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Core Curriculum in Nephrology

Unique Considerations in Renal Replacement Therapy in Children: Core Curriculum 2014

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INTRODUCTION

Improvements in technology in recent decades have allowed long-term dialysis to become a viable treatment option for kidney failure in children, from newborns to adolescents. Acute kidney injury (AKI) commonly occurs in patients who are critically ill. It affects nearly 30%-40% of patients admitted to the pediatric intensive care unit and is associated with high mortality rates of 40%-50%. Approximately 5% of pediatric intensive care unit patients have AKI requiring renal replacement therapy (RRT). The preferred treatment for all patients with end-stage renal disease (ESRD), of course, is successful kidney transplantation. However, nearly 75% of children with ESRD must be on maintenance dialysis therapy for a month or 1 to several years as they wait for a transplant.

In order to determine the optimal care for children who require RRT, one must understand the patterns and causes of both AKI and multiorgan dysfunction syndrome. Similarly, local expertise and equipment resources for ESRD management are necessary to provide for the multidisciplinary needs of a child affected by kidney disease. This review provides a reference on the unique considerations in RRT in children.

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PRINCIPLES OF RRT

Physiology

All forms of RRT rely on the principle of allowing water and solute transport through a semipermeable membrane and then discarding the waste products. Ultrafiltration is the process by which water is transported across a semipermeable membrane. Solute clearance occurs by 2 physiologic mechanisms: diffusion and convection.

In peritoneal dialysis (PD), clearance occurs by diffusion, ultrafiltration (which is exerted by the osmotic gradient of glucose and other osmotic substances), and convective mass transfer. In hemodialysis (HD), blood flows on one side of a semipermeable membrane and dialysate flows on the other. The composition of HD and PD solutions is presented in Table 1.

Classification of Renal Support Therapy Modalities

RRTs can be classified as intermittent or continuous, based on the duration of treatment (Fig 1). The duration of each intermittent therapy is less than 24 hours, whereas the duration of continuous therapy is at least 24 hours. Intermittent therapies include intermittent HD (IHD) and sustained low-efficiency dialysis (SLED). The continuous therapies include PD and continuous RRT (CRRT).

CRRT is defined as any extracorporeal blood purification therapy that is used to substitute for decreased kidney function over an extended period and is prescribed for 24 hours per day. CRRT classically is used as a substitution term for either continuous venovenous hemofiltration (CVVH), continuous venovenous hemofiltration with dialysis (CVVHD), or a combination of convective and diffusive clearance of continuous venovenous hemodiafiltration (CVVHDF).

Choice of Renal Replacement Modality

There are 2 key criteria that affect the clinician's choice of dialysis modality: the indication for dialysis and the patient's overall clinical status. HD, CRRT, and PD are effective in the management of AKI. The choice of modality is based on 4 factors: first, the patient's age and size; second, the patient's cardiovascular status; third, whether vascular access is available or the condition of the peritoneal membrane and abdominal cavity; and fourth, the available expertise.

Table 1. Composition of Dialysis Solutions

Constituent	Peritoneal Dialysis	Hemodialysis
pH	5.8	7.1-7.3
Dextrose (g/dL)	1.5-4.25	0.1
Sodium (mEq/L)	130	135-140
Potassium (mEq/L)	0	0-3
Chloride (mEq/L)	100	108
Buffer	Lactate 35-40 mEq/L; Neutral pH (7.0-7.6) solutions: 34 mEq/L of bicarbonate, or 25 mEq/L of bicarbonate + 15 mEql/L of lactate	35-40
Magnesium (mEq/L)	1.5	0.5-1.5
Calcium (mEq/L)	3.0	2.5-3.2

Note: Conversion factor for units: lactate in mmol/L to mg/dL, ×0.0667.

In developing countries, the majority of children who require dialysis are treated with PD because it is simpler in both its implementation and the equipment it requires. In addition, PD offers a gradual rate of fluid removal and correction of metabolic imbalances, which can be very helpful in critically sick children or small infants. Children who have cardiovascular conditions also tolerate this procedure better than IHD. There are a large number of acute PD catheters available that allow easy insertion, even in the smallest infant.

HD should be considered if rapid removal of toxins is desired, the size or age of the child makes PD difficult, or anatomic impediments to efficient PD are present (eg, ileus, adhesions, and recent abdominal surgery).

Furthermore, if vascular access and use of anticoagulation are not limitations, a slow continuous process (CRRT) may be applied in hemodynamically unstable patients in an intensive care unit. Patients who have severe AKI or intoxications can be treated by IHD with either standard or high-flux membranes. When patients with pulmonary edema require the urgent removal of fluids, HD or CRRT must be used. However, if there is only mild volume overload, any modality can be used for treatment.

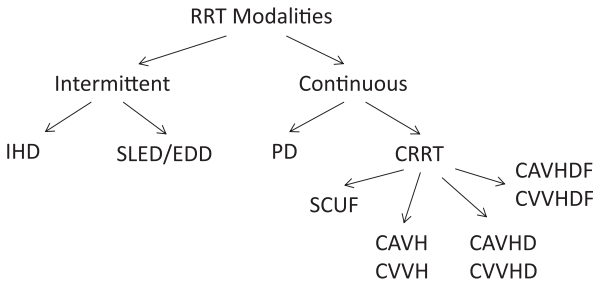

Figure 1. Classification of renal replacement therapies (RRTs). Abbreviations: CAVH, continuous arteriovenous hemofiltration; CAVHD, continuous arteriovenous hemodialysis; CAVHDF, continuous arteriovenous hemodiafiltration; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; CRRT, continuous renal replacement therapy; EDD, extended daily dialysis; IHD, intermittent hemodialysis; PD, peritoneal dialysis; SCUF, slow continuous ultrafiltration; SLED, sustained low-efficiency dialysis.

The smaller the child, the greater the challenge in obtaining vascular access. This is one of the reasons that PD is used more commonly in smaller children. In certain clinical situations, such as infants with postcardiac AKI, PD may offer improvement in survival.

However, the greatest change in the last decade in children with AKI has been the increased use of CRRT, and at times the hybrid therapy SLED. In patients with AKI associated with hemodynamic instability or continuous needs, these modalities are becoming common practice in intensive care units throughout the developed world.

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RRT IN AKI

Indications for Initiation of RRT in AKI

There are a number of conditions that indicate the need for RRT initiation, including fluid overload (such as severe hypertension or pulmonary edema), uremic encephalopathy, severe or persistent hyperkalemia, severe metabolic acidosis (carbon dioxide level $>$ 10-12 mEq/L), hypernatremia, or hyponatremia (sodium level of 120 mEq/L or symptomatic). When deciding to initiate dialysis therapy, an overall assessment of the patient should be made, keeping in mind the likely course of kidney failure. Indications for dialysis not related to renal causes include preventing or treating tumor lysis syndrome and removing toxins, either ingested or from inborn errors of metabolism.

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PD in AKI

The preferred RRT for patients with AKI has been acute PD for decades because it is both simple and safe and can be performed in very small patients with relative ease. A particular advantage for small children and infants is that it does not involve vascular access, often a limiting factor in these patients. Although not a frequent problem, excessive ultrafiltration with PD can lead to significant hemodynamic consequences, particularly in small patients. Another concern requiring attention is the insertion of PD catheters. Catheter-related infections are still the most frequent complication of acute PD in infants and children, as well as being the most common cause of catheter removal.

