Hemodialysis and Continuous Renal Replacement Therapy

17

Megan M. Lo and Timothy E. Bunchman

Core Messages

- Renal replacement therapy through vascular means in neonates is significantly more complicated than in older patients. A higher level of vigilance and attention to detail with staff familiar with neonates and neonatal hemodialysis are necessary.
- Vascular access is one of the most important components of hemodialysis and continuous renal replacement therapy success. Placement in the right internal jugular vein is preferred for flow and recirculation concerns.
- Because most of the equipment and supplies have been developed for larger patients, clearance, anticoagulation, ultrafiltration, and blood flow are different for neonates.
- Data on neonatal vascular renal replacement therapy remains limited, and outcomes remain guarded for these smallest of patients who need to start dialysis at such an early age.

Case Vignette

You are called to the NICU for a 32-week, 1.7-kg premature male who had oligohydramnios and was receiving amnioinfusion therapy in utero. The baby is intubated and respiratory status is stabilized on low ventilation settings. However, he is anuric and renal ultrasound shows bilateral renal agenesis. The family would like to proceed with all possible courses of action to save their baby. Despite his small size, peritoneal dialysis is initiated and proceeds with multiple complications. After 2 months, he has peritoneal membrane failure and is changed to hemodialysis. A temporary 7-French left subclavian catheter is used emergently due to the presence of a tunneled right internal jugular Broviac. Blood primes are used with frequent monitoring of vital signs with dopamine needed to

M.M. Lo (✉)
Department of Pediatric Nephrology,
VCU School of Medicine, McGuire Hall Annex 1112
East Clay St., Richmond, VA 23298, USA
e-mail: mlo@mcvh-vcu.edu

T.E. Bunchman
Department of Pediatric Nephrology,
Children's Hospital of Richmond,
VCU School of Medicine, Sanger Hall 12-024C1101
East Marshall St, 980498,
Richmond, VA 23298, USA
e-mail: tbunchman@mcvh-vcu.edu

A.S. Chishti et al. (eds.), *Kidney and Urinary Tract Diseases in the Newborn*,
DOI 10.1007/978-3-642-39988-6_17, © Springer-Verlag Berlin Heidelberg 2014

support blood pressure. Dialysis is only used for the first hour of each session with ultrafiltration only for the remainder due to the high clearance rates on a small baby. Ativan boluses are used to improve fluid removal. Flow and clotting complications occur with his subclavian catheter, and his Broviac is exchanged for a tunneled 8-French hemodialysis catheter. Chronic hemodialysis proceeds until the patient is transplanted with a kidney from his mother.

17.1 Introduction

Neonatal hemodialysis (HD) for acute or chronic renal failure is a rare but important component of pediatric nephrological care. The needs for dialysis in infants are usually related to three different indications. Cause can be related to end-stage renal disease (ESRD), acute kidney injury (AKI), and finally inborn error of metabolism [2]. In larger children and rarely in infants, the other indication for renal replacement therapy is intoxication [9]. Because of the rarity of this cause in neonates, it will not be addressed in this chapter.

Data from the North American Pediatric Renal Trials and Collaborative Studies database (NAPRTCS) estimates the incidence of dialysis-treated (all modalities) neonatal ESRD as 0.32 cases per 100,000 live births [13]. This number probably underestimates the total, however, as NAPRTCS is a voluntary reporting system and patients in smaller centers have been missed. Alternatively, larger centers may be too busy to report on all incidences. The general trend over time has been to move to peritoneal dialysis (PD) due to access and feasibility concerns. However, certain situations still require the use of hemodialysis such as the presence of a hostile abdomen or the need for rapid clearance. These smallest of patients suffer from a lack of appropriately sized equipment (partially dictated by physics) as well as increased risk of complications. Their management, therefore, is different from that of a general pediatric dialysis patient. This chapter will not focus on peritoneal dialysis, for it is discussed in another chapter, but will address the use of extracorporeal therapies including hemodialysis and the use of continuous renal replacement therapy (CRRT).

17.2 Indications

Very few neonatal series exist regarding dialysis at all and hemodialysis specifically. However, the therapy has been used in this age group at least as far back as the 1970s. Initial indications were mostly for acute kidney injury. All five patients under 1 month of age had "medical ATN" (acute tubular necrosis) as the indication for hemodialysis in a single-center analysis from 1978 [25]. Out of ten patients dialyzed starting at age 13 weeks at the oldest, six patients had indications of "acute renal failure," mostly from sepsis and one for posttransplantation [26].

In more recent reports, indications for starting dialysis varied by study, at least partially a consequence of variable practice preferences and type of referral center. Infants were more likely to have dysplasia/hypoplasia (7/20 patients) compared to older children (up to age 36 months at the start of dialysis) who tended to have diffuse mesangial sclerosis (7/14 patients). Infants were more likely to start with PD (16/20 versus 4/14 patients age 13–36 months). Nine of those 16 transitioned to HD due to PD failure [20]. The preference for non-HD in this age group was supported by NAPRTCS data. Hemodialysis was less likely to be the chosen modality, occurring in 2.1 % of patients compared to 9.5 % of patients up to 24 months of age. The most likely indication for neonatal dialysis of any modality was dysplasia (37 %) [13].

In contrast, in a series of 33 patients between 1980 and 1991, 18 were dialyzed for acute kidney injury, seven had primary renal disease, and eight had hyperammonemia. AKI was associated with the need for extracorporeal membrane oxygenation therapy (11 patients) or with hemodynamic compromise from other causes [35]. Other studies have also shown that as much as 25 % of infants will have some degree of AKI in the neonatal intensive care unit [1]. AKI in this population is

often related to a catastrophic illness of sepsis or hypoxia-ischemia. Most of these infants do not need to undergo renal replacement therapy.

In terms of ESRD, the etiology in infants is often related to congenital renal abnormalities. This can run the gamut of obstructive uropathy, polycystic kidney disease, (either recessive or dominant), or the rarer forms of nephrotic syndrome. Furthermore, children who suffer catastrophic illness in the first few days of life from hypoxia-ischemia can develop cortical necrosis and loss of kidney function, resulting in AKI-induced need for chronic dialysis.

