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REVIEW

Prolonged intermittent renal replacement therapy in children

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Abstract Wide ranges of age and weight in pediatric patients makes renal replacement therapy (RRT) in acute kidney injury (AKI) challenging, particularly in the pediatric intensive care unit (PICU), wherein children are often hemodynamically unstable. Standard hemodialysis (HD) is difficult in this group of children and continuous veno-venous hemofiltration/dialysis (CVVH/D) has been the accepted modality in the developed world. Unfortunately, due to cost constraints, CVVH/D is often not available and peritoneal dialysis (PD) remains the common mode of RRT in resource-poor facilities. Acute PD has its drawbacks, and intermittent HD (IHD) done slowly over a prolonged period has been explored as an alternative. Various modes of slow sustained IHD have been described in the literature with the recently introduced term prolonged intermittent RRT (PIRRT) serving as an umbrella terminology for all of these modes. PIRRT has been widely accepted in adults with studies showing it to be as effective as CVVH/D but with an added advantage of being more cost-effective. Pediatric data, though scanty, has been promising. In this current review, we elaborate on the practical aspects of undertaking PIRRT in children as well as summarize its current status.

Keywords SLED · Dialysis · Sustained low efficiency dialysis · PIRRT · Prolonged intermittent renal replacement therapy · PICU

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Introduction

Acute kidney injury (AKI) continues to contribute significantly towards morbidity and mortality in critically ill children and there has been an ongoing intense search to identify any early interventions [1]. Recent trials have generated some evidence in favor of avoidance of fluid overload as well as early initiation of renal replacement therapy (RRT) in reducing mortality [2–4]. AKI in pediatric intensive care units (PICU) is often secondary to sepsis/shock and these children are usually hypotensive and on various types of vasopressor support despite being fluid overloaded [3, 5]. Standard extra-corporeal RRT such as conventional intermittent hemodialysis (IHD) in this subgroup of AKI can be problematic since it is likely to aggravate hypotension and precipitate catastrophic events [5–7]. Peritoneal dialysis (PD), although feasible even among hemodynamically unstable patients [8], does have its drawbacks [9–11]. There is the theoretical risk of intra-peritoneal distention and worsening of ventilation parameters among ventilated children, although clinical evidence has been contrasting [11–14]. Moreover, unlike HD, one cannot control the rate of ultra-filtration in PD, which can be erratic [8–10]. Hence, continuous veno-venous hemofiltration/dialysis (CVVH/D) has been preferred, especially in developed countries, for a slow but continuous mode of extra-corporeal RRT [2, 15–17]. Unfortunately, CVVH/D requires expensive

sophisticated machines and consumables, trained staff, and is usually very labor intensive. Hybrid therapies providing RRT over an extended period but on an intermittent basis (prolonged intermittent RRT i.e., PIRRT) using standard HD machines has been envisaged to include the best of both these worlds, i.e., slow sustained modality of CVVH/D ensuring hemodynamic stability and better biochemical clearance along with cost-effectiveness of conventional IHD (Table 1). Although evidence has accumulated in its favor, this has primarily been among adults, with pediatric literature still scanty [18–27]. In this review, we aim to summarize the current status of PIRRT with a focus on children.

Definition of prolonged intermittent renal replacement therapy (PIRRT)

Broadly speaking, any extracorporeal mode of RRT given intermittently over a prolonged session (i.e., ≥6 h) can be defined as PIRRT [28]. Hence the original description of hemodialysis by Kolff (duration = 690 min, blood flow of 116 ml/min) could be described as the initial PIRRT [29, 30]. Subsequent development in the field of HD saw the acceptance of standard IHD as 3–4 h duration with a high blood flow (Qb) and dialysate flow (Qd). The concept of hybrid therapy combining the efficiency of HD and the hemodynamic stability of CVVH was re-explored by Kudoh in 1988 (slow continuous HD), and after its use by Schlaeper et al. among a cohort of critically ill adults, it has become quite in vogue [31–33]. Thereafter, various modifications in dialysis prescription have been undertaken, primarily influenced by available machines and the dialysis unit requirements, such as the type of case loads encountered, resource needs, and available expertise. Table 2 explains the multiple terminologies in use describing the hybrid varieties of extra-corporeal RRT. The use of PIRRT as an umbrella terminology describing both diffusive and or convective methods of extended extracorporeal blood purification is becoming the accepted norm. In this review, the term PIRRT and sustained low-efficiency HD (SLED) will be used interchangeably. Although the duration has been fixed as ≥6 h, rate of Qb and Qd can be variable. Overall Qb is usually ≤5 ml/kg/min and Qd ≤ twice the Qb. Lack of a rigid definition is often construed as a major disadvantage but can be in fact advantageous in its flexibility both