PD Catheters

Traditionally, the most commonly used catheters for acute PD in children and infants are the noncuffed rigid acute catheter and the surgically placed cuffed silicone Tenckhoff catheter. Once inserted, a stiff catheter can be used safely for a maximum of 72 hours, beyond which there is an increasing risk of peritonitis. Thus, when one anticipates that the patient will need PD for more than 1 week, a single or a double-cuffed Tenckhoff soft catheter should be placed. Safely placing a single-cuff soft Tenckhoff peritoneal catheter at the bedside may lead to positive outcomes for infants and children with AKI who are treated with PD.

A retrospective review of North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) data found that early (<14 days) use of Tenckhoff catheters was associated with increased risk of leakage, although no difference in risk of infection was observed. In addition, a review of the Italian PD registry did not show a difference in the incidence of leakage or length of catheter survival comparing catheters used early (<7 days) versus late. Because there is no conclusive evidence supporting a rest period of any particular length, prospective studies should be conducted. That said, for cases in which early use is needed, an attempt to decrease the intraperitoneal pressure should be made by using small exchange volumes in the supine position with a cycling device.

PD Techniques and Prescription in AKI

After insertion of a PD catheter, it is important to individualize the dialysis prescription according to the clinical situation of the patient. In addition, the infusion volume should be adjusted according to the size of the patient's peritoneal cavity and uremic syndrome severity. In children, a typical fluid volume is 800-1,100 mL/m^2, beginning with the smaller volume. The peritoneal surface area of children is linked more closely to body surface area than to weight. The most commonly used exchange time is 1 hour, allowing 10 minutes for inflow, 30 minutes for dwell, and 20 minutes for outflow. However, the session's duration will depend on how large a dose of acute PD needs to be delivered. Patients with AKI require continuous removal of fluids and solutes, and this is especially the case when a patient is hypercatabolic, oliguric, or in need of ongoing therapeutic and nutritional support. In those situations, PD sessions may last 24-72 hours with hourly exchanges, but the PD dose is considered efficient if it meets the patient's daily requirements for energy and protein and maintains stable near-normal fluid and electrolyte homeostasis.

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Methods to Increase Dialysis Adequacy in Acute PD

There are several techniques available to increase dialysis adequacy in PD.

Continuous equilibrated PD. This type of PD uses a larger fill volume than usual for acute intermittent PD (IPD), approximately 40-45 mL/kg (1,200 mL/m^2), with long dwells of 2-6 hours.

High-volume continuous PD. This method provides a dialysis dose that has been shown to approach that of high-dose CRRTs or daily HD in adults. It uses a Tenckhoff catheter with an automated cycler and Kt/V_{urea} prescription of at least 0.65 per session. However, in hypercatabolic patients with AKI, Kt/V_{urea} is a controversial index of adequacy because the urea volume of distribution is variable, exceeding total-body water.

Tidal PD. Tidal PD (TPD) involves maintaining a volume of dialysis solution of at least 30% of the fill volume (15 mL/kg) in the peritoneal cavity throughout the dialysis session, which optimizes solute clearance. The tidal drain volume is replaced with fresh dialysate, referred to as the tidal fill volume. It is possible to increase the tidal fill volume, thus increasing the clearance of small solutes. Because of the increased duration of contact between dialysate and peritoneum, the efficiency of dialysis is improved further, with increased middle-molecule clearance.

Continuous flow PD. In this type of PD, either synchronized inflow and outflow of sterile dialysate or recirculation of a single large exchange through an external regenerating apparatus increases the dialysate flow rate up to 100-300 mL/min, corrected for body surface area, in a single pass.

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Complications and Limitations of PD

Leakage can be a difficult problem, and it most often occurs around the catheter. Using proper surgical technique when inserting a Tenckhoff catheter or resuturing around a percutaneous catheter can help reduce the incidence of leakage.

Because newborns and infants are at higher risk of hypothermia, PD solutions should be warmed to body temperature and a strict temperature chart should be maintained in young children.

Impaired drainage is an important issue that may occur due to catheter malposition, kinking, omental wrapping, and fibrin clot. This is common in small-bore noncuffed peritoneal catheters in infants. Inadequate drainage also may be due to constipation, which responds to cathartics and catheter repositioning. The first response should be to flush the catheter and prevent fibrin from accumulating by increasing the heparin dosage. In neonates and infants, particularly males, hernias can be problematic. Normally these hernias do not require that PD be interrupted because they can be repaired electively after the child is in an improved or stabilized clinical condition.

Another concern is poor ultrafiltration, especially in infants who are critically ill, due to the low fill volume with inadequate fluid reservoir intraperitoneally. Critically ill infants often require inotropic support for hypertension. The vasoconstriction of the mesenteric vessels results in decreased bowel perfusion, which contributes to the poor ultrafiltration.

Two considerable drawbacks of acute PD compared to CRRT are its inconsistent ultrafiltration and its inefficient and slow removal of molecules. Moreover, acute PD may not provide adequate clearances in a highly catabolic patient.

Peritonitis remains a constant threat, especially if the catheter is manipulated. There are limited data about the incidence of peritonitis in acute PD. In the recent 2011 NAPRTCS report, a total of 4,248 episodes of peritonitis have occurred in 6,658 years of follow-up (4,687 PD courses), yielding an annualized rate of 0.64, or one episode every 18.8 months. Peritonitis rates should not exceed one episode every 18 months (0.67 per year at risk) at centers involved with maintenance PD in infants and children.

Factors associated with reduced risk of peritonitis include older patient age; use of double-cuffed swan neck Tenckhoff catheter with downward directed exit-site flush before fill procedure, prophylactic antibiotics (1 dose of intravenous vancomycin at the time of catheter placement), exit-site care with daily application of mupirocin cream to the skin around the exit site, and prolonged training for care providers.

Another factor influencing how frequently peritonitis occurs is the type of PD modality. Patients receiving automated PD experience somewhat lower rates of peritonitis compared with patients receiving CAPD. Fifty percent of the cases had their first peritonitis episode by 19.3 months compared in both groups. At 1 year post initiation, 42.1% of CAPD patients and 40.1% of automated PD patients had experienced at least one episode of peritonitis.

Common organisms causing peritonitis are coagulase-negative staphylococcus and *Staphylococcus aureus*, followed by Gram-negative organisms. Patients present with cloudy effluent, pain, and fever. An effluent count $>$ 100 leukocytes/mL (after a dwell of at least 2 hours) with $>$50% neutrophils is suggestive of peritonitis.

There currently are no guidelines for acute PD catheter peritonitis. If a child has a stiff catheter in place, the catheter should be removed. If a child has a soft Tenckhoff catheter in place, intraperitoneal antibiotic therapy may be started empirically. Generally, the majority of centers use a combination of a first-generation cephalosporin or vancomycin/teicoplanin to cover Gram-positive organisms and a third-generation cephalosporin or an aminoglycoside to cover Gram-negative organisms.

Reinsertion of a new catheter should be avoided for 2-3 weeks. During this time, the child may be continued on maintenance HD therapy.

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Contraindications of PD

Absolute contraindications to PD include necrotizing enterocolitis or a recent abdominal surgery; both are frequent causes of AKI in neonates and

infants. Another contraindication is having a ventriculoperitoneal shunt because this type of shunt has a high risk of peritonitis.