Hyperammonemia is a definitive indication for hemodialysis as this modality has been shown to be more rapidly effective in inborn errors of metabolism [16, 37]. Additional steps include starting a glucose infusion while planning management with genetics. These are classically infants who show up between day two and five of life who have cardiovascular collapse associated with a significant metabolic acidosis, Kussmaul ventilation, and evidence of significantly high and lethal levels of ammonia. Time is of the essence as prolonged exposure to high ammonium levels leads to prolonged neurological damage [31]. Therefore, hemodialysis and CRRT by CVVHD or CAVHD are first-line modalities unless limited by surgical or dialysis nursing expertise locally. If HD is not available immediately, PD is a reasonable alternative while further medical interventions are proceeding to decrease ammonium production.

Another case report included a 1,220-g ex-28-week-gestational-age infant successfully treated with hemodialysis for theophylline toxicity at 8 days of life. The patient had seizures with a serum level of 82 mg/L at the start of dialysis and decreased to 11.8 mg/L after 2 h, with resolution of seizure activity 15 min after starting [22].

17.3 Location of Therapy

Initiation and performance of hemodialysis or CRRT must occur where the physician, hemodialysis nurses, and support staff have the experience and expertise to safely manage these patients. Rapid interventions such as fluid boluses, code drugs, and accessibility of the pediatric nephrologist, critical care physician, anesthesia, and ancillary staff at bedside are critical. Regardless of the location chosen to perform the procedures, consistency is vital to progressive success. Many programs treat less than 10–15 children per year on CRRT. Therefore, the lack of ongoing experience makes this a relatively higher risk and higher anxiety-producing maneuver. With these considerations, although the patients are neonates, due to the infrequent nature of these procedures, the pediatric (rather than neonatal) intensive care unit may be the better choice dialysis/CRRT site to concentrate incidences. Wherever the chosen venue, all neonatal sessions should be performed there, with the patients taken care of by a core group of intensive care and dialysis/CRRT nurses. This will allow the core group of caregivers to develop adequate experience with these patients and situations that are relatively few and far between.

17.4 Vascular Access

Access is one of the most important factors to dialysis success. If the initial catheter location fails, then that major blood vessel may become unusable for future access attempts. Therefore, it is very important to obtain the highest blood flow possible, lest the attempt be wasted. Given that flow is proportional to radius to the 4th power, an 8-French double-lumen catheter would have a per-lumen flow rate approximately three times higher than a 6-French double lumen of the same length. In a study of CRRT patients, 5-French catheters had significantly decreased survival times compared to any other catheter. Although not specified, these were presumably double-lumen catheters for CRRT. Internal jugular placement conferred a significant advantage [23]. Catheter tips ending in the right atrium tended to demonstrate more consistent blood flow rates [35]. Care must be taken to avoid placements which are too deep and risk arrhythmias. Therefore, the patient should start with a 7- to 8-French catheter at a minimum, placed in the

Table 17.1 Possible hemodialysis catheters for neonates

Company	Size (Fr)	Length (cm)	Cuffed	Design	Material
Medcomp: Soft-Line	7	7, 10	No	Coaxial	Polyurethane
Soft-Line	9	12, 15	No	Coaxial	Polyurethane
Hemo-Cath ST	8	12	No	Coaxial	Silicone
DuoFlow	9	12, 15	No	Coaxial	Polyurethane
Hemo-Cath LT	8	18	Yes	End ports	Silicone
Pediatric Split Cath	10	15	Yes	Split offset	Polyurethane
Mahurkar	8	9, 12, 15	No	Double-D	Polyurethane
Arrow	8	11	No	Coaxial	Polyurethane

Not all catheters may be available in all areas. In general a catheter at least 8Fr in size will provide better flow. Shorter lengths also reduce resistance as long as tip reaches superior vena cava-atrial junction at least. Cuff presence may be determined by expected length of treatment needed, although cuffed catheters may provide improved line survival (See text)

right internal jugular vein, and end just inside the atrium for the best chance at long-term success. Femoral catheters should be avoided if possible due to decreased longevity [23] and to prevent the risk to future transplant vascular access sites.

Uncuffed catheters may be used in the acute setting; however the duration of therapy is not always immediately obvious. Neonates pose a particular challenge with their relatively short necks and frequent manipulations in an intensive care setting. Therefore, a cuffed catheter may be the correct choice even for what appears to be an AKI. In a review of patients who were dialyzed (by HD alone or with PD) for at least 6 months, cuffed catheters lasted 5.7 ± 2.2 months versus only 1.3 ± 0.8 months for uncuffed catheters [20]. Medcomp (Harleysville, PA) and Cook Critical Care (Bloomington, IN) both make 7-French 10-cm uncuffed catheters. This catheter is still longer than these patients need, but shorter catheters are not commonly available. Medcomp also makes 8-French 12- and 18-cm catheters that could be used in children as small as 2.5–3 k as a source of chronic vascular access. Table 17.1 summarizes the catheters which are currently available.

The size of neonatal vessels relative to that of the cannulas, in conjunction with low blood flows, makes recirculation more likely. Mechanistically, using a double-lumen catheter with a distal end-hole return and a proximal side-hole arterial draw would appear to reduce this problem. Single-lumen access (using a Y-connector near the access point) has been proposed as an option to increase the available flow rate. A variable amount of recirculation (depending on the design of the tubing) will occur distal to the Y-connector. Limitations of this method include the need for a machine compatible with single-needle dialysis.

Two separate 5-French catheters in the umbilical veins have been used previously but have shown a higher complication rate, most likely due to the pliability of the catheters (personal experience).

Shunts and fistulas are not an option for a variety of reasons, but there was a report on three infants, with a maximum longevity of 60 days [26].

Lastly, there is no established cutoff on minimal size criteria for initiating HD, this decision depending more upon the patient's comorbidities, available surgical expertise, and familiarity of the dialysis staff. Babies as small as 1.6 kg have been reported although not with good outcomes [26].