Table 1 Comparison of various modalities

	IHD	CRRT	PIRRT	Peritoneal dialysis
Machine	Standard IHD machine	Standard CRRT machine	Can be done by standard IHD machine	Can be even done manually without any aid of machine, i.e., cyclers
Mode of clearance	Primarily diffusion	Diffusion, convection, or both	Diffusion, convection (not allowed in USA), or both	Both diffusion and convection
Qb (ml/min)	5–10 ml/kg/min	3–5 ml/kg/min	3–5 ml/kg/min	NA
Qd	500–800	25–30 ml/kg/h	100–300 ml/min	
Standard duration	3–4 h	Continuous	6–12 h	Usually is a continuous process until renal recovery. If using a stiff catheter, it should not be kept for >72 h
Frequency of procedure	3 days/week	Continuous	3–7 days/week	As above
Timing of procedure	Usually daytime	Continuous	Daytime or night	As above
Anticoagulation	Heparin/saline	Heparin/citrate/saline rarely	Heparin/saline	Can be added in the PD fluid without any risk of systematic anti-coagulation
Vascular access	AVF/AVG/CVC	CVC	CVC	NA. Needs a catheter to access the peritoneal cavity. This can be stiff or soft catheters like Tenkoff
Intensity of nursing	Low	High	Low to moderate	Low
Patient location	ICU, ward, step-down unit	ICU	ICU or step down unit	Can be done even in the ward if the child is stable
Cost	+	+++	++	+ (With use of stiff catheter the cost is minimal)

AVF arteriovenous fistula, *AVG* arteriovenous graft, *CVC* central venous catheter, *CVVH* continuous veno-venous hemofiltration/dialysis, *ICU* intensive care unit, *IHD* intermittent hemodialysis, *PIRRT* prolonged intermittent renal replacement therapy, *PD* peritoneal dialysis, *Qb* blood flow, *Qd* dialysate flow, *USA* United States of America

Table 2 Terminologies used to describe various modes of prolonged intermittent hemodialysis

Various terminologies that have been interchangeably used in medical literature but nowadays falls under the umbrella term of prolonged intermittent renal replacement therapy (PIRRT):
a) S- HDF: Sustained hemodiafiltration- Abe and colleagues, Japan, 2010 [22]
b) SLED: sustained low-efficiency dialysis- Berbece and colleagues, Canada, 2006 [34], Clark and colleagues, USA, 2008 [35], Fiaccodori and colleagues, Italy, 2013 [36], Marshall and colleagues, USA, 2001 [23]
c) SLED-BD: sustained low-efficiency dialysis with single-pass batch dialysate- Schwenger and colleagues, Germany, 2012 [37]
d) ED- extended dialysis- Kielstein and colleagues, Germany, 2004 [38]
e) EDD- extended daily dialysis- Kumar and colleagues, USA, 2000 [39]
f) E-HFD- extended high-flux hemodialysis;- Lonnemann and colleagues, Germany, 2000 [40]
g) PIRRT- prolonged intermittent renal replacement therapy; Albino and colleagues, Brazil, 2015 [41]
h) PDIRRT- prolonged daily intermittent renal replacement therapy - Naka and colleagues, Australia, 2004 [24]
i) SLED-F: sustained low-efficiency dialysis with convection [42]

in terms of duration and intensity, which can be adjusted as per patient requirement and the HD unit's capability.

Indications for PIRRT

Indications for initiating RRT in a pediatric intensive care unit (PICU) are varied and include [43, 44]:

- Non-obstructive oliguria with fluid overload 10% above baseline.
- Refractory metabolic acidosis or hyperkalemia
- Uremic organ involvement (pericarditis, encephalopathy, neuropathy, myopathy)
- Severe refractory dysnatremia ($Na^+ > 160$ or <115 meq/l)
- Overdose with a dialyzable drug
- Neonatal hyperammonemia and other inborn errors of metabolism
- Coagulopathy requiring large amounts of blood products in patients at risk of pulmonary edema or acute respiratory distress syndrome (ARDS)
- Refractory edema not responding to high-dose diuretics.