IHD in AKI

HD is the most efficient method of RRT, accomplishing molecular transfer at much higher rates than either PD or CRRT. It is highly effective in acute settings for the management of critical volume overload or intoxication and serves as an important method for maintenance dialysis. HD is ideal for diseases causing acute disruptions in homeostasis; these include ingestions of drugs, hyperammonemia, and tumor lysis syndrome. Another advantage of HD is that it can accomplish isolated ultrafiltration, and the dialysis fluid solute concentration can be titrated to correct metabolic disturbances such as dysnatremias. Providing optimal HD therapy in children requires an integrated specialized health care team to manage the medical, nursing, nutritional, developmental, and psychosocial aspects of patient care.

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Vascular Access and Catheters

Achieving venous access in infants and young children has been challenging for pediatric nephrologists and pediatric surgeons for many years. The small size of the child, the small size and caliber of their veins and arteries, and the lack of easily visible veins makes the creation and maintenance of adequate access difficult in these young patients.

In order to provide HD adequately, a properly functioning vascular access is needed. Currently there are 2 categories of access options: permanent access, including arteriovenous fistulas (AVFs) and arteriovenous grafts (AVGs), and semipermanent access, including catheters with a subcutaneous cuff for long-term dialysis or without a cuff for short-term HD. In this review, we discuss only temporary vascular access used in the acute setting.

Acute vascular access for HD most often is accomplished by placement of a double-lumen dialysis catheter in the internal jugular or femoral vein. These sites usually provide adequate blood flow and are acceptable for short-term use in a hospitalized patient. The subclavian vein catheter should be avoided because of the risk of venous stenosis. Acute double-lumen dialysis catheters lack a subcutaneous cuff and are designed for insertion at the bedside using the Seldinger technique. The size of the acute dialysis catheter is shown in Table 2. It is advisable to avoid 5F double-lumen catheters in newborns to avoid poor blood flow.

Table 2. Acute Dialysis Catheter Choices

Patient Size	Catheter Choice
Neonate	7F double-lumen
	5F double-lumen (2 separate catheters)
3-6 kg	7F double-lumen
6-15 kg	8F double-lumen
15-30 kg	9F double-lumen
>30 kg	10-12.5F double-lumen

The HD catheter requires special care. As with any central venous catheter, the exit site must be kept clean and dry. An appropriate dressing is applied to the exit site. In the outpatient setting, patients and families must be taught to care for the catheter between dialysis sessions. To limit the chances of thrombosis, a heparin or citrate lock may be instilled into the catheter. The heparin concentration is often 1,000-5,000 U/mL.

Dialyzers

The clinician selects the dialyzer with consideration to the biocompatibility of the membrane, priming volume, clearance, and ultrafiltration characteristics. A dialyzer with a larger surface area and greater permeability permits greater mass transfer and ultrafiltration, but the volume of blood required to fill such a dialyzer may be too large for a small child. Slow blood flow, as might be seen with a small-caliber catheter in a child, will reduce the efficiency of mass transfer even with a larger dialyzer and may increase the likelihood of clotting.

Consequently, the choice of dialyzer depends on a balance of multiple factors. Most commonly, the surface area of the dialyzer should approximate the surface area of the child on HD therapy. Newer generation dialysis membranes constructed from materials such as polysulfone and polymethylmethacrylate cause less proinflammatory cytokine activation than older generation membranes made from cellulose or cuprophane.

HD Prescription in AKI

Extracorporeal volume. With the use of catheters, small hemodialyzers, and smaller volume blood tubing, the extracorporeal blood volume often can be maintained at <8%-10% of the intravascular volume. Blood tubing is available in 3 sizes that vary in their priming volume: neonatal 25 mL, pediatric 75 mL, and adult 127 mL. The extracorporeal circuit volume includes the dialyzer priming volume and the volume of the blood tubing. If this volume is >10% of the total blood volume, blood or 5% albumin should be used to prime the blood tubing and dialyzer. Blood prime is very important for infants and young children. The total blood volume is approximately equal to 100 mL/kg

of body weight in neonates (aged < 1 month) and 80 mL/kg of body weight for infants and children aged up to 16 years. An anemic child may develop hypotension when the HD procedure is started due to loss of blood into the extracorporeal system. This child may require priming the circuit with packed red blood cells before starting the HD procedure.

Blood flow rate. Blood flow rates generated by the dialysis pump usually range from 3-5 mL/kg of body weight per minute, often starting at the lower blood flow rate and slowly increasing the rate during the procedure.

Dialysate flow rate. The standard dialysate flow rate is 500 mL/min. Some dialysis machines permit wider variation of the dialysate flow rate, allowing flows as high as 800 mL/min. Urea clearance increases as blood flow increases from zero, but the rate of clearance decreases because blood flow is faster. Similarly, increases in dialysate flow will increase clearance.

Ultrafiltration. Ultrafiltration is the movement of fluid under hydrostatic pressure from the blood to the dialysate compartment. The amount ultrafiltered depends on transmembrane pressure, the pressure difference between the blood and dialysate compartments. The maximum ultrafiltration rate is 0.2 mL/kg/min. Each dialyzer has a specified ultrafiltration coefficient that is a measure of the amount of fluid that will pass from the membrane in 1 hour. Dividing the fluid removal needed by hours of treatment gives the ultrafiltration rate. It is critical to accurately determine the target dry weight because underestimating dry weight may lead to hypovolemia. Continually overestimating target weight may lead to long-term volume overload, potentially resulting in hypertension, left ventricular hypertrophy, congestive heart failure, and pulmonary edema.

Anticoagulation. Anticoagulation with heparin is provided during the HD procedure, typically with a pre-HD infusion of 10-20 U/kg/dose, with bedside monitoring of the activated clotting time. HD also can be performed successfully without anticoagulation, especially if the risk of bleeding is high. In this situation, intermittent flushing of the dialyzer with saline solution (40-50 mL) can maintain circuit patency. Although this technique avoids heparin exposure, the risk remains that the extracorporeal circuit may clot, with subsequent loss of extracorporeal blood volume. The amount of ultrafiltration (fluid volume to be removed from the patient during the dialysis process) will depend on the extent of the predialysis volume status (including the presence of edema), blood pressure, and weight gain noted between dialysis procedures.

Complications of HD in Children

The complications associated with HD in infants and children include problems related to vascular access, including thrombosis, stenosis, and infection. Of these, thrombosis is the most common reason for loss of access to the child's circulation. Because of the smaller blood volume in children, hypotension during the HD treatment occurs more commonly than with adults. This requires close monitoring of vital signs, blood pressure, and body weight. Hypovolemia often is associated with tachycardia, muscle cramping, nausea, and vomiting. Prompt relief of these symptoms is achieved with rapid restoration of circulating volume with normal saline solution, 5% albumin, or mannitol. Slower ultrafiltration rates can reduce the risk of hypotension. Linear sodium modeling, readdressing target weight, and step-up ultrafiltration profiling may help prevent intradialytic hypotension.

Given their increased susceptibility to hypothermia, infants typically are dialyzed against higher dialysate temperatures of 37.5°C-38°C in combination with external warming strategies.

Muscle cramping may occur during the HD treatment and may be related to hypovolemia, hypotension, and electrolyte shifts. Treatment of cramping includes increasing the dialysate sodium concentration and administration of hypertonic saline solution or glucose during the cramping episode.