Between treatments, the catheter should be closed with heparin (1,000 units/mL), 4 % sodium citrate, or tissue plasminogen activator (TPA, 1 mg/mL) to maintain patency [30]. Our practice is to reserve TPA for signs of catheter malfunction. The volume of the solutions is equal to the priming volume of each catheter lumen, which is often written on the hub. Only experienced dialysis personnel who know to withdraw

the packing solution first, rather than flush the lines as other central lines are treated, should access these dialysis catheters under sterile conditions. Pushing these solutions into a neonate could have severe consequences. Some programs suggest "overfilling" the lumens by adding an additional 0.1–0.2 mL of the packing solution. However, we do not recommend this practice as this procedure could result in delivery of a significant drug dose unintentionally.

The dialysis catheter should not be used for any purposes other than dialysis to minimize infection or clotting complications that could impair proper blood flow. Only dialysis nurses or nephrologists familiar with these lines should access them.

17.5 Specifics of Hemodialysis

17.5.1 Dialysis Filters and Machines

A dialysis machine that accounts for the special needs of small infant patients is preferable and would include features such as proper pump speeds for small circuit lines and very tight tolerances on ultrafiltration errors. The latter concern can be a difference of as much as 50 mL/h, leading to possibly 150 mL over a 3-h treatment [6]. For a 3-kg infant, this would be 5 % difference and even larger in smaller patients. Volumetric ultrafiltration monitoring systems (which continuously monitor the actual volume removed rather than relying on calculated or expected volumes) reduce this error. All sources of fluid input (parenteral nutrition, intravenous fluids, gastric feeds, medications, etc.) and output (urine, nasogastric suction, diarrhea if very watery, surgical drains, blood draws, etc.) must be taken into account. The patient must be weighed using the same scale with as little external equipment, bedding, and clothing as possible just before and after each dialysis session. One must keep in mind that even "minimum UF" can be 100 ml/h, a significant amount for a baby.

The smallest artificial kidney currently available is the Gambro Polyflux 2H and has a priming volume of 17 mL and 0.2-m^2 triple-layer polymer surface; this product is not approved in the USA, however. The smallest one available in the USA is the Fresenius F3 and has a 24-mL priming volume with 0.4-m^2 surface area for contact using polysulfone fibers. These small-volume dialyzers are not high flux and rightly should not be, as the small ultrafiltration rates could lead to backflow of dialysate. The lowest priming volume for tubing is still 32 mL giving a total volume of 56 mL. At 80-mL/kg blood volume and a maximum of 10 % of this blood in the extracorporeal space, this means that the smallest patient on hemodialysis who would not need a blood prime would be 7 kg, which is well outside of the neonatal range. Therefore, to minimize antigen exposure from the blood primes, 1 unit of donor blood should be split and leukoreduced. The blood should be diluted from the baseline hematocrit of about 70–35 %. Depending on the storage time of the blood, significant amounts of potassium may be contained as well. Unless the patient needs to be transfused, the patient should not receive a "blood return" at the end of dialysis as this would give the patient the excess volume and red cells. If the transfusion is desired, it must be returned slowly (5–10 mL/min maximum) with close monitoring of hemodynamic changes from a rapid volume infusion. Development of a gallop rhythm warrants immediate cessation of blood flow and possibly removal of the excess volume [15]. The saline used to flush the blood out of the line can also constitute a large volume relative to the patient which must be accounted for in the ultrafiltration target. An air return, with a slow blood pump rate drawing in air instead of saline, would decrease the volume infusion, but extreme care must be taken to prevent air emboli.

Other considerations in neonates include settings on machines which are not adapted for low body weight patients. For example, until recently, the neonatal lines on the Gambro dialysis machine required a blood flow rate setting of four times the desired speed (i.e., setting the rate at 160 mL/min to achieve a true flow rate of 40 mL/min – this has since been remedied with a software upgrade). Heat loss is also of special concern due to the large proportion of extracorporeal volume and suboptimal thermoregulation in

small infants. The dialysate temperature can be increased to compensate, but alternative methods must be used if the patient is running in ultrafiltration only mode.

A manual system that used two syringes to shift blood back and forth through the filter until adequate ultrafiltration was achieved was described in three infants under 1,000 g. However, all three infants died of comorbidities within 4 months [14]. The last report from this group was from 2007, at which time seven patients had been treated with this system for clearance needs as well [18, 19]. However, as of this writing there appear to be no further updates, and this mechanism has not been approved for use in the USA.

17.5.2 Water Supply

Regardless of the brand of dialysis equipment used for chronic or portable HD, the dialysate water supply must conform to standards set by the Association for the Advancement of Medical Instrumentation (AAMI). The details of these requirements are beyond the scope of this chapter, but the latest update from 2012 can be found and purchased on the AAMI website.

17.5.3 Prescriptions

The frequency of dialysis will be determined by the patient's needs. Polyuric renal failure may require less frequent dialysis (3–4 times a week for 3 h per session) for clearance rather than fluid removal. Anuric renal failure will likely require at least 4–5 sessions per week with longer runs each time. Determination of frequency and length of therapy should be based on solute clearance and fluid removal in the acute patient and proper growth in the chronic patient. Nutrition should never be decreased or withheld due to inadequate dialysis, but rather dialysis must be increased to meet nutritional demands.

Frequent if not constant vital signs monitoring in the form of temperature, heart rate, blood pressure, and pulse oximetry is essential. Neonates can suffer rapid heat loss from the extracorporeal volume. Supportive measures such as oxygen, ventilatory equipment, pressor agents, and isotonic or colloid fluids must be readily at hand to respond to hemodynamic changes. This generally means the procedure must be carried out in an intensive care setting. Staff familiar with neonatal signs of distress (heart rate changes, irritability, color changes, emesis) is needed.