The uniqueness of children admitted to the ICU does influence the choice of mode of RRT. Critically ill children usually end up having a high obligatory fluid requirement due to hyper-catabolic state. Other reasons are the need for blood products to combat co-existing coagulopathy and multiple antibiotics and inotrope infusions. In the presence of oliguria/anuria, administering a high volume of intravenous fluid is likely to precipitate pulmonary edema. This mandates removal of fluid by RRT (ultrafiltration (UF)), but is challenging as these children are often hypotensive and on multiple vasopressor support. The hemodynamic advantage of CVVH/D over IHD has been attributed to a slower UF rate, as the same UF goal is achieved over 24 h instead of the standard 3–4 h. PIRRT also has a similar advantage but at a lower cost [18–27]. Additionally, unlike CVVH/D, PIRRT allows sufficient time for any ancillary procedures/treatments such as imaging or surgical interventions. The choice of PIRRT or CVVH/D is also influenced by availability of CVVH/D machines and trained staff, as well as cost implications. As evidenced by various reports primarily consisting of adult studies, PIRRT can be used as the initial modality as well as in transition from CVVH/D to IHD once the patient is stable enough to discontinue CVVH/D, but still not sufficiently hemodynamically stable to sustain IHD [13–17]. Although PIRRT is still not the primary mode of RRT, surveys have pointed to it being increasingly acknowledged as a feasible mode of dialysis in the adult ICU [45–48].

Dialysis setup required for PIRRT

The setup for PIRRT is classically similar to IHD with some modification to the HD machine.

Machines for PIRRT

The prerequisite for performing PIRRT is the ability to extend the dialysis session length beyond the conventional 4–5 h of IHD and the ability to vary the Qb and Qd. Hence, any machine with the ability to lower the Qb/Qd and increase the duration of HD can be used for PIRRT. Traditionally, the same machines used for IHD have been tweaked to cater for PIRRT to make it cost-effective. In fact, in a busy HD unit it may be economical to use the same machine for maintenance IHD during daytime and for PIRRT overnight. Unfortunately, few HD machines are able to provide the low range of Qb/Qd, which are often required for critically ill hemodynamically unstable small children. Fresenius Medical Care Company has been the pioneer in marketing HD machines with additional specification for PIRRT. These machines can be classified as single pass (uses dialysate generated online from reverse osmosis purified water and bicarbonate proportioning system) or batch machine (dialysate generated from prepackaged salts and sterile water that is stored in the machine). The single-pass machines such as the 2008, 4008, and now 5008 series, or the batch dialysate machine such as the Genius machine, have been used worldwide [20, 38–42].

The advantages of batch dialysate machines include: user friendliness, ultrapure dialysate, and no need for on-

the-spot water purification, as access to ultrapure water (required for high flux dialyzers and hemodiafiltration) is available in a limited number of ICUs. The Genius (batch dialysate) machine utilizes a dual-headed roller pump for both blood and dialysate flow; hence the ratio of Qb/Qd is 1 with this machine. The dialysate is contained in a 75- or 90-l jacketed tank to maintain thermal stability; fresh dialysate, which has a lower specific gravity, is drawn from the top of the tank while spent dialysate with a higher specific gravity is discharged into the bottom of the tank. An ultraviolet tube is located in the center of the tank to prevent bacterial contamination and growth. The machine requires dedicated tubing sets, which do not have a bubble chamber. This avoids an air–blood interface and decreases clotting risk. Using a flow of 70 ml/min and a 75-l dialysate tank, a session of 18 h can be carried out with a single batch of dialysate. A separate ultrafiltration pump removes a portion of the dialysate from the closed loop into a separate receptacle.