Dialysis disequilibrium syndrome occurs in children, with symptoms often resembling those of hypovolemia. Children at risk often have calculated or measured osmolality > 330 mOsm/kg (in the setting of elevated serum urea nitrogen [SUN], sodium, or glucose levels), preexisting neurologic disease, severe metabolic acidosis, and high ultrafiltration goal. The cause of dialysis disequilibrium syndrome is not entirely clear and may relate to the brisk lowering of serum osmolality that occurs during HD, with the subsequent development of acute cerebral edema. Manifestations include headache, nausea, vomiting, blurred vision, restlessness, and, in severe situations, significant mental status disturbances, including disorientation and coma.

At the initiation of HD therapy, it is recommended to target a urea reduction ratio around 30%-40% to prevent the acute shift in osmole. After 3-4 HD sessions, a full dialysis prescription can be started. Dialysis disequilibrium syndrome usually can be avoided by reducing the decrease in osmolality by shortening dialysis time and reducing blood flow rates. For situations in which the patient's SUN level is high and HD is being initiated, administration of 0.5 g/kg of body weight of mannitol is useful in preventing intracellular fluid accumulation. After several HD treatments, with lowering of the SUN level, this therapeutic intervention usually is no longer needed.

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Slow Dialysis Therapies

Comparison of SLED to CRRT

The major difference between SLED and CRRT is the number of hours and length of treatment; CRRT classically is 24 hours a day, and SLED often is 4-12 hours a day. SLED can be performed nocturnally in the intensive care unit, allowing for daytime procedures without dialysis interruption. The disadvantage of SLED, as mentioned, is the limitation of the number of hours, making volume management and kinetics of drugs and nutrition delivery a bit more challenging. We are unaware of any head-to-head studies comparing CRRT to SLED in children.

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Convective Versus Diffusive CRRT

CRRT can be done with either CVVH, CVVHD, or CVVHDF mode. In North America, convective clearance (CVVH) often is used with a prefilter sterile solution that is physiologic to the needs of the patient. In Europe and Australia, the convective replacement fluid often is given postfilter. Historical data for adults suggest that postfilter convection allows for greater solute clearance, but has a higher risk of clotting because of distal membrane hemoconcentration. When factoring in the time that the machine is not operating because of a clotted filter, there perhaps is little effect of solute clearance over time.

CVVHD allows for diffusive clearance. This is similar to the concept used in PD and HD. A sterile physiologic solution flows across the membrane, allowing for solute clearance down a gradient. In all dialysis membranes, there is some degree of back filtration; therefore, it is important that these solutions be sterile.

In the United States, the Food and Drug Administration has identified convective solutions as drugs and diffusive solutions as devices. In the present setting in the United States, dialysate solutions are not to be used in a convective mode. In other parts of the world, this designation is less concerning. For the most part, these solutions used for both convective and diffusive clearance are identical in terms of their components and sterility and are physiologic to the needs of the patient.

The decision to use convection versus diffusion is based on experience and style of practice. In septic patients with AKI, there may be a significant improvement in cytokine clearance in a convective mode over the diffusive mode. It is clear that small-molecular-weight substances such as urea and citrate are cleared equally by the diffusive and convective modes. As the molecular weight increases and protein binding becomes greater, there is enhanced solute clearance using the convective mode. Work by Flores et al has identified that in the highly catabolic bone marrow transplant population, there appears to be improved survival rates in patients using the convective mode.

If the goal of CRRT is clearance of small-molecular-weight solutes such as urea, there is no advantage of one mode over the other. In highly catabolic or septic patients, there may be an advantage to using the convective mode. Long-term and multisetting studies are needed to look at final outcome data of convection versus diffusion.

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Technique

Vascular access. Vascular access for SLED and CRRT are identical to those used in HD. Classically, vascular accesses are proportional to the size of the patient. This would suggest that smaller children require smaller vascular access, and larger children, larger access. The typical configuration of vascular access would allow for a short relatively stiff catheter to be placed in the vascular space. Studies by Hackbarth et al have identified that in children, improved outcome, as measured by circuit life, is greater with an internal jugular–placed catheter compared to a subclavian or femoral catheter.

Anticoagulation. Classically, anticoagulation is achieved with heparin. Heparin has a distinct advantage because it is inexpensive and caregivers throughout the world have experience with anticoagulation with heparin. Heparin classically is infused prefilter to anticoagulate the system. The disadvantage of heparin is the systemic anticoagulation. Historical data have identified that systemic anticoagulation with heparin of the circuit with protamine infusion back to the patient does not improve circuit life and may cause rebound hypercoagulability or coagulopathy in the patient.

Further, heparin-induced thrombocytopenia rarely can occur in patients with recurrent heparin exposure.

If the initial coagulation factors are negative, a bolus with 20-40 U/kg of heparin is given and a continuous infusion of 10-20 U/kg/h is started. Titration of heparin infusion is targeted to an activated clotting time of 180-200 seconds or a partial thromboplastin time of 2 times normal.

Citrate anticoagulation has become more common since work by Mehta et al. A recent survey suggests that 70% of North American–based CRRT programs in children use citrate-based anticoagulation. A very simple citrate protocol allowing one to chelate calcium prefilter to make the system hypocoagulable is suggested (Box 1). This coagulopathy is reversed by giving calcium back prior to reinfusing blood into the patient. The risk of citrate anticoagulation is 2-fold, related to calcium flux, either low or high, and metabolic alkalosis. With the use of low bicarbonate dialysate or replacement fluids, the risk of metabolic alkalosis essentially can be resolved.

If one is delivering more citrate than is being cleared, either by hepatic synthesis or the CRRT membrane, citrate accumulation can occur in the patient. This is referred to as citrate lock (also called citrate excess) and occurs when the amount of citrate delivered is greater than the patient's clearance through the liver. Citrate concentrations then increase in the blood, acting as a buffer by binding to calcium. Citrate lock is manifested by a decreasing serum ionized calcium level in the presence of increasing total calcium level. In order to treat citrate lock, citrate must be discontinued for 4 hours and then can be restarted at a lower delivery rate. A number of recent studies report safe practical protocols of citrate anticoagulation for children. Studies by Brophy and colleagues have identified that saline flushes give a very short circuit life as opposed to heparin; heparin and citrate are similar in terms of their circuit life, with less risk of complication when using citrate anticoagulation.

Box 1. Citrate Protocol for CRRT in Children

The commercially available ACD-A (Baxter Healthcare) is used in conjunction with calcium-free dialysis and replacement solutions in children. This contains 220 mEq/L of sodium and 24 g of glucose. These 2 issues need to be noted to avoid excessive sodium infusion or hyperglycemia.

Components needed for citrate anticoagulation include

- ACD-A
- CaCl, 8 g/L, or normal saline solution or dextrose 5% in water
- Normal saline solution (may not always be needed)
- Standard 140-mEq/L sodium dialysate or replacement fluid, with a preference of 25 mEq/L of sodium bicarbonate

The infusion rates of each are BFR dependent. Using BFR as 1, the ACD-A rate is 1.5 × the BFR (mL/h) and CaCl is 0.4 × the ACD-A rate (mL/h).