17.5.4 Blood and Dialysate Flow Rates

Blood flow rates used have been reported at as high as 25–50 mL/min [35]. A blood flow rate of 20 mL/min was sufficient to achieve the targeted 15 mL/min of BUN clearance using older parallel-plate dialyzers [26]. A general guideline of at least 3–5 mL/kg/min blood flow rate can be used; however, a minimum of 20 mL/min may be needed to maintain circuit patency. Dialysate flow rates should be kept as low as possible (generally 500 mL/min) as this provides high clearance relative to the blood flow rates. Electrolyte composition will be determined by patient needs. Phosphorus may need to be added due to the blood flow/dialysate flow mismatch, and more frequent sessions are often needed.

17.5.5 Anticoagulation

Heparin can be of special concern in the premature population due to the risk of cerebral hemorrhage. Although the slow flow rates increase the risk of circuit clots, attempts can be made initially to run the dialysis using saline flushes only. When heparin is used, the dosing is 10–20 units/kg to load and then a maintenance dose of 10–20 units/kg/h depending on patient response on the circuit and bleeding risk factors. If heparin is contraindicated, regional anticoagulation with citrate, calcium-free dialysate, and a separate intravenous calcium infusion has also been used [27]. Target circuit post-filter ionized calcium levels have been reported to be less than 0.3 mM [27]. However, higher levels up to 0.5mM are used successfully in continuous veno-venous hemofiltration, which requires longer anticoagulation times and hence greater risk of

circuit loss [5]. Therefore, if citrate is to be used, we recommend tolerating the higher target levels to decrease the risk of complications. Patient's ionized calcium levels should be kept in the 1.1- to 1.3-mM range. Certain centers have also rarely used calcium-free dialysate without citrate, as the latter is not always available. For any of these methods involving calcium manipulation, immediate ionized calcium level results must be available throughout the dialysis run to prevent dangerous systemic hypocalcemia. Lastly, anticoagulation is not always necessary; we have had success with chronic hemodialysis using only saline flushes (accounting for this volume in the UF) and a blood flow rate of 40 mL/min in a 4-kg patient.

17.5.6 Complications of Therapy

17.5.6.1 Clotting/Blood Loss

Despite the use of anticoagulation, blood volume can still be lost in clotted circuits. The frequency is not well reported. Given that most neonates require blood primes on circuits available at this time, this does not translate into worsening anemia necessarily but does increase antigen exposure and the possibility of catheter malfunction. Blood loss due to other aspects of HD care was estimated in chronic HD patients up to 1 year of age. The estimated residual blood volume in the circuit was 15.7 mL/kg/month. Higher heparin doses can decrease this residual. An additional 12.1 ± 5.9 mL/kg/month was lost due to blood draws. This led to an average transfusion rate of 25 ± 17 mL/kg/month in the first 3 months of therapy. These volumes decreased as patients grew and generally stabilized [20]. The use of erythropoiesis-stimulating agents has also decreased transformation needs.

Blood priming is of special concern for antigen exposure and dialysis management (see above in Dialysis Filters and Machines).

17.5.6.2 Disequilibrium and Hypotension

As for all dialysis patients, disequilibrium syndrome can be of concern, especially in the face of a small infant patient dialyzed against a filter and dialysate flow rate with a large (relative to the patient) clearance. Signs can include agitation, irritability, vomiting, or skin discoloration. A high-glucose (up to 700 mg/dL for BUN levels over 100 mg/dL) dialysate bath with a mannitol infusion (1 g/kg) was used to help prevent disequilibrium, and no apparent episodes were noted with this plan. Additionally, clearance was limited to 2–3 mL/min/kg of BUN to prevent rapid shifts [26].

Approximately 60–70 % of patients can have an episode of hypotension during a hemodialysis session [35]. Intradialytic hypotension may occur if the volume to be removed is greater than 5 % of the patient's weight. This risk can be reduced with the use of sodium modeling (increasing dialysate sodium concentration to as high as 150 mEq/L by the end of therapy) or the infusion of colloid such as mannitol (no more than once weekly) or albumin (remembering to account for these excess volumes in the targeted ultrafiltration). These measures can also help with disequilibrium [15].

17.5.6.3 Electrolytes

As with HD on any size patient, electrolyte abnormalities are a risk if there is a mistake or machine error in the dialysate bath. Contrary to older patients who generally need to be more severely restricted, infants often require higher levels of potassium, calcium, and phosphorus for growth. Renal dietary formulas tend to be low in these components. Phosphorus levels (obtained pre-dialysis), specifically were very dependent on food intake and binder use. A dialysate bath containing phosphorus has been recommended [26].

17.5.7 Outcomes

The outcome of infants initiating dialysis early in life is generally dismal and has not improved significantly over time. All nine patients in a series from 1973 died, of which only two were able to discontinue dialysis before dying of other causes. None of the deaths were attributed to the dialysis procedure; however, one

patient died at the end of the first session, and intracranial hemorrhage ("of many days duration") was found on autopsy. Another died at the second session, no reason given. The three patients dialyzed for chronic kidney disease died after transplantation [26]. All five infants who were started on hemodialysis due to "medical ATN" from meconium aspiration, pneumonia, RSD, or cardiac abnormalities died in a 1978 case review [25].

When compared to patients who started dialysis at age 1–24 months in the self-reported NAPRTCS database, those who started dialysis under 1 month of age were slightly more likely to die (11 versus 8 %), less likely to be transplanted (46.5 versus 57.7 %), and more likely to recover native kidney function (15 versus 4 %). There was no difference in the hazard ratio for death or transplant when comparing patients from 1992 to1998 versus 1999 to 2005; there was a trend for patients of the more recent cohort to go to transplant slightly sooner, but the difference was not significant [13]. Again, these numbers do not give the complete picture due to the nature of the database, but 193 neonates were included in this review. In a much smaller series, during a follow-up of 3 years, only one of eight patients who initiated any dialysis in the first month of life received a kidney transplant but subsequently died. Five out of the eight patients died during a follow-up of 3 years. This was not significantly different from patients who initiated dialysis before 1 year of life [20].