Single-pass machines from various manufacturers have been more frequently utilized for PIRRT, and a comparison of some of the commonly available machines is shown in Table 3. The ArrT plus 5008 series, the AK200 Ultra machines, and the ARTIS machine possess additional unique features of cold sterilization or ultrafiltration of the dialysate, which results in a 4-log reduction of bacteria and a 2-log reduction in endotoxin, producing a sterile, pyrogen-free fluid suitable for intravenous infusion. This enables them to add convection clearance (though not allowed in the United States of America) to the predominant diffusion clearance of standard HD machines. This has been described as sustained low-efficiency daily diafiltration (SLEDD-f). They do require ultrapure water and sterile dry powder concentrates for the dialysate preparation. High flux dialyzers or hemo-filters from the AV 600 series, having UF coefficients >20 ml/mmHg/h, are required for this treatment. At least a part of the replacement fluid should be delivered pre-filter and the blood flow has to be proportionally higher than usual in order to avoid a filtration fraction >20%. Giving part of the replacement fluid pre filter reduces the viscosity of the fluid caused by the high ultrafiltration rates and therefore decreases the chances of filter clotting. The volume of fluid required is higher with predilution but not necessarily so when only a part of it is given pre filter. Moreover, as the fluid is prepared online, cost is not a major issue (around USD 0.14 per liter in an Indian center). Blood flow needs to be higher in post- as compared to predilution replacement in order not to exceed the chosen filtration fraction.

Table 3 Machines for prolonged intermittent renal replacement therapy (PIRRT)

Parameter	Machine					
	Fresenius 4008 NG	Fresenius ArrT plus	Fresenius 5008S	Althin (Tina)	AK Series (Gambro)	Diamax
Blood flow (ml/min)	5–500	5–500	5–500	50–500	20–500	15–600
Dialysate flow (ml/min)	300, 500, and 800	200, 300, 500, and 800	100–1000 in increments of 100	300–1000 in increments of 100	300–700 in increments of 100	300–700 in increments of 100
Heparin pump	Syringe	Syringe	Syringe	Syringe	Syringe	Syringe
Ultrafiltration	1 ml/h to a maximum of 9990 ml	1 ml/h to a maximum of 9990 ml	1 ml/h to a maximum of 9990 ml	10 ml/h to a maximum of 3600 ml/h	0–4000 ml/h	100–5000 ml/h
Maximum treatment time	10 h	10 h	24 h	12 h	24 h	6 h
Compatibility with multiple dialyzer and tubing sets	Yes	Yes	Dedicated tubing sets	Yes	Yes	Yes
Sodium and ultrafiltration profiling	Custom	Custom	Custom	Flexible	Custom	Flexible
Dialysate sodium/ conductivity range	128–148 meq/l	128–148 meq/l	128–148 meq/l	131–160 meq/l	130–150	10–17 mS/cm
Dialysate temperature range	35–39 °C	35–39 °C	35–39 °C	35–39 °C	30–39 °C	30–40 °C
Dry powder concentrate use*	Yes (Bibag)	Yes (Bibag)	Yes (Bibag)	No	Yes (Bicart)	No
Online replacement fluid preparation	No	Yes	Yes	No	Yes	No
Heated citrate disinfection	Yes (85 °C)	Yes (85 °C)	Yes (85 °C)	Yes (90 °C)	Yes (85 °C)	Yes (65 °C)
System self-test	Yes	Yes	Yes	Yes	Yes	Yes

Prerequisites for performing SLEDD-f:

1. Sterile dry powder concentrates (Bicart and Bibag): This has replaced the liquid bicarbonate concentrate, which traditionally predisposes to bacterial growth. The acid concentrate is also a powder or a liquid with a low pH, depending on the configuration of the machine.
2. Ultrapure water: This is generated by either a system in the ICU or a portable reverse osmosis (RO) system. The European Union (EU) standard of ultrapure water (bacterial count of 0.1 cfu/ml and an endotoxin level of 0.03 EU /ml) needs to be consistently maintained. Several systems have been utilized to provide this, including double-pass (RO) and an electro-deionizer or an ultrafiltration system online. The important feature of any system is elimination of a storage tank and a frequent disinfection cycle at least daily, preferably with heat.
3. Cold sterilization or controlled ultrafiltration: This technology pioneered by Gambro and now available with Fresenius and other users makes use of 2 or 3 ultrafilters in the dialysate flow path operating in cross flow mode. The ultrafilters have a pore size of 0.05 μm, surface area of >2 m^2 and are located after the dialysate mixing chamber. The dialysate is thus filtered prior to being delivered to the dialyzer with a 2-log reduction in its bacterial and endotoxin load. A portion of the dialysate is then passed through a second ultrafilter repeating the process, and this fluid which is sterile and has a 10,000 times lower concentration of endotoxin than normal dialysate is delivered directly into the blood circuit at a predetermined rate. The integrity of the ultrafilters is cyclically tested using a pressure holding test.