Example: If BFR is 100 mL/min, begin the ACD-A post patient prefilter (ie, infusing into the hemofiltration circuit) at 150 mL/h using an intravenous pump. Begin the CaCl at 60 mL/h. Using initially 30-min, then hourly, then eventually 6-hourly analysis of ionized calcium, titrate the patient's ionized calcium to normal and titrate the circuit to 1/3 of what is considered normal.

Abbreviations: ACD-A, Anticoagulant Citrate Dextrose-A; BFR, blood flow rate; CaCl, calcium chloride; CRRT, continuous renal replacement therapy.

Solutions. Solutions used in CRRT have changed significantly during the last 2 decades. Prior to 2000, solutions were either lactate based or acetate based, delivering acetate and lactate to the patient and often causing some degree of lactic acidosis. Work done in early 2000 showed that bicarbonate-based solutions in children are superior to lactate-based solutions. Since 2000 in North America and Europe, bicarbonate-based solutions have become commonplace. The combination of bicarbonate-based solutions with bicarbonate concentrations > 30 mEq/L and citrate anticoagulation often will result in metabolic alkalosis. Therefore, if a citrate anticoagulation protocol is used, it is best to use a bicarbonate level in the 22- to 25-mEq/L range, as well as a zero calcium bath.

The other components of convective or diffusive solutions are sodium, calcium (adjusted for heparin- or calcium-based protocols), bicarbonate (adjusted for heparin- or citrate-based protocols), and magnesium. Studies have shown that patients on CRRT, whether convective or diffusive, are at risk of developing hypophosphatemia. Research is ongoing to assess adding phosphorus to these baths. In theory, the combination of bicarbonate, calcium, and phosphorus in the same bag may increase the risk of precipitation. Therefore, phosphorus should be given to the patient separate from the circuit. Many protocols add potassium in physiologic levels in the form of potassium acid phosphate to the solution.

It is observed that pharmacy-made solutions are not only at risk for causing complication, but can even result in death. Studies by Barletta et al identified a significant number of complications including death in children with pharmacy-made solutions. Therefore, pharmacy-made solutions should be avoided at all costs from a safety perspective.

Machines. Machines used for CRRT are commonplace throughout the world. These machines have a heater, an accurate ultrafiltration monitor, and adjustments of blood flow and convective or diffusive flow. Data have shown that the AN69 polyacrylonitrile membrane (Gambro Health Care) when used in septic animal models improves outcome. However, in children, use of the AN69 membrane has been associated with the "bradykinin release

Box 2. CRRT Protocol

Mode: CVVH or CVVHD or CVVHDF; these are equally effective for clearance of small-molecular-weight compounds, eg, urea, but for large-molecular-weight proteins, eg, vancomycin, there is a preference of convection for clearance
Blood flow rate: Access dependent; range 5-10 mL/kg/min
Dialysate/replacement flow rate: 35-40 mL/kg/h or 2.5-3 L/1.73 m^2/h
Ultrafiltration: Dependent on patient's hemodynamic status; begin at zero and slowly increase to 0.5-2 mL/kg/h net until fluid balance goal is achieved
Thermic control: Maintained by the machine with addition of external warming devices if needed

Abbreviations: CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration.

phenomenon," in which there is a steep decline in blood pressure 5-10 minutes after the initiation of CRRT, in particular when a blood prime has been used. When the blood is exposed to the highly negatively charged AN69 membrane, pre-kallikrein and Hageman factor are coactivated, resulting in the release of bradykinen, a potent vasodilator. It has been shown that buffering the blood to physiologic pH before priming the circuit or infusing the blood postfilter at the same rate as a saline prime are effective in minimizing bradykinin release syndrome.

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CRRT Prescription

The prescription for CRRT is based on local style of practice. A standard pediatric CRRT prescription is shown in Box 1. Classically, the blood flow rate is determined by the vascular access. Protocols have ranged from 3-10 mL/kg/min based on the vascular access.

Conflicting data for clearance have been a debate over the last decade. The Ronco et al 2000 article in *The Lancet* suggested that those having convective clearance $>$ 40 mL/kg/h may have greater survival. This has been a significant question since publication of the ATN (Acute Renal Failure Trial Network) and RENAL (Randomized Evaluation of Normal Versus Augmented Level Replacement Therapy) trials, which failed to demonstrate that more dialysis is better. It should be appreciated that all data from Ronco et al are based on convective clearance, whereas the ATN and RENAL trials are based mostly on diffusive clearance, making a direct comparison incomplete. Since the original article by Maxvold et al that showed that 2,000 mL/h/1.73 m^2 gives a urea clearance of 30, many pediatric programs follow this guide. However, studies in children have not been done on "optimal prescription," and there is a need for a study looking at clearances in children on varying doses of CRRT. Therefore, the range in children should be 25-40 mL/kg/h or 2,000-3,000 mL/1.73 m^2/h of either convective or diffusive clearance.

Ultrafiltration should take into consideration the patient's hemodynamics, volume status, and fluid requirements. It is imperative that one not look at aggressive ultrafiltration needs unless the patient has hemodynamic stability. Without hemodynamic stability, removing fluid rapidly from that patient would not be in the best interest of the child. Clearly in such a setting, solute clearance can be achieved without net ultrafiltration, avoiding hemodynamic compromise.

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SLED Prescription

SLED is a slower dialytic modality that runs for long periods using conventional dialysis machines with low blood pump speeds and dialysate flow rates for 6-12 hours daily (Box 3). The slowest dialysate flow is about 100 mL/min, or 6 L/h. This can be used in only a diffusive mode. Vascular access and anticoagulation are identical in SLED and CRRT. The solution used in SLED is from online production using reverse-osmosis water or ultrapure solution mixed with an acid and base solution commonly used in HD. Therefore, bicarbonate, sodium, or calcium concentrations can be adjusted with potassium based on the needs of the patient and within the constraints of the conductivity of the HD machine. The level of ultrafiltration with SLED machines is identical to that accomplished by CRRT.

Nutrition Dosing in CRRT

Work by Maxvold et al has identified significant nutritional losses with CRRT and SLED. Patients can lose from 15%-35% of amino acids while on these modalities. Further work by Zappitelli et al has looked at vitamin and mineral losses associated with these treatments. Thus, nutrient issues during CRRT may affect the nutritional support to the child and should be taken into account when prescribing nutrition for children receiving CRRT.

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Box 3. SLED Protocol

Mode: Can only be CVVHD
Blood flow rate: Access dependent; range 5-10 mL/kg/min
Dialysate flow rate: Minimal dialysate flow rate is 100 mL/min or 6 L/h
Net ultrafiltration: Hemodynamic dependent; begin at zero and slowly increase to 0.5-2 mL/kg/h net until fluid balance goal is achieved
Thermic control: maintained by the machine with addition of external warming devices if needed

Abbreviations: CVVHD, continuous venovenous hemodialysis; SLED, sustained low-efficiency dialysis.

Choosing Between CRRT and SLED

The decision to use CRRT or SLED is based primarily on equipment. The advantage of a SLED machine is that if it is used for nocturnal SLED, that same machine could be used during the day for HD. The other advantage of SLED is that the solutions can be purchased from commercial vendors and are much less expensive than solutions made for CRRT. The disadvantage of SLED is its lack of continuous dialyzing.

In conclusion, the vast majority of centers throughout the world use CRRT in hemodynamically compromised children. Data would suggest that in septic or highly catabolic bone marrow transplant patients, there is an advantage of convective over diffusive clearance. There always is a risk of underdosing medications, as well as sieving nutrition from patients. Experience with SLED is much more limited, with very few published articles involving children receiving SLED.