17.5.8 Growth

Studies in older children have suggested that growth on PD is better than growth on HD [33]. However, long-term studies on patients initiating dialysis in infancy have not been done. No difference was observed in height and weight SDS changes between PD and HD in 6 months of follow-up [20]. Two out of nine patients in a prior series had dialysis long enough to study their growth and development. Both made gains but at significantly decreased rates from expected [26].

17.6 Specifics of Continuous Renal Replacement Therapy (CRRT)

17.6.1 CRRT Machines

CRRT is used in an ICU setting for critically ill infants. These machines can offer either convective clearance in CVVH mode (continuous veno-venous hemofiltration) or diffusive clearance in CVVHD mode (continuous veno-venous hemodialysis). Additionally, one can undergo both convective and diffusive clearance using CVVHDF, which is continuous veno-venous hemodiafiltration. The question of whether convective or diffuse clearance is better is an ongoing question. Work by Maxvold and colleagues in 2000 identified that clearance of small molecular weight proteins such as urea or citrate is identical whether one is in a convective or a diffusive mode [28]. High molecular weight or high-protein binding solutes have preferential clearance in convective versus diffusive mode. Studies by Flores and colleagues showed that in highly catabolic stem cell transplant patients, survival is improved with the use of convective clearance [21]. In unpublished studies by our group, we identified improved solute clearance of cytokines in convective versus diffusive mode.

Often the decision of convection or diffusion is made by available local solutions. Physiologic solutions have been bicarbonate based since 2000 in North America and have been used earlier throughout the world. In the USA, the Food and Drug Administration (FDA) identifies any medication that goes in the vascular space as a drug. Therefore, those solutions that are used in a convective mode whether it is pre-filter or post-filter are considered a drug. The FDA has then identified any medication that goes outside the vascular space as a device. Therefore, those solutions that are used as dialysate solutions are considered device. Experience has identified that the companies that make both convective and diffusive solutions have similar products with different labels. Both of these solutions are sterile and have physiologic levels of solute. Further, in the solutions that are used in the diffusive mode, one

has to know there is some degree of back filtration at the level of the membrane; therefore, diffusive solutions will still enter the vascular space. Going back to the question of which is better, convection or diffusion, it may not only be based on the metabolic needs of the patient but also may be based on the clinical indication and local availability of solutions. Specifically in septic or otherwise highly catabolic patients, there is an advantage based on data mentioned above in the use of convective solutions. In patients with inborn errors of metabolism, no studies to date have identified whether diffusion or convection is superior to one or the other. Personal experience has identified that each of these are equal and therefore the modality does not matter.

17.6.2 Solutions Used for CRRT

As mentioned, since the year 2000, solutions are now available in the USA that are bicarbonate based. Historically, many programs used solutions mixed through in-house pharmacies instead of using industry-made solutions. Work by Barletta et al identified catastrophic complications including death using pharmacy-made solutions for CRRT [3]. Suspected causes may include repeated compounding in the pharmacy rather than batch processing from industry sources, increasing the number of possible chances for error. Given the immediate need of pharmacy solutions when ordered, there is also no confirmation testing of the products prior to use. Therefore, since the advent of industry-made solutions, pharmacy-made solutions should no longer be considered.

Many companies make both a convective and diffusive solution. Often the choice of the solution will be based on what type of anticoagulation is done. In patients receiving systemic heparinization, a normal physiologic calcium solution is reasonable. In patients receiving citrate anticoagulation, a zero-calcium solution is needed to avoid clotting of the circuit. As metabolic alkalosis is a possible complication of citrate use, a lower bicarbonate solution is preferable. Otherwise these solutions essentially contain a normal physiologic level of sodium, chloride, and magnesium, with bicarbonate levels ranging between 22 and 40 mEq/L. Specific compositions of the numerous solutions available can be obtained from each manufacturer.

The amount of potassium in the solution is based on the needs of the patient. In patients with intoxication or inborn error of metabolism, these patients need to have a normal physiologic potassium level. In patients with AKI, perhaps starting with a lower potassium bath initially and then adjusting up to normal physiologic potassium concentrations would be in order.

Presently, in the USA as well as many other parts of the world, phosphorus is not commonly placed in solutions by industry. Phosphorus over time is cleared very easily by CRRT; therefore replacing phosphorus either enterally, intravenously, or through the convective or diffusive mode is important. Personal experience for over a decade shows that one can place a potassium phosphate in a calcium-free bath either in a diffusive or convective mode in order to maintain physiologic levels of phosphorus and avoid hypophosphatemia.

17.6.3 Anticoagulation

Anticoagulation choices between heparin and citrate differ across programs. What is clear is that the smaller the child is, the smaller the vascular access becomes. The smaller vascular access is associated with slower blood flows; this in turn is associated with a higher incidence of clotting, and so maintaining proper anticoagulation becomes very important.

Heparin-based protocols have commonly been used for the last two decades. Heparin dosing has targeted an activated clotting time (ACT) of about 200 s on HD which is a common protocol also used in extracorporeal membrane oxygenation [8]. This requires a bolus of heparin typically at 20 units/kg per dose and a continuous infusion of heparin anywhere between 10 and 40 units/kg/h in order to target the same level of ACT. The benefit of heparin-based anticoagulation is the ease of its use. The risk is systemic

heparinization to the patient. Historical adult-based protocols have used protamine post-filter pre-patient in order to rescue the patient from the anticoagulation. This not only resulted in no improvement of circuit life but also rebound hypercoagulability or hypocoagulability in the patient, causing more complications.

Since the early 2000s, these authors as well as others have developed the use of citrate anticoagulation used in infants and children [10]. Citrate protocols are based on giving citrate to chelate ionized calcium in the circuit, preventing the coagulation cascade. The target ionized calcium in the circuit is one-third of the normal physiologic level. Then calcium, preferably in the form of calcium chloride, is infused back to the patient separate from the dialysis catheter. The calcium is titrated back to the patient for physiologic normal levels. Table 17.2 provides a suggested titration protocol. The recommended starting rate for citrate is 1.5 times the blood flow rate but in mL per hour, e.g., for a blood flow rate of 100 mL/min, the initial citrate rate is 150 mL/h. Initiation of calcium chloride is 40 % the citrate rate; hence, for the current example, the calcium chloride would start at 0.4×150 mL/h which is 60 mL/h. Monitoring schedules vary but it is reasonable to check an initial ionized calcium within half an hour of starting the circuit to ensure that the patient is not becoming hypocalcemic. Further checks can then be spaced out to as far as every 4–6 h, depending on patient stability and whether any infusion rate adjustments have been needed.