The process of cold sterilization by ultrafiltration was validated by Lebedo [49] for the Gambro system. It was shown that whereas 90% of the incoming water had bacterial growth and 35% had endotoxin detectable after three ultrafiltrations, no bacteria could be detected even in 30 l of infusate fluid. Similarly, Vasalaki validated the Fresenius system on 216 samples and showed levels in online substitution fluid comparable with that in commercially available bags meeting pharmacopeia standards [50]. Thus, the online system allows an almost unlimited supply of a sterile bicarbonate-based substitution fluid for replacement. The online plus system delivers the replacement fluid into the venous or arterial bubble chamber according to the rate set for the substitution pump, while the machine's software ensures that the ultrafiltration pump removes an amount equal to the sum of replacement fluid and desired ultrafiltration from the blood compartment. The 5008 system has two substitution pumps with the ability to deliver replacement fluid either pre- or post-filter or both. One dry powder bicarbonate cartridge generally allows around 160 to 200 l of dialysate generation. With a dialysate flow of 100 ml/min and a replacement of 30 ml/kg/h for a 20-kg child, a treatment could actually be run for 24 h, making it even more efficient than CRRT.

Extra-corporeal circuit

Similar to IHD, the extra-corporeal volume (volume of blood tubing + dialyzer) should be less than 10% of the child's total blood volume for PIRRT. If this is not possible, even with the use of size-specific blood tubing, one may need to prime the tubing + dialyzer with either colloid or crystalloid. The dialyzer used can be the same as in IHD (appropriate for the body surface area of the child). High flux dialyzers or hemofilters (AV series-Fresenius) will be needed if hemofiltration, i.e., convection component of clearance is to be added. The FX Paed dialyzer from Fresenius made of helixone deserves a special mention as it is suitable for very small children with a surface area of 0.2 m^2, and requires a priming volume of just 18 ml. This dialyzer has a clearance of 65 to 75 ml/min and a UF coefficient of 7 ml/h/mmHg at blood flow rate of 30–100 ml/min. The large UF coefficient in such a small dialyzer allows ease of use for PIRRT even with additional convective clearance.

Prescription for PIRRT (Table 4)

PIRRT is more commonly done in the PICU, and vascular access is usually by cuffed or non-cuffed HD catheter of size appropriate for the child's weight (detail available at http://pcrrt.com/ProtocolsAccess.html). Even in the unlikely presence of arterio-venous fistula (AVF), catheters are preferred, as the chance of needle dislodgment and subsequent bleeding is minimized. This is important given the prolonged duration of the sessions in contrast to standard HD.

Children in the PICU are quite different compared to those on chronic/maintenance HD. They are usually vasoconstricted by catecholamine treatment, may have hypoalbuminemia, low intravascular volumes, fluid overload, and are less likely to tolerate standard ultrafiltration without a precipitous drop in blood pressure. The target ultrafiltration will be determined by the balance between the degree of fluid overload, the obligatory fluid intake (comprising nutrition, blood products, antibiotics, and inotrope infusions) and the hemodynamic stability of the child. Achieving target ultrafiltration without disturbing hemodynamic stability is a special advantage of PIRRT compared to conventional HD, with only a minority of patients (<20%) requiring discontinuation of the HD due to refractory hypotension [27, 28, 34, 41, 51, 52]. A randomized controlled trial (RCT) compared cardiovascular stability between PIRRT and CVVH in adults. No significant differences in inotrope dose or numbers were seen between the two groups [38].

Table 4 Example of a prolonged intermittent renal replacement therapy (PIRRT) prescription

A 9-year-old girl (wt 28 kg, height 130 cm, body surface area 1.1 m^2) was admitted in PICU with fulminant sepsis. Her urine output progressively declined and she has been passing urine at 0.1 ml/kg/h over the last 6 h. She did require multiple saline boluses and is currently on three inotropes. Her current total intake (including drugs) is 56 ml/h. Despite this, her mean arterial pressure is 62 mmHg and systolic blood pressure is 98 mmHg. Her latest biochemical parameters: sodium 130 mmol/l, potassium 5.6 mmol/l, bicarbonate 14 mmol/l, urea 170 mg.dl, and creatinine 2.3 mg/dl. Her positive cumulative fluid balance since admission is 4200 ml. Coagulation profile: international normalized ratio 2.2, activated partial thromboplastin time 50 s. Please write a PIRRT prescription.