Ongoing research is necessary to look at optimal drug dosing, optimal nutrition dosing, and optimal prescription in these highly catabolic and challenging patients.

RRT in Special Circumstances

Sepsis and Stem Cell Transplantation

Patients with sepsis and stem cell transplant recipients with AKI often are associated with the need for volume and blood pressure support. Indications for RRT are volume overload and the need for solute clearance. Data for volume excess and mortality have been demonstrated by a number of authors, observing that the amount of fluid overload at the initiation of RRT may predict mortality. Indication of RRT commencement is more difficult when solute clearance is considered. The work of Ronco et al on prescription delivery and outcome identified that those with lower SUN levels at RRT initiation have improved survival.

Superior cytokine clearance occurs in sepsis-associated AKI using convection. Flores et al also demonstrated a preference of convective over diffusive CRRT in children with AKI and stem cell transplants.

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Intoxications

The use of RRT for overdoses or intoxications has been studied for decades. The use of CRRT as the initial mode of RRT for intoxications should not be considered. The combined use of high-flux HD in tandem with CRRT is a reasonable therapy for removal of intravascular and tissue-bound intoxicants.

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Inborn Errors of Metabolism

Inborn error of metabolism with associated hyperammoninemia is considered a medical and dialytic emergency. Picca et al have performed comparison studies suggesting that HD is superior to CRRT, which is superior to PD for clearance of the ammonia. RRT initiation needs to be considered early, but in combination with medical therapy, including reduced protein intake and adequate glucose delivery to avoid hypermetabolism. McBryde et al as well as Bunchman et al have demonstrated that the use of RRT will clear not only the ammonia, but also the medications used to treat the underlying condition. Sequential use of HD and CRRT may be the most effective RRT prescription for treatment for inborn error of metabolism and prevention of ammonia rebound.

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Tumor Lysis Syndrome

Tumor lysis syndrome, like intoxication and inborn error of metabolism, is a potential RRT emergency. Coutsouvelis et al reflect the current belief of many hematologists/oncologists that with the availability of rasburicase to normalize uric acid levels, the need for RRT is limited. Although normalization of plasma uric acid level improves kidney function, it will not correct potassium, phosphorus, and calcium level derangements. Brochard et al demonstrated that there is an ongoing risk of AKI and associated need for RRT in these very high-risk patients. Use of rasburicase and white blood cell pheresis may lessen the tumor and solute load, but will not eliminate the need for RRT. It is suggested that affected children be placed on citrate-based anticoagulation CRRT with a potassium- and phosphorus-free convective or diffusive solution for 2-4 days during tumor reduction. This approach allows normalization of calcium levels and use of CRRT as an adjunct to the native kidney function of the child.

Additional Readings

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MAINTENANCE RRT

Choice of Modality

There is general consensus that kidney transplantation offers much better opportunities for a near-normal life for children than does dialysis, irrespective of which modality is chosen. Of the dialysis modalities, PD is the preferred initial RRT for children (particularly of younger age and smaller size). For technical reasons, PD is indicated in almost all children younger than 2 years and for 80% of children younger than 5 years.

Other factors that play a role in modality selection are patient age, medical factors (nonavailability of intact peritoneum), geographic location of the medical center, and presence of caregivers. An additional advantage of PD is that residual kidney function is better preserved than with HD. Maintenance PD allows patients to be managed in the home environment, avoids the need for anticoagulation, and is hemodynamically less stressful. It allows dialysis in young children and enables a less restrictive diet, resulting in better nutrition.

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Maintenance PD

We are not aware of any comparative studies of PD and HD outcomes in children with ESRD that suggest superiority of one modality over the other. Although the majority of children who have ESRD requiring dialysis can be managed with maintenance PD, the choice of dialysis modality generally is based on the preference of the patient and family, the philosophy of the center, and availability of the desired modality (Table 3).

Prescription

Most solutions use glucose as an osmotic agent. It not only can have systemic effects such as hyperinsulinemia and hyperlipidemia, but can cause peritoneal damage. It remains a useful option for short dwell times. Long-term PD therapy using dextrose is associated with cellular and morphologic changes in the peritoneal membrane, including angioneogenesis and submesothelial fibrosis. Repeated exposure to hypertonic, nonphysiologic pH and high glucose-containing fluids have been implicated in causing these changes, although it is uncertain whether the toxicity related to PD fluids is from the glucose or the glucose degradation products produced as a result of sterilization. Glucose degradation products are thought to contribute to both cellular dysfunction and membrane damage.

Alternatively, icodextrin can be used as an osmotic agent. It is absorbed into lymphatic channels at a slow rate and allows for sustained ultrafiltration over a longer dwell. It is equivalent to 3.86% dextrose Dianeal (Baxter Health Care; 45% absorption over 14-hour dwell) and is metabolized by amylase to maltose and other oligosaccharides. It is biocompatible because it is iso-osmolar, lacks glucose, and has significantly lower glucose degradation product content. Icodextrin solutions have a slow but prolonged ultrafiltration profile, whereas dextrose solutions have a rapid ultrafiltration profile early in dwell, which is reduced slowly as dextrose is absorbed and eventually glucose-induced transcapillary ultrafiltration ceases. Its uses include long night-time dwell in CAPD, long daytime dwell in continuous cyclic PD (CCPD), type 1 ultrafiltration failure, and peritonitis-associated ultrafiltration failure.

In some countries, amino acids have been used as osmotic agents, providing superior biocompatibility, providing less acidity (pH 6.2-6.7), and containing no glucose. Amino acids also limit protein loss in dialysate.

Continuous Cyclic PD

CCPD, just like CAPD, represents a continuous regimen of PD. In the morning at the conclusion of the overnight automated PD session, the patient disconnects from the cycler and leaves a fresh exchange in the abdomen (50%-100% of the night fill volume). The daytime dwell increases solute removal and ultrafiltration. CCPD is recommended in cases of negligible residual kidney function and if the nocturnal IPD regimen cannot achieve the desired solute and fluid removal. Looking at the peritoneal membrane transport characteristics also is important in selecting the optimal PD schedule for CCPD.

Patients who have high-average transport rates have the best outcomes on CCPD. When there is a long day dwell, most of the glucose is absorbed, so it is possible to achieve sustained ultrafiltration using an icodextrin-based PD solution. In the case that an additional increase in solute clearances is necessary and/or net ultrafiltration is still not sufficient, as can be observed in patients who have low-average transport status, it is possible to use more than one diurnal exchange.

Table 3. Comparison of Different Modes of PD

Type of Modality	Advantages	Disadvantages	Patient Selection	Issues
NIPD; short nocturnal cycle without daytime dwell	Preservation of membrane, no daytime glucose or fluid absorption	Decrease middle-molecule clearance	High urine output	Anuria and low/low-average transporter
CCPD; short nocturnal cycles with daytime dwell	Sustained daytime ultrafiltration/clearance, improved middle-molecule clearance	May require daytime exchange	Low urine output	High glucose absorption
CAPD; daytime and nighttime cycles	Complete equilibration of solutes and middle molecule	Occurrence of hernia, increased risk of peritonitis, patient discomfort, and continuous glucose absorption	Cost-effective, can be used for low/low-average transporter	Recurrent peritonitis and social issues

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cyclic peritoneal dialysis; NIPD, nocturnal intermittent peritoneal dialysis.