This is now a common practice in up to 70 % of programs throughout North America. Younger patients often metabolize citrate poorly, leading to a higher risk of citrate accumulation. This may result in high physiologic levels of total calcium ("citrate lock") with rebound hypercalcemia as one discontinues CRRT, the citrate is broken down, and the calcium is released. Therefore, even in experienced hands, the use of citrate anticoagulation in premature infants, small infants, or those with liver dysfunction is very difficult requiring significant attention to detail. The additive advantage of citrate anticoagulation is the attention to maintaining an adequate ionized calcium to children, especially if they have some degree of cardiac compromise or sepsis. Calcium is a reasonable inotrope and can improve cardiac output.

Table 17.2 Citrate and calcium titration protocols

Titrate the citrate infusion according to the citrate sliding scale below:		
Prisma ionized Ca++ (mmol/L)	Citrate infusion adjustment	
	>20 kg	<20 kg
<0.35	↓ rate by 10 ml/h	↓ rate by 5 ml/h
0.35–0.5 (optimum range)	No adjustment	
0.5–0.6	↑ rate by 10 ml/h	↑ rate by 5 ml/h
>0.6	↑ rate by 20 ml/h	↑ rate by 10 ml/h
Notify MD if citrate infusion rate >200 ml/h		
Titrate the calcium infusion according to the calcium sliding scale below:		
Patient ionized Ca++ (mmol/L)	Calcium infusion adjustment	
	>20 kg	<20 kg
>1.3	↓ rate by 10 ml/h	↓ rate by 5 ml/h
1.1–1.3 (optimum range)	No adjustment	
0.9–1.1	↑ rate by 10 ml/h	↑ rate by 5 ml/h
<0.9	↑ rate by 20 ml/h	↑ rate by 10 ml/h
Notify MD if calcium infusion rate >200 ml/h		

Source: Pediatric Continuous Renal Replacement Therapy website (www.pCRRT.com). Used with permission

Studies by Brophy et al identified that citrate and heparin result in identical CRRT circuit life in older children [5]. There have been very limited experience and clearly no direct study using heparin versus citrate as a source of anticoagulation in infants to date. Therefore, each program will have to decide the best use of anticoagulation for the child.

17.6.4 CRRT Prescription

A prescription for CRRT for AKI is based on local standard of practice. Work by Maxvold and colleagues has suggested that a blood flow rate of roughly about 4 mL to 5 mL/kg/min along with

either a diffusive or convective clearance at 2,000 mL/1.73 m^2/h would result in roughly about 30 % urea clearance [28]. Work by Ronco and colleagues in adults identified that 40 mL/kg/h of convective clearance results in improved survival in adults with AKI [34]. The 40 m/kg/h equates to roughly about 2,500 to 3,000 mL/1.73 m^2/h of either convective or diffusive clearance.

In reality, the optimal prescription is based on:

1. The blood flow. The blood flow is maximized based on the vascular access. The higher the blood flow, the less the likelihood of clotting. The higher blood flow will not result in hemodynamic compromise.
2. Whether one is using convective or diffusive clearance, one should target based on the catabolic needs of the patient. Thus, using 2,000 to 3,000 mL/1.73 m^2/h would be a reasonable starting point, and then one would titrate the solution exposure upward or downward based on the needs of the patient.

Net ultrafiltration rates are based on the hemodynamics of the patient. Classically, urine output is 0.5–2 mL/kg/h. If one uses that as the standard, then that may be a target that may be best obtained in the patient. This author's experience has suggested that for the first 6–12 if not 24 h of initiation of CRRT, the net ultrafiltration should be zero unless there is pulmonary compromise. This means that the ultrafiltration rate set should equal to the patient's hourly intake from medications and nutrition. This will allow for a maximal solute clearance and then slowly begin fluid removal as tolerated. Vasopressor agents may need to be increased or decreased based on the ultrafiltration needs of the patient. Therefore, many programs will increase the direct use of vasopressor agents as a way to support hemodialysis in order to "dry out" the patient.

17.6.5 Complications

Complications of CRRT in infants are similar to those in older children. This includes hypotension associated with the extracorporeal membrane. The hypotension can be associated with a large extracorporeal volume compared to the intravascular blood volume of the patient. Historically, in chronic hemodialysis, one was always taught not to have more than 10 % of blood extracorporeal to the patient. This data, which is no longer valid in the outpatient chronic hemodialysis world, has been extrapolated to the inpatient CRRT world. This comparison is not valid because one is comparing hemodynamically stable outpatients to hemodynamically unstable inpatients.

What is known is that the larger extracorporeal volume at the initiation of CRRT, the more chance of causing some degree of hypotension. Therefore, the use of blood priming may be necessary if one has 5, 10, 15, or even 20 % of blood volume extracorporeal. The use of blood priming is primarily based on the hemodynamics of the patient. The risks of blood priming are twofold. One is related to the acidotic, hypocalcemic, and hyperkalemic composition of the blood itself, and the second is the potential of a significant membrane reaction associated with the AN-69 membrane which is made by Gambro. A study by Brophy and colleagues identified that the acidotic milieu (pH of 6.2), elevated potassium (up to 40 mEq/L), and low ionized calcium (down to 0.02 mM due to the citrate to prevent clotting) of banked blood can interact with the AN-69 membrane and cause anaphylaxis when post-filter blood returns to the patient [4]. This is related to a pH-dependent bradykinin reaction. Studies by Brophy as well as Hackbarth have identified methods to avoid this reaction [24]. Other membranes such as polysulfone are not associated with these problems.