- Vascular access: 10F double lumen in right femoral vein under ultrasound guidance (right internal jugular was tried once but failed. In view of coagulation dysfunction, further attempt were avoided).
- Dialyzer: F4 dialyzer. (In view of the hypotension and it being the first dialysis, a dialyzer with surface area of 75% of body surface area was used). Use high flux, e.g., FX5 for adding convection clearance.
- Blood flow rate (BFR): 90 ml/min (3 ml/kg/min, minimum BFR should be 30–50 ml/min to avoid clotting)
- Anti-coagulation: In view of deranged clotting, anti-coagulation was not used and repeated saline flushing was done, or pre-filter replacement can be added.
- Ultrafiltration rate (UFR): 280 ml/h, expected net UFR = 230 ml/h [total intake = 1.3 l, urine output = 67.2 ml, insensible loss = 440 ml, expected balance = +793 ml. In addition, she is already 4.2 l overloaded. Max UFR/ h = 10 ml/kg/h = 280 ml. If SLED done over 8 h, then UF = 2240. Net expected UF will be 2240–400 (saline flushes 50 ml × 8) = 1840 ml]
- Duration: 8 h
- Dialysate: sodium = 140 (difference of sodium between blood and serum should not exceed 10), potassium = 2 (we might have to add extra K if post SLED K is low), calcium = high [both of these steps will help in increasing hemodynamic stability].
- Dialysate flow rate: 200 ml/min
- Replacement fluid: If convection is added, replacement fluid (pre-filter mostly) can be added at least 25 ml/min. This is the minimum replacement fluid allowed by 5008-S, and can also help in heparin free sessions.

Limited pediatric data and author's experience also suggest SLED to be well tolerated with adequate fluid removal [27].

The rates of Qb and Qd in PIRRT are decided based on the hemodynamic stability and are usually similar to those used in CVVH (Table 5). The Qd (dialysate flow rate) is kept low (usually ≤2 × Qb), which allows the same amount of dialysate to be used as in a standard HD session with higher flow rates despite longer sessions. The low Qd also helps in hemodynamic stability. The blood flow should be set based on the dialysate flow to allow a better saturation in diffusive mode. Usually, a Qd/Qb of 1.6 to 2 is considered to provide satisfactory dialysate saturation. Duration needs to be individualized as per the clinical status of the child and can vary between 6 to 18 h. As stated before, if SLEDD-f is being used, the blood flow may have to be adjusted according to the replacement fluid rate so that the filtration fraction does not exceed 20%.

Table 5 Blood flow in prolonged intermittent renal replacement therapy (PIRRT) in children

Weight in kg	Blood flow
5–20 kg	30–75 ml/min
20–40 kg	75–125 ml/min
> 40 kg	> 150 ml/min

Standard dialysate fluid consists of sodium, potassium, calcium, and bicarbonate, the concentration of which can be varied as per the clinical requirement. Similar to conventional HD, higher sodium or calcium can enable better hemodynamic stability. Compared to conventional IHD, PIRRT offers better small solute clearance. Large molecule clearance can be improved with the use of a high flux dialyzer and hemofiltration/hemodiafiltration, i.e., SLEDD-f [47]. An important finding reported with PIRRT has been low phosphate levels, which sometimes have to be replaced either intravenously or added to the dialysate [20]. Even though albumin is not lost, amino acid loses can be significant, requiring supplementation if PIRRT has to be continued for a longer period [38].

Anticoagulation in PIRRT

Unlike CVVH/D, PIRRT without anticoagulation is feasible, albeit with some risk of circuit clotting. Use of anticoagulation in PIRRT evokes mixed opinion as to whether to anticoagulate or not, and if anticoagulation is considered, whether to go for an unfractionated heparin or regional citrate anticoagulation protocol. A number of studies have examined the advantages and disadvantages of each of these protocols, although most of these trials were done in the adult population. The incidences of extracorporeal circuit clotting in these studies have varied between 26 and 46% with no anticoagulation and 10–26% with heparinization/citrate, respectively [23, 34–37, 39, 41, 42, 53–56].