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Tidal PD

CCPD provides patients with an option to dialyze during the evening, freeing them for activities during the day. However, even with this therapy, not all patients are able to achieve adequate clearances. Therefore, TPD was proposed in an attempt to increase dialysis efficiency without sacrificing the advantages of CCPD. The rationale was that TPD would improve small-solute removal through better mixing of the PD fluid by the use of tidal cycles and create a reduction in nondialysis transit time through the creation of a tidal flow. This tidal flow allows dialysate to be in constant contact with the peritoneal membrane. TPD is both a technique and a cycling modality of PD. The tidal technique starts with an initial fill that is followed by a partial drain and replacement with fresh dialysate for each cycle. This process leaves a part of the dialysate in constant contact with the peritoneal membrane reservoir, and the inflow and outflow of the exchanges creates a wave or tide. During a typical CCPD/IPD treatment, significant time may be spent instilling and draining dialysis solution, during which time no dialysis occurs (nondialysis transit time). TPD is designed to improve clearances of small molecules through 2 mechanisms. First, in TPD, the reserve volume provides continuous contact of dialysate with the peritoneal membrane, thereby maximizing actual dialysis time. Second, the drain time in TPD is flow regulated; that is, when the programmed inflow and drain volumes are achieved, the cycler automatically moves into the next phase of the exchange. This may decrease the transit time in which there is no dialysate in contact with the peritoneal membrane, as seen with CCPD/IPD.

PD Prescription

The PD prescription includes the selection of PD solutions and determination of fill volume, dwell time, and number of exchanges. The prescription is based on the individual patient needs for solute transfer and removal of fluid, both of which can be increased by changes in the prescription.

It is suggested that a peritoneal equilibration test be performed in all children undergoing CCPD to determine the solute transfer characteristics of the peritoneal membrane, which can assist in developing an adequate dialysis prescription. Transport capacity of a patient's peritoneal membrane is one of the most important characteristics to consider when determining the dialysis prescription. It categorizes patients based on their solute transport rates and serves as the basis for the patient's dialysis prescription. In children, this standardized test measures small-solute transfer across the peritoneal membrane and net ultrafiltration during a 4-hour dwell using an exchange volume of 1,100 mL/m^2 of body surface area of a 2.5% dextrose-containing dialysate. However, infants and young children (aged <2 years) may not tolerate a test volume of 1,100 mL/m^2. In these patients, the test volume generally used is the clinically prescribed fill volume. There are 3 types of ultrafiltration failure: type I is a rapid solute transport, type II is impaired solute transport, and type III is excessive lymphatic absorption. Treatment varies depending on the type of membrane failure. If the ultrafiltration failure is increased solute transport (type I), therapy should involve shortening the dwell time and performing more frequent exchanges. In addition, eliminating the long dwell exchanges of CAPD or CCPD is strongly recommended. If the cause appears to be reduced lymphatic absorption, large dialysate volume should be avoided.

The PD treatment variables that can be adjusted include patient time, fill time, dwell time, and number of cycles. Standard prescriptions can be modified through adjustment of any of these variables. PD modeling software is available to facilitate prescription adjustment.

Adequacy

In children, adequacy of PD treatment cannot be defined solely by the removal of solutes and fluid. In order to determine the adequacy of PD treatment, the clinician also should consider clinical, metabolic, and psychosocial factors.

The weekly Kt/V_{urea} in patients receiving continuous PD can be estimated from the following parameters: the daily peritoneal urea clearance (Kt) is the sum of all drain volumes (residual kidney and peritoneal) and the ratio of the urea concentration in the pooled drained dialysate or urine to that in plasma (D/P urea). In cases in which the patient has significant residual urine production (arbitrarily defined as >100 mL/d), both the peritoneal and residual kidney components of solute clearance are used in the calculation of total solute clearance.

Various studies in adults have shown that to maintain adequate clearance, minimal delivered total solute clearance of Kt/V_{urea} should be at least 1.7/wk for patients undergoing CAPD. The same target was set for children. Preserving residual kidney function in PD patients is highly recommended because patients with more kidney solute clearance initially may be treated with IPD (such as nightly cycler PD with a

dry day). This may allow less intensive regimens while still providing adequate overall clearances.

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Maintenance HD

Access

There are 3 main types of access for long-term HD in children: creating a primary AVF, placing an AVG, or using a cuffed central venous catheter. The choice of access generally is based on a number of factors, including the patient's diagnosis, the patient's size, the procedural risk, the likelihood of transplantation, and the probability of long-term patency. Current data support the concept of "fistula first" in children who require long-term RRT and have distant kidney transplantation prospects.

Although data support using primary AVFs in children, a majority of infants and children initiate HD with a central venous catheter according to the NAPRTCS 2011 dialysis report. HD access devices include external percutaneous catheters (78.7%), external arteriovenous shunts (0.3%), internal AVFs (11.8%), and internal AVGs (6.7%).

It takes significantly longer for primary fistulas to mature in children than in adults. In some patients, it may take up to 4 months compared to the usual 6 weeks expected for adolescents and adults. In cases in which the primary fistula has failed or it is not technically possible to create one, an AVG is an alternative. For AVGs in children (as in adults), polytetrafluoroethylene (PTFE) is the preferred conduit due to better biocompatibility. AVGs most often are placed in the forearm; straight grafts (radial artery to brachial vein) are used more often in smaller children, and loop grafts (brachial artery to brachial vein) are used more often in larger children. Compared with AVFs, the rate of infectious complications and access stenosis in AVGs is much higher, which may require removal of the synthetic material.

The catheters used for long-term HD in children are Silastic cuffed dual-lumen catheters. Similar to acute catheter placement, it is recommended that the smallest effective catheter be used, avoiding the subclavian vein. Risks associated with catheter insertion for long-term HD include emboli formation, hemothorax, arrhythmias, vessel perforation and hemorrhage, and pneumothorax. In addition, long-term use of HD catheters often has complications, including kinking or displacement, infection, and thrombosis.

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Prescription

When writing an initial prescription for dialysis, the clinician should use the principals of kinetic modeling, specifically using the equation Kt/V assessed by C1/C0, where K is dialyzer urea clearance (in mL/min), T is time of treatment (in min), V is estimated total-body water (0.6 L/kg), C0 is the predialysis SUN level (in mg/dL), and C1 is postdialysis SUN level (in mg/dL). When using this formula, the process to determine the prescription includes first determining desired urea removal (eg, 50%); second, choosing the appropriate dialyzer size (K); third, estimating V (600 mL/kg); fourth, obtaining predialysis [SUN] C0, performing dialysis for prescribed t, and obtaining postdialysis [SUN] C1; fifth, calculating V using K, t, and measured C0 and C1; and sixth, repeating steps 1-5 using calculated V.

To prevent disequilibrium in new ESRD starts, aim for urea clearance of 30% for the first treatment (Kt/V = 0.7), 50% for the second treatment (Kt/V = 1.0), and 70% for the third and subsequent treatments (Kt/V = 1.2). If initial SUN level is $<$100 mg/dL or mannitol is used, aim for urea clearance of 50% for

the first treatment and 70% for the second and subsequent treatments.

