Renal Replacement Therapy in the Pediatric Critical Care Unit

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Abstract

Keywords

- ▶ continuous renal replacement therapy
- ▶ hemodialysis
- ▶ peritoneal dialysis
- ▶ dialysis modalities

Renal replacement therapy is becoming more prevalent in the pediatric intensive care units for a large variety of disease states, including multiorgan dysfunction syndrome, fluid overload, and electrolyte imbalance. Three modalities—continuous renal replacement therapy, hemodialysis, and peritoneal dialysis—are commonly used. When deciding among the three therapies, there are several advantages and disadvantages of each modality that must be considered. This manuscript provides an overview of each modality as well as its pros and cons.

Introduction

Renal replacement therapy (RRT) in pediatric intensive care units is becoming widely prevalent for a large variety of disease states. The most common indication for dialysis in the pediatric population remains fluid overload combined with electrolyte disturbances.^{1–3} With the development of new techniques, dialysis machines, and filters, RRT can now be successfully performed in even small and very low-birth-weight infants.^{4–8}

Principles of Dialysis

Two main principles are involved in RRT: diffusion and osmosis. The process of dialysis occurs through a semipermeable membrane by molecules passing down the concentration gradient by diffusion until the two sides of the membrane equilibrate. Ultrafiltration involves the movement of water across the semipermeable membrane due to osmotic forces. In addition, in continuous renal replacement therapy (CRRT), convection is used for solute clearance. Convection describes movement of solute across the membrane as it is “dragged” by the movement of water. Molecules 500 Da or less can easily be dialyzed. Molecules greater than 50,000 Da, such as albumin, are not dialyzable.

Indications for Dialysis

The following are some common primary diseases that may require dialysis:

- Multiorgan dysfunction syndrome
- Acute kidney injury (AKI)
- Inborn error of metabolism
- Hemolytic uremic syndrome
- Tumor lysis syndrome
- Drug intoxications
- AKI after cardiopulmonary bypass

Fluid Overload

The pediatric patient CRRT (ppCRRT) registry, which was a large, multicenter, observational collaboration across the United States, gathered data on pediatric patients receiving CRRT. From this registry Sutherland et al evaluated the relationship between severity of fluid overload and mortality risk in 297 children receiving CRRT.⁹ The investigators determined the percentage of fluid overload at the time of CRRT initiation and correlated this to mortality. The study found that patients with 20% or greater fluid overload had a mortality odds ratio of 8.5, and that even after multivariate analysis adjusting for severity of illness and intergroup differences, patients with a higher percentage of fluid overload had

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a higher mortality rate. Other studies concurred that higher percentage of fluid overload prior to the initiation of RRT in pediatric patients results in a higher mortality rate.^{10,11} The optimal time for initiation of CRRT in regard to fluid overload remains unclear, although some studies suggest that starting CRRT when fluid overload is less than 10% may decrease mortality.^{9,11}

Electrolyte Imbalance

Acute electrolyte disturbances frequently seen in AKI (e.g., life-threatening hyperkalemia, symptomatic uremia, and intractable metabolic acidosis) may necessitate RRT.

Toxins

Frequently the indication for renal replacement is the removal of toxins. However, not all toxins can be removed by renal replacement. Some factors that determine whether a toxin can be removed include water solubility, molecular weight of the toxin, volume of distribution, the rate of redistribution, and whether it is protein bound. Smaller molecules (< 500 Da) diffuse easily across the dialysis membrane and are more effectively removed. Larger molecules can still be dialyzed via convection but typically are less efficiently removed. Molecules bound to protein are more difficult to remove because the protein-toxin complex renders it too large to pass through the dialysis membrane. The ability of a toxin to be removed by dialysis also depends on its volume of distribution in the body. For instance, a toxin that is highly tissue bound, and therefore has a high volume of distribution, will be harder to remove by dialysis compared with a toxin that remains primarily intravascular (smaller volume of distribution). Finally, the rate of distribution of the toxin from tissue, intracellular, or other extravascular space to the intravascular space also affects the effectiveness of toxin clearance. Toxins with a slow rate of distribution will be more difficult to remove and may demonstrate a rebound effect after cessation of dialysis. In general, because of its associated risks, RRT should be considered for toxin removal only if it can increase total body elimination of the toxin by at least 30%.¹² Common toxins that can be removed by RRT include lithium, salicylates, phenobarbital, ethylene glycol, and methanol.¹³

