription correctly displays an inverse relationship with the decrease of patient age, because weight and BSA are not related linearly. Weight physiologically increases from neonatal to adult age by

about 20 to 25 times and the BSA by only 10. From an operational point of view, this means that provided the same prescription of 2 L/hr/1.73 m^2, neonates and infants are treated 1.5 to 3 times more intensely than an adult patient (or if the prescription was 35 mL/kg/hr).

Although clinically reasonable, because of the different clinical features of small children and adults, and the need to reach a higher efficiency to cope with the increased solutes' volume of distribution, still the "BSA method" may prescribe systematically a "high dialytic dose" to pediatric patients. Currently, mostly all studies prescribing higher dose to adult patients (whether septic or not) have failed to show an increased survival. No clinical observation (prospective or retrospective) has been carried out in the pediatric setting to verify (upon surrogate markers such as creatinine and urea) what is the clinical effect of one dose versus another. Furthermore, high dialytic doses repeatedly have shown potential severe drawbacks in the adult and pediatric setting: small elements such as amino acids, phosphate, antibiotics, and brain natriuretic peptide are lost. High doses require high blood flow rates and big double lumen venous catheters to run the treatments that often may limit CRRT delivery in children. This lack of substantial evidence on pCRRT prescription, associated with the increased utilization and application of extracorporeal dialysis to critically ill patients, has caused the complete absence in scientific literature of any reliable standard treatment that could be used as a reference for clinical evaluation of alternative approaches.

Studies on the Dose of Pediatric Continuous Renal Replacement Therapy

We recently conducted a systematic review on pCRRT dose with the intention of exploring published literature in this field.[14] Overall, 66 papers were obtained initially. After further exclusion of reviews and case reports, 39 papers were selected. Interestingly, 13 studies were excluded because no information on dialytic prescription, CRRT dose, blood flow rate, or machines setup was provided. Of the remaining 26 studies, 11 were retrospective, 4 were small case series presenting less than 10 patients, and 9 were prospective observational data collection (7 of which coming only from 2 authors' groups).[14] Overall 1773 patients were described, even if significant overlap among different papers' data is likely. Four papers only verified if delivered dialytic doses were significantly different in surviving and nonsurviving pCRRT patients[17–20]; these were all retrospective studies. No randomized controlled trial or prospective observations on patients receiving different doses has ever been attempted to search for outcome benefits in children. Surprisingly, of the reviewed papers, 5 over 25 did not explicitly report the delivered dialytic dose in results or average prescription in methodology, and the authors chose to only describe blood flow rates. However, the reported dosage ranged from less than 1000 to more than 4000 L/hr/1.73 m^2 (excluding inborn errors of metabolism) and from 20 to 150 mL/kg/hr. All modalities were described without any clear preference among different authors among hemofiltration, hemodialysis, or hemodiafiltration. Interestingly, only one study systematically analyzed the effect of pCRRT dose over time on serum markers such as creatinine and urea, and it showed that even a relatively small dose (35 mL/kg/hr) was effective in controlling such molecules' blood levels.[21] Another study analyzed the significant loss of amino acids during CRRT[22] occurring at the standard prescription of 2 L/hr/1.73 m^2.