Other complications in children are related to thermic instability. Because of the large extracorporeal blood volume and the relatively slow blood flow rate, blood may be extracorporeal to the patient for 3–4 min. This allows for significant cooling and puts the child at risk for hypothermia and masking fevers.

The other two major complications of CRRT in infants are related to nutritional losses, as well as drug dosing. Maxvold and colleagues identified that roughly 15–35 % of parenteral TPN amino acids may be lost through CRRT [28]. Therefore, many programs including this author will titrate the protein load to keep the patient at a BUN of roughly 40–60 mg/dL. Experiences show that some infants

require 8–9 g/kg/day of TPN protein in order to have a BUN of 20–30 mg/dL for adequate protein load. Work by Zappitelli and colleagues have identified that standard practice still usually orders about 2.5 g/kg/day, which is usually insufficient for children and even more so for infants on CRRT [38]. Further work by Zappitelli and colleagues has identified trace elements as well as vitamins being removed by CRRT system [39]. Therefore, overall attention to detail with nephrology input is very important to compensate for the nutritional stealing that occurs on the CRRT machine.

Medication dosing in children on CRRT is very difficult. Smaller molecular weight and less-protein-bound drugs have higher levels of clearance. Given the continuous nature of CRRT, however, many medications which do not fit that profile are still significantly cleared over time. To determine relative clearance on CRRT, vasopressor agent use and levels of antibiotics such as aminoglycosides or vancomycin can help. Vancomycin is about 1,500 Da and about 75 % protein bound. It is not unusual that infants or children on CRRT require normal dosing of vancomycin with normal kinetics. This experience with vancomycin then can allow one to identify how to dose other medications in general. Vasopressor agents such as epinephrine, norepinephrine, and dopamine have small molecular weight and are poorly protein bound. Therefore, it is imperative to know that at the initiation of CRRT, these medications are cleared quite rapidly and doses may need to be increased over time to give adequate hemodynamic control.

Lastly, the placement of vascular access in these children is important in relation to other points of access. If the tip of another central venous line delivering vasopressor agents is in immediate proximity to the CRRT dialysis catheter (as they often are due to the nature of these medications), there may be an immediate loss of these medications at the initiation of CRRT.

17.6.6 Tandem Therapies

Patients with inborn errors of metabolism can undergo hemodialysis or CRRT. Work by Picca and others has identified that optimally, hemodialysis and CRRT are superior to peritoneal dialysis for removal of ammonia [32]. Recent work by our group has identified the use of sequential hemodialysis followed by CRRT as the optimal way to take care of infants with inborn errors of metabolism [7]. Furthermore, a recent paper by Eding and colleague has identified the use of transitioning blood from the hemodialysis machine to the CRRT machine not only to avoid membrane reactions associated with AN-69 filters but also to avoid extra blood exposure to that patient [17]. In contrast to the dialysate used in AKI which may be low in phosphorus, and potassium, the bath used in inborn errors of metabolism needs to be physiologic.

Like intoxications, the duration for hemodialysis or CRRT in inborn error of metabolism would be targeted based on the clearance of ammonia. Recent studies identified that the "cocktail" that is used in the treatment of hyperammonemia is cleared easily on CRRT. Work done by McBryde and colleagues has shown that arginine is easily cleared [29]. Phenylacetate and benzoate are easily cleared on CRRT but not at the compromise of improving ammonia in the patient [7].

17.6.7 Outcome

There is a paucity of data on the outcome of infants on CRRT. Most studies combined modalities as well as patient ages, involving both pediatric and infant groups together [11, 12]. In a multicenter retrospective database study looking at survival in children less than 10 kg, there was an overall survival of 40 %. In those less than 3 kg, the mortality was roughly 25 %, pointing out that even in experienced hands, this is a very difficult population to effectively dialyze [36].

In essence, CRRT is a commonly used therapy in children with AKI and intoxications and less commonly used in infants. The typical difficulties are usually around the issues of vascular access and the complications related to a large extracorporeal circuit. Developments out of Europe identified smaller and smaller extracorporeal therapies for CRRT in infants perhaps making this an easier therapy to use in this population.

17.7 Social Supports

The importance of supporting the family during this time cannot be stressed enough. Caregivers must be careful not to impose their value system on families while at the same time guiding parents in what, for them, is an extraordinary situation that they have likely never prepared for. Given the complications and unsure outcomes discussed above, some families may choose never to start renal replacement therapy in the first place, and caregivers must be prepared to discuss and possibly accept these decisions with the family.

Conclusion

Neonatal renal replacement therapy using HD or CRRT has many indications and may need to be modality of choice for some ESRD patients. The prognosis remains grim for many of these patients, and much work remains to be done to improve their outcome. In the meantime, careful attention to detail regarding vascular access, location of therapy, core staff members, access placement, vigilant monitoring during each session, preparation ahead of time for possible complications, and the care and management of non-dialysis factors such as nutrition and family support are vital to increasing the chances of success for these vulnerable patients.