Hyperammonemia

Infants with an inborn error of metabolism can develop severe hyperammonemia and may require RRT for ammonia clearance. Because of their superiority in ammonia clearance, dialysis with hemodialysis (HD) or CRRT is preferable to peritoneal dialysis (PD).^{14–16}

Tumor Lysis Syndrome

In oncology patients at high risk of tumor lysis syndrome (TLS), such as non-Hodgkin lymphomas, the rapid development of hyperkalemia, hyperphosphatemia, and hypocalcemia may warrant initiation of RRT early in the course of treatment. Calcium and phosphorus can precipitate in the kidneys leading to or exacerbating AKI.¹⁷ Because tumor lysis is continuous, CRRT is frequently the preferred modality, although HD may sometimes be needed for rapid clearance in cases of life-threatening hyperkalemia. PD, because of its slow clearance, is not a useful modality in TLS.

Continuous Renal Replacement Therapy

Advantages

Some advantages of using CVVH/CVVHD/CVVHDF, collectively termed *continuous renal replacement therapy* (CRRT), compared with HD and PD are listed in the ►Table 1. CRRT frequently is the modality of choice in an intensive care setting because of its gradual and controlled fluid removal along with solute clearance. Patients in the ICU are often severely ill and cannot tolerate rapid shifts in intravascular volume. Compared with HD where large amounts of fluid are removed in a shorter period of time, CRRT allows for controlled, hourly fluid removal that can be adjusted according to the patient's clinical status. Additionally, because fluid is removed continuously, CRRT allows for more liberal fluid intake, particularly nutritional and continuous infusions.

Disadvantages

One disadvantage of CRRT is limited use in very small patients. Extracorporeal volume in the circuit should be less than 10% of the patient blood volume. In smaller patients, such as neonates and infants less than 10 kg, the large extracorporeal circuit volume relative to the patient's blood volume and higher blood relative blood flows pose a challenge in CRRT. Therefore, to maintain adequate blood volume on CRRT, patients 10 kg or less will need a packed red blood cell prime. Studies have shown that patients 10 or less kg have higher mortality than those who are greater than 10 kg.⁵ CRRT also has slower blood flow rates than HD, so that clearance with CRRT is slower as well. However, because of its continuous nature, CRRT can achieve similar solute clearance as HD over a longer period.

Other disadvantages of CRRT compared with other dialysis modalities include the potential hemodynamic instability, the need to be relatively immobile for 24 h/day, and the need for anticoagulation. The potential hemodynamic

Table 1 Pros and cons of each dialysis modality

	Access	Length of time	Patient size	Mobility	Fluid restricted	Anticoagulation
CRRT	Vascular	Continuous	Some limitation	Limited	No	Heparin/citrate
HD	Vascular	Intermittent	Limited	Unlimited	Yes	Heparin
PD	Nonvascular	Either	No limit	Unlimited	Yes	None

Abbreviations: CRRT, continuous renal replacement therapy; HD, hemodialysis; PD, peritoneal dialysis.

instability on CRRT typically is seen in the first 15 minutes of starting CRRT. Occasionally, vasodilation and hypotension can be noted during this period and is thought to be secondary to bradykinin release. Hypotension should be quickly mitigated with volume support, with saline or colloid, calcium gluconate, and/or vasopressor support. If hypotension persists and is nonresponsive to medical management, CRRT may need to be discontinued. Because the CRRT machine is sensitive to changes in blood flow, excessive patient movement may cause the machine to automatically shut off. This is generally not a problem in a critically ill, sedated patient. However, in small children who are active and mobile, HD may be a better option than CRRT. Anticoagulation considerations are addressed in section "Anticoagulation in Continuous Renal Replacement Therapy."

Access in Continuous Renal Replacement Therapy

CRRT requires a good central venous catheter. Generally, using as large of a catheter as possible will allow for better blood flow and reduce the risk of clotting the filter. Results from the ppCRRT registry demonstrated that catheters smaller than 5.0F dual lumen lasted less than 20 hours.¹⁸ Catheters inserted in the internal jugular vein compared with femoral vein catheters generally remain patent longer.¹⁹ ▶ **Table 2** shows various catheter sizes.