Individualizing the HD prescription using Kt/V can be accomplished with urea kinetic modeling, which allows for variation in dialysis time, use of larger high-efficiency high-flux dialyzers, and optimizing dietary protein need. Urea kinetic modeling is a method for verifying that the amount of dialysis prescribed (prescribed Kt/V) equals the amount of dialysis delivered (effective Kt/V). Kinetic modeling also quantifies the amount of urea generated, which is a marker of protein catabolic rate and protein intake.

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Adequacy

There is no consensus on the ideal HD dose for children receiving maintenance HD. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) and the Renal Association guidelines both recommend the same delivered dialysis dose as is used for adults, namely equilibrated $Kt/V_{urea} > 1.2$, delivered 3 times a week. In addition, the HEMO (Hemodialysis) Study observed that there is no difference in survival between patients who have a mean equilibrated Kt/V of 1.16 and those who achieve Kt/V of 1.53. Moreover, a recent study of 613 adolescents receiving HD found that although risk of hospitalization increased with a single-pool $Kt/V < 1.2$ compared to 1.2-1.4, a single-pool $Kt/V > 1.4$ did not improve outcomes.

Drug Administration in Dialysis

When ≥25% of an administered dose of a drug is removed by dialysis, it is considered clinically significant. It is vital to identify the extent of drug removal and provide supplemental dosing because failure to do so may lead to underdosing and thus to therapeutic compromise. In dialysis, both diffusive and convective mechanisms eliminate drugs. Dialysis is able to remove only free drugs from the body because drugs that are bound to plasma proteins and other cellular constituents do not cross the peritoneal or dialyzer membrane. HD has the greatest efficiency of drug removal, followed by CRRT and then PD. Although CRRT and PD are less efficient at drug removal than HD, overall, they may provide an equivalent level of drug removal because they are performed over a longer period.

When prescribing a drug to children with kidney failure, the physician should estimate residual kidney function and how much of the drug will be eliminated by the kidneys and other routes and assess whether the child needs a supplemental dose to account for the clearance of drug during dialysis. Therapeutic drug monitoring when available also can guide the therapy.

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Cognitive and School Performance in Children With CKD and on Dialysis

Children and adolescents on dialysis therapy are at greater risk for problems with psychological adjustment. In addition, difficulty adjusting to the diagnosis and to dialysis therapy is associated significantly with nonadherence in children and adolescents on dialysis therapy.

We are unaware of any studies that specifically explore the connection between intellectual function and adherence to dialysis therapy. However, there is literature showing the negative effect of decreased kidney function on cognitive function, so persistent nonadherence may negatively affect cognitive development and functioning.

With regard to children who require dialysis, no study has demonstrated that one modality, either PD or HD, will yield a better neurocognitive outcome. However, the stage of chronic kidney disease (CKD) affects neurocognitive development. Hulstijn-Dirkmaat et al showed that patients with earlier stages of CKD had better cognitive performance scores compared with those receiving maintenance dialysis.

Studies have yielded variable results when testing intelligence. Children with CKD have been reported to demonstrate lower scores on IQ testing compared with their non-CKD siblings. Specific deficits have been reported to include problems with verbal abstraction and verbal performance, diminished attention span, lower memory scores, and poor executive function. Deficits in problem solving, ability to maintain attention, advanced problem solving, and initiation behaviors also have been described. Most children with CKD are reported to test close to average on IQ evaluation and can participate in school at or near grade level.

For patients with neurocognitive delays, problems seem to persist into adulthood. Further, adults who had CKD as children report lower scores on health-related quality of life testing and greater psychosocial impairment compared with their non-CKD peers. Health-related quality of life testing shows that school

attendance may be significantly impaired in patients with ESRD because of either the time required for the dialysis treatment (especially HD) or related illnesses. Thus, the neurocognitive issues related to CKD appear to put children at risk for long-term consequences. In a long-term study of infants who were younger than 18 months at dialysis therapy initiation, 58% of those who survived (18/31) attended regular school, but 13 (42%) had significant neuropsychological impairment, and of these, 9 children (25% of all survivors) required special education and 4 (13%) were severely impaired and required residential care. A relatively substantial percentage of children who develop CKD, especially those with congenital anomalies of the kidney and urinary tract, have underlying genetic diseases. Some of these syndromes may confer neurocognitive delays and affect long-term development independent of CKD.

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Adherence to Dialysis in Children

The estimated rate of nonadherence to treatment regimens in children with chronic illnesses is estimated to be ~50%. There is only one published study looking at nonadherence in children on dialysis therapy. The study showed that older age, low family socioeconomic status, duration of dialysis, and living in a single-parent home were associated with reduced adherence. Decline in adherence during adolescence is common because this is a developmental stage with a drive for autonomy. There is a need to establish interventions to promote adherence. A recent meta-analysis looking at interventions aimed at adherence in children found that behavioral and multicomponent interventions are the most effective in improving adherence behaviors.

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Transition to Adult Renal Care

Better patient survival in recent years has increased the number of young patients graduating from pediatric to adult renal care. Because young people are in transition from 14 to 21 years, it is important to have good communication and rapport between both pediatric and adult services. One method that may promote a successful transition is a transition clinic, where both pediatric and adult specialists jointly see the young adult patient before he or she finally is transferred to the adult nephrologist. However, time and finances may remain an issue in this method. A consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA) recently has been published that addresses all the issues related to transition.

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Mortality on Dialysis

All the studies we are aware of have shown a higher mortality rate in children on dialysis therapy compared with adults. According to the NAPRTCS, the highest mortality is in children who are younger than 1 year at the start of dialysis therapy, with survival rates of 83.2%, 74.3%, and 66.4% at 1, 2, and 3 years, respectively. The 2011 US Renal Data System (USRDS) report showed that the adjusted all-cause mortality rates for children aged 0-4 years were higher than those found in their older counterparts. For children who began ESRD therapy in 2000-2004, the overall probability of surviving 5 years was 0.88. This ranged from a low of 0.78 in patients aged 0-4 years to 0.92 for ages 10-14 years. In terms of dialysis modality, the highest probability of survival occurred in patients with a transplant, at 0.95, compared to 0.74 for those treated with HD. According to the USRDS, the primary diagnosis independently determines mortality for children on dialysis therapy; children who have glomerulonephritis and hereditary or congenital

disease have greater 5-year survival than those who have secondary glomerulonephritis or vasculitis.

The incidence and prevalence of kidney failure in children has increased tremendously worldwide, reaching 2% of national dialysis or transplant programs. Children initiate dialysis therapy with the goal of successful kidney transplantation to provide the best survival and outcome measure. However, a long transplant list, social factors, and disease-related morbidity may require long-term dialysis therapy. Factors that influence outcome are age at the start of dialysis therapy, duration of dialysis, modality of dialysis, comorbid conditions, and the cause of primary disease that led to ESRD. Treatment factors that affect outcomes are vascular access, dialysis adequacy, residual kidney function, nutrition, and growth. Meticulous care of modifiable risk factors such as anemia, vascular calcification, and dyslipidemia is important for individuals who have a lifetime of RRT ahead.

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CONCLUSIONS

The new innovations in dialysis techniques for children have contributed to improved quality of life, psychosocial outcome, nutritional status, neurologic development, and patient survival. Particular attention needs to be paid to technical aspects that have been shown to be helpful in meeting children's specific clinical needs. Hopefully this review will serve as a valuable tool for successfully caring for this challenging patient population.

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