References

1. Askenazi DJ, Ambalavanan N et al (2009) Acute kidney injury in critically ill newborns: what do we know? What do we need to learn? Pediatr Nephrol 24(2):265–274
2. Barletta GM, Bunchman TE (2004) Acute renal failure in children and infants. Curr Opin Crit Care 10(6):499–504
3. Barletta JF, Barletta GM et al (2006) Medication errors and patient complications with continuous renal replacement therapy. Pediatr Nephrol 21(6): 842–845
4. Brophy PD, Mottes TA et al (2001) AN-69 membrane reactions are pH-dependent and preventable. Am J Kidney Dis 38(1):173–178
5. Brophy PD, Somers MJ et al (2005) Multi-centre evaluation of anticoagulation in patients receiving continuous renal replacement therapy (CRRT). Nephrol Dial Transplant 20(7):1416–1421
6. Bunchman TE (1995) Chronic dialysis in the infant less than 1 year of age. Pediatr Nephrol 9(Suppl): S18–22
7. Bunchman TE, Barletta GM et al (2007) Phenylacetate and benzoate clearance in a hyperammonemic infant on sequential hemodialysis and hemofiltration. Pediatr Nephrol 22(7):1062–1065
8. Bunchman TE, Donckerwolcke RA (1994) Continuous arterial-venous diahemofiltration and continuous veno-venous diahemofiltration in infants and children. Pediatr Nephrol 8(1):96–102
9. Bunchman TE, Ferris ME (2011) Management of toxic ingestions with the use of renal replacement therapy. Pediatr Nephrol 26(4):535–541
10. Bunchman TE, Maxvold NJ et al (2003) Pediatric convective hemofiltration: normocarb replacement fluid and citrate anticoagulation. Am J Kidney Dis 42(6):1248–1252
11. Bunchman TE, Maxvold NJ et al (1995) Continuous venovenous hemodiafiltration in infants and children. Am J Kidney Dis 25(1):17–21
12. Bunchman TE, McBryde KD et al (2001) Pediatric acute renal failure: outcome by modality and disease. Pediatr Nephrol 16(12):1067–1071
13. Carey WA, Talley LI et al (2007) Outcomes of dialysis initiated during the neonatal period for treatment of end-stage renal disease: a North American Pediatric Renal Trials and Collaborative Studies special analysis. Pediatrics 119(2):e468–473
14. Coulthard MG, Sharp J (1995) Haemodialysis and ultrafiltration in babies weighing under 1000 g. Arch Dis Child 73(3):F162–165
15. Donckerwolcke RA, Bunchman TE (1994) Hemodialysis in infants and small children. Pediatr Nephrol 8(1):103–106
16. Donn SM, Swartz RD et al (1979) Comparison of exchange transfusion, peritoneal dialysis, and hemodialysis for the treatment of hyperammonemia in an anuric newborn infant. J Pediatr 95(1):67–70
17. Eding DM, Jelsma LR et al (2011) Innovative techniques to decrease blood exposure and minimize interruptions in pediatric continuous renal replacement therapy. Crit Care Nurse 31(1):64–71
18. Everdell NL (2007) A haemodialysis system for the treatment of acute renal failure and metabolic disorders in neonates. Med Eng Phys 29(4):516–524
19. Everdell NL, Coulthard MG et al (2005) A machine for haemodialysing very small infants. Pediatr Nephrol 20(5):636–643
20. Feinstein S, Rinat C et al (2008) The outcome of chronic dialysis in infants and toddlers–advantages and drawbacks of haemodialysis. Nephrol Dial Transplant 23(4):1336–1345
21. Flores FX, Brophy PD et al (2008) Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group. Pediatr Nephrol 23(4): 625–630

22. Gitomer JJ, Khan AM et al (2001) Treatment of severe theophylline toxicity with hemodialysis in a preterm neonate. Pediatr Nephrol 16(10):784–786
23. Hackbarth R, Bunchman TE et al (2007) The effect of vascular access location and size on circuit survival in pediatric continuous renal replacement therapy: a report from the PPCRRT registry. Int J Artif Organs 30(12):1116–1121
24. Hackbarth RM, Eding D et al (2005) Zero balance ultrafiltration (Z-BUF) in blood-primed CRRT circuits achieves electrolyte and acid-base homeostasis prior to patient connection. Pediatr Nephrol 20(9): 1328–1333
25. Hodson EM, Kjellstrand CM et al (1978) Acute renal failure in infants and children: outcome of 53 patients requiring hemodialysis treatment. J Pediatr 93(5): 756–761
26. Kjellstrand CM, Mauer SM et al (1973) Haemodialysis of premature and newborn babies. Proc Eur Dial Transplant Assoc 10:349–362
27. Kreuzer M, Ahlenstiel T et al (2010) Management of regional citrate anticoagulation in pediatric high-flux dialysis: activated coagulation time versus post-filter ionized calcium. Pediatr Nephrol 25(7):1305–1310
28. Maxvold NJ, Smoyer WE et al (2000) Amino acid loss and nitrogen balance in critically ill children with acute renal failure: a prospective comparison between classic hemofiltration and hemofiltration with dialysis. Crit Care Med 28(4):1161–1165
29. McBryde KD, Kudelka TL et al (2004) Clearance of amino acids by hemodialysis in argininosuccinate synthetase deficiency. J Pediatr 144(4):536–540
30. Moran JE, Ash SR (2008) Locking solutions for hemodialysis catheters; heparin and citrate–a position paper by ASDIN. Semin Dial 21(5):490–492
31. Msall M, Batshaw ML et al (1984) Neurologic outcome in children with inborn errors of urea synthesis. Outcome of urea-cycle enzymopathies. N Engl J Med 310(23):1500–1505
32. Picca S, Dionisi-Vici C et al (2001) Extracorporeal dialysis in neonatal hyperammonemia: modalities and prognostic indicators. Pediatr Nephrol 16(11): 862–867
33. Potter DE, San Luis E et al (1986) Comparison of continuous ambulatory peritoneal dialysis and hemodialysis in children. Kidney Int Suppl 19:S11–14
34. Ronco C, Bellomo R et al (2000) Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 356(9223):26–30
35. Sadowski RH, Harmon WE et al (1994) Acute hemodialysis of infants weighing less than five kilograms. Kidney Int 45(3):903–906
36. Symons JM, Brophy PD et al (2003) Continuous renal replacement therapy in children up to 10 kg. Am J Kidney Dis 41(5):984–989
37. Wiegand C, Thompson T et al (1980) The management of life-threatening hyperammonemia: a comparison of several therapeutic modalities. J Pediatr 96(1):142–144
38. Zappitelli M, Goldstein SL et al (2008) Protein and calorie prescription for children and young adults receiving continuous renal replacement therapy: a report from the Prospective Pediatric Continuous Renal Replacement Therapy Registry Group. Crit Care Med 36(12):3239–3245
39. Zappitelli M, Juarez M et al (2009) Continuous renal replacement therapy amino acid, trace metal and folate clearance in critically ill children. Intensive Care Med 35(4):698–706