Anticoagulation in Continuous Renal Replacement Therapy

Heparin was traditionally used as anticoagulation in CRRT to prevent clots from forming in the extracorporeal circuit. However, because of its increased risk of bleeding especially in critically ill patients and its potential for developing heparin-induced thrombocytopenia, an alternative method of anticoagulation was developed using citrate. Citrate binds to free, ionized calcium in the blood and thereby inhibits the clotting cascade. Citrate is infused prefilter and prevents coagulation within the circuit only. Calcium is then infused to the patient to prevent hypocalcemia. Some protocols require the calcium to be infused via a separate line, and this should be considered when line access is placed. A typical start rate of citrate is around 1.5 times the blood flow rate, and the start rate of calcium is normally around 0.4 times the citrate rate. The citrate infusion can then be titrated within the extracorporeal circuit to maintain an ionized calcium level of 0.3 to 0.4 mmol/L, which should effectively prevent clots from forming. Similarly, the calcium infusion to the patient can be titrated to maintain a normal serum ionized calcium. While citrate is effective as an anticoagulant, in a patient with liver dysfunction or failure, "citrate lock" can

develop. Citrate is normally metabolized by the liver. However, in patients with liver dysfunction, citrate infusion may exceed hepatic metabolism, resulting in potentially dangerously low ionized calcium. "Citrate lock" should be suspected in patients on CRRT who have a rising total calcium level despite a dropping ionized calcium level. If citrate lock is identified, the citrate infusion should either be reduced or held for several hours to allow time for liver metabolism. Despite its potential complications, several studies have shown that citrate anticoagulation, compared with heparin, is as effective and results in a longer circuit life and reduced risk of bleeding in both adults and children.^{20–25}

If heparin is desired as the anticoagulant, a bolus is given followed by a continuous infusion of heparin. The concentration of heparin used is typically 10,000 IU/1000 mL. Depending on the patient's anticoagulation state, the initial dose of heparin is typically around 30 to 50 IU/kg followed by a continuous infusion of 0 to 30 IU/kg/h. Activated partial thromboplastin time ratio needs to be checked frequently and kept 2 or less to prevent overcoagulation. Ostermann et al have suggested an algorithm for using heparin as anticoagulation in CRRT.²⁶

Prescription

In CRRT, a typical blood flow rate is around 2 to 5 mL/kg/min with usually a maximum flow of 100 mL/min. However, if needed, this blood flow can be increased further to provide better clearance. Dialysate flow rate is estimated at $(2000 \times \text{body surface area in m}^2)/1.73$. The replacement rate is around 30% of the dialysate rate. Depending on the machine, it is given either all prefilter or divided into pre- and postfilter. Adjustments in the blood flow rate, as well as the dialysate flow rate, can increase or decrease the rate of solute and fluid removal.

The typical CRRT dialysate content is listed in ▶ **Table 3**. Depending on the electrolyte content of the dialysate and the needs of the patient, additional electrolytes (e.g., calcium, potassium, phosphorus, and magnesium) may be added to the dialysate.

Conventional Hemodialysis

Advantages

One clear advantage that hemodialysis (HD) has compared with other modalities is its ability to quickly remove fluids and solutes over a short period of time. Adequate clearance and fluid removal on HD can usually be accomplished in 2 to 4 hours. This is particularly advantageous in emergent situations, such as life-threatening hyperkalemia or certain drug intoxications. Patients can be mobile in between treatments. If needed for long term, HD can also be easily transitioned to an outpatient or lower acuity setting, unlike CRRT that will require constant intensive care unit supervision.

Disadvantages

Because of its rapid fluid removal, some critically ill patients, particularly those with hemodynamic instability, will not be able to tolerate such large fluid shifts. Moreover,

Table 2 Catheter sizes

Neonate < 6 kg	Dual-lumen 6.5–7.0F	10 cm length
6–15 kg	Dual-lumen 8.0F	15 cm length
15–30 kg	Dual-lumen 9.0F	15–20 cm length
> 30 kg	Dual-lumen ≥ 10F	15–20 cm length

Table 3 Typical electrolyte content of CRRT dialysate^a

Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Magnesium (mEq/L)	Lactate (mEq/L)	Calcium (mEq/L)	Glucose (mg/dL)
140	2–4	110	32–35	1–1.5	0–3	0–3	100

Abbreviations: CRRT, continuous renal replacement therapy.

^aContents vary depending on the manufacturer.

in these hemodynamic unstable patients, these periods of hypotension associated with rapid fluid removal can further diminish blood flow to the kidney and exacerbate AKI. Dialysis disequilibrium, which occurs when a large amount of urea is removed too quickly resulting in rapid osmolar shifts, can lead to headaches, vomiting, or even more serious seizures. Because HD can only remove a certain amount of fluid and solute at a time, the patient's fluid, protein, and electrolyte intake (i.e., sodium and potassium) need to be limited between treatments. HD requires a purified water supply and trained personnel. For patients less than 10 to 15 kg, a prime with blood, saline, or albumin will be needed due to the large extracorporeal volume.