TECHNICAL ASPECTS OF PEDIACTRIC CONTINUOUS RENAL REPLACEMENT THERAPY

During the last decade CRRT technology has improved significantly. We are facing the release into the market of the fourth generation of dialytic monitors, equipped with multiple safety features and control algorithms, coupled with extreme accuracy of pumps and scales. "Standard" CRRT is today a safe practice.[23] However, pCRRT cannot be considered as part of "standard" routine. On one hand, CRRT machines designed for adults have been equipped with pediatric circuits and lines demonstrating an attempt to comply with the specific requirements of the very small patient. With this in mind, we can state reasonably that most machines, if not all, are used off label in patients below 10 kg. This is due mainly to the small number of pediatric cases that eventually causes the limited interest of industries to develop a fully dedicated device. Furthermore, manufacturers of dialysis or CRRT machines do not perform specific tests for treatments in patients smaller than 10 to 15 kg, and safety features in these patients are not created specifically. Legal concerns may arise when operators decide to prescribe these therapies. In current practice, clinical application of dialysis equipment to pediatric patients is adapted substantially to smaller patients with great concerns about outcomes and side effects of such extracorporeal therapy. In these conditions, smaller patients do not rely on the same extremely accurate delivery of therapy as adults, especially as far as fluid balance is concerned. In this context, the Cardio-Renal, Pediatric Dialysis Emergency Machine (CARPEDIEM) was designed in Vicenza back in 2011 to create the basis for the conception of a renal replacement therapy equipment specifically dedicated to newborns and small infants with a weight range of 2.0 to 9.9 kg and with an approximate body surface area from 0.15 to 0.5 m^2. In these patients the total blood volume ranges from less than 200 mL to about 1 L, meaning that total body water content varies from 1 to 5 L. In such conditions, circuits priming volumes should be reduced to a minimum level, and roller pumps should be able to run at slow speed, maintaining a good level of accuracy together with the possibility of warranting lines integrity (small roller pumps running small tubes are expected to cause a quick decline in their performance).[24] The first patients currently are being treated and relevant results recently have been published[25] (Fig. 209.1). As a confirmation of the growing interest of research in this field, another pediatric monitor for continuous dialysis, the Nidus (Newcastle infant dialysis and ultrafiltration system) has been described recently. The Nidus[26] is an original machine driven by syringes instead of roller pumps, providing single needle vascular access. The circuit volume is only 13 mL and, very interestingly, there is no need for circuit blood-priming. Recently, Coulthard et al. treated 10 babies weighing between 1.8 and 5.9 kg and reported satisfactory machine performance as far as adequacy of clearance and machine accuracy are concerned.[26] Another interesting report on specific pediatric technology concerned the application of the Aquadex machine for small infants' hemofiltration.[21] The authors conducted about 100 CVVH sessions in 12 infants (median weight 3.4 kg) by using an adult adopted technology that features a smallest priming volume (about 30 mL), but it is conceived for slow continuous ultrafiltration. To deliver replacement solution the authors had to apply an external nonintegrated pump to the system. The described results are encouraging and the

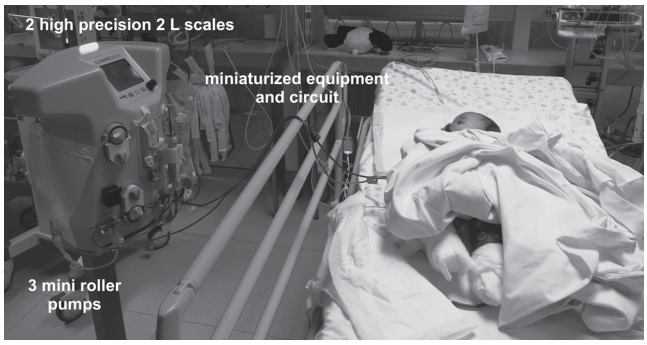

FIGURE 209.1 The CARPEDIEM machine treating a small baby in the pediatric intensive care unit. The monitor features a miniaturized circuit, three small roller pumps (for blood flow, effluent flow, and hemofiltration or dialysate flow), and two scales carrying 2 L bags (one for hemofiltration/dialysate solution and one for effluent).

technology feasible for children. The accuracy and safety of a peristaltic pump for replacement delivery in a nonexpert environment remain to be ascertained.[21]

CONCLUSION

Severe AKI requiring RRT is a severe clinical condition burdened by death in more than 50% of treated patients. To dialyze critically ill children is further complicated by several technical issues. Early diagnosis, prevention, conservative measures, and novel technology are part of a multidimensional approach to dialytic adequacy in critically ill children. The outcomes may vary significantly, depending on the underlying disease, the severity of illness, the time of intervention, and the institutional expertise and practice. Several aspects still require significant research and are burdened by great uncertainty. First of all comes pCRRT timing. So far, outcomes of critically ill children requiring CRRT are poor and strongly need a strategy for improvement. Long-term outcomes of survivors, especially those who do not completely recover baseline function and younger patients, potentially are hampered by the threat of chronic renal dysfunction. In this scenario, new technologic advances such as miniaturized circuits and membranes, accurate CRRT machines, and effective prescription schedules, promise to help the clinician in improving quality of treatment.

Key Points

1. Occurrence of severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) in children is increasing.
2. Running an extracorporeal CRRT in a small baby is a clinical and technical challenge.
3. Several aspects of pediatric CRRT (timing, prescription, technology) currently have to be addressed to optimize the unfortunately poor short-term outcomes of these patients.
4. New machines will surely concur to the process of improved management of children with severe AKI.

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A complete reference list can be found online at ExpertConsult.com.

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