Access in Hemodialysis

Similar to CRRT, HD also requires vascular access, and a temporary internal jugular line is preferred for short-term, acute treatments. If dialysis is needed for a prolonged period and will likely be needed in an outpatient setting, the temporary catheter can be exchanged for a more permanent tunneled HD catheter.

Anticoagulation in Hemodialysis

Like CRRT, anticoagulation is needed to perform HD. Heparin currently is the anticoagulant of choice. A typical prescription for heparin is 50 units/kg with 60% of this total given as an initial bolus and the remaining 40% continuously infused throughout the remainder of the treatment. The dose of heparin may be increased or decreased depending on the patient's coagulation status and whether clots form in the line.

Prescription

The first session of HD is usually shorter, around 2 hours, so that dialysis disequilibrium syndrome can be avoided. At each initial treatment, only 30% of the urea should be removed at a time to avoid rapid osmolar shifts. The blood pump rate is usually 6 to 8 mL/kg/min but can be adjusted depending on tolerance. Fluid removal at the first session should be limited due to concern for hypotension, but, if tolerated, subsequent treatments can have increasing ultrafiltration. If the patient experiences hypotension, saline or albumin may be needed to support the blood pressure.

Peritoneal Dialysis

While CRRT and HD in the ICU setting are becoming more prevalent, in certain cases, peritoneal dialysis (PD) is superior to CRRT. For instance, in neonates with AKI secondary to

posterior urethral valves, congenital renal hypoplasia and dysplasia, or autosomal recessive polycystic kidney disease, PD will be an ideal dialysis modality, especially if the patient is anticipated to be on dialysis for a prolonged period of time.

Advantages of Peritoneal Dialysis

Some advantages of PD are its ability to be used in even very small infants and in hemodynamically unstable patients. The only patient size limitation with PD is the ability to place a PD catheter. PD is the least expensive of all modalities, and can be done as manual exchanges without the need for an automated machine. There is no anticoagulation needed in PD, making it an ideal modality for the patients in whom bleeding is of extreme concern. In emergent situations, a temporary percutaneous catheter can be placed easily at bedside, although a more permanent Tenckhoff catheter is ideal.²⁷ Because PD does not require vascular access, it allows for preservation of vasculature for future needs.

Disadvantages of Peritoneal Dialysis

Compared with CRRT, PD is slower and less efficient at removing waste and toxins. Patients who have had multiple abdominal surgeries will frequently have diffuse scarring of the peritoneal membrane, rendering it ineffective for dialysis. Patients with limited lung capacity or respiratory distress may not be able to tolerate PD due to the force it may exert on the diaphragm. Likewise, patients with diaphragmatic defects will not be candidates for PD. The PD catheter can become obstructed with omentum or debris. Ideally it will be best to wait a few days between placement of the PD catheter and using it for dialysis to allow the skin around the catheter to heal and prevent leakage. However, in emergent situations, a PD catheter can be used immediately with smaller fill volumes to reduce the risk of leakage. Patients who have had multiple episodes of peritonitis, especially fungal peritonitis, will not be ideal candidates for PD.^{28–31}

Technique/Prescription

PD can be performed either with manual exchanges or automated exchanges with a PD machine. Manual exchanges are easy and cost-effective but require dedicated personnel. Most automated PD machines have a lower limit of approximately 100 mL fill volumes, so typically small infants will require manual exchanges until they are able to tolerate large fill volumes. A typical fill volume to start with is around 10 to 20 mL/kg body weight. With a fresh catheter, an even smaller fill volume may be considered to reduce the risk of leakage around the catheter. The fill volume should be gradually increased over several days or weeks to a goal volume of

800 mL/m² for a child younger than 2 years and 1400 mL/m² for a child aged 2 years or older.^{32,33} The amount of ultrafiltration is determined by the dextrose content of the peritoneal dialysate. Typical commercial dialysate dextrose content ranges from 1.5 to 4.25%, with the higher dextrose content resulting in more ultrafiltration. If the catheter becomes slow flowing secondary to fibrin deposits, heparin can also be added to the dialysate (500 units/L).

Summary

In conclusion, there are several modalities of RRT that can be offered to pediatric patients who require dialysis. Each modality has its own advantages and disadvantages that must be considered when choosing among the different modalities. With the significant advancement in RRT, dialysis can now even be offered to very small children, including neonates.

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