No anticoagulation Unlike CVVH/D, avoidance of anticoagulation is feasible in SLED with frequent saline flushing. In a study by Berbece et al. involving critical care patients on SLED for a mean duration of 8 h with blood and dialysate flow rates of 200 and 350 ml/min, respectively, anticoagulation with heparin was used in 35% of treatments and saline flushes in 65%. This study was done in comparison with continuous renal replacement therapy (CRRT) with citrate and heparin anticoagulation. The incidence of filter clotting in SLED therapy was 18% with heparin use and 29% without anticoagulation. There were no major adverse events reported [34]. In another study by Marshall et al., involving critically ill patients on SLED for a mean duration of

10.4 h with blood and dialysate flow rates of 201 ± 7.5 and 100 ml/min respectively, 41 of 145 treatments were without anticoagulation. The incidence of extracorporeal circuit clotting in this study was 26%, without a statistically significant difference between rates of clotting in heparin and heparin-free treatments [23]. Recently, Kitchlu et al. explored clinical outcomes in SLED therapy without anticoagulation compared to CRRT with citrate and heparin anticoagulation. The mean duration of SLED therapy was 7.11 h with blood and dialysate flow rates of 200 and 350 ml/min, respectively. The majority of SLED treatments (86.2%) were done without anticoagulation, but no significant differences in complications were noted [55]. All of these studies have demonstrated the feasibility of conducting PIRRT without anticoagulation, which is considered to be a major advantage of PIRRT over CVVH/D. It is generally suggested that that blood flow rate may have to be increased by 20 to 25% for an anticoagulation-free session provided it is hemodynamically tolerated [52, 56]. Removal of extra volumes of saline used for flushes should be considered and included in the ultrafiltration rate calculation. This can be problematic in a hemodynamically unstable child, but because of the slow and prolonged nature of PIRRT, this is often possible, albeit with some increased risk of circuit clotting. Madison and Depner at the University of California Davis studied 336 SLEDD sessions using saline flushes, 87 using citrate dialysate, and 72 with regional citrate anticoagulation [57]. The incidence of clotting with premature termination was 26% among saline flushes, 14% among citrate dialysate group ($p = 0.005$), and 2% among those receiving regional citrate anticoagulation 2% ($p = 0.026$).

Unfractionated heparin As discussed above, use of unfractionated heparin in PIRRT does reduce the incidence of extracorporeal circuit clotting, but unfortunately this comes with the disadvantage of the higher risk of bleeding and thrombocytopenia requiring careful monitoring of activated partial thromboplastin time (APTT) and platelet count. PIRRT in contrast to CVVH/D requires a lower cumulative dose of anticoagulation although the amount of difference has varied between different studies [23, 37].

Regional citrate anticoagulation Regional citrate anticoagulation (RCA) has evolved as an alternative form of anticoagulation, which is safe and yet effective [35, 36, 53, 54]. Fiaccadori et al. demonstrated the use of a simplified citrate-based protocol in SLED, which is less expensive and does not require monitoring of citrate accumulation [36]. The only disadvantage is that many hemodialysis units do not have sufficient experience in using citrate-based anticoagulation protocols.

Prostacyclin There have been reports from Italy of using prostacyclin as an anticoagulant in SLED. However, it is expensive and further research is required to validate its use in routine practice [58]. Overall, it is generally advocated that the choice of anticoagulation (if used) should be made based on the local unit's experience.

One has to keep in mind that most of the studies have been in adults, and children with their proportionately higher body surface area make direct correlation difficult. The only pediatric study by Lee et al. used a blood flow rate of 5 ml/kg/min for children who weighed 20–40 kg and 200 ml/min if weight > 40 kg, and a dialysate flow rate of 260 ml/min. Duration of therapy was 8–10 h/day and anticoagulation with unfractionated heparin was done in 76.6% of treatments with a bolus of 10–20 IU/kg and maintenance dose of 5–10 IU/kg/h. Adjusted doses of heparin were used if any of the following risk factors were present, i.e., APTT >75 s, international normalized ratio > 2, activated clotting time (ACT) >275, platelet count <50,000/μl and increased risk of bleeding. There were no bleeding complications observed in this study [27]. In our own experience, we have been able to conduct most of the SLED sessions in children with altered clotting off anticoagulation without any significant increase in adverse effects.

Dialysis dose

Determining the dosing of PIRRT in terms of duration, frequency, and dialysate or replacement fluid rate is difficult. Urea kinetic modeling (UKM) has been used to predict adequacy of dialysis in chronic RRT, but is unreliable in a non-steady evolving state such as AKI. Additionally, there is an as-yet-unanswered question regarding the relative merits of removal of small vs. large molecules. The rationale of encouraging middle-molecule clearance lies in its postulated benefit in removal of inflammatory mediators, which may have a role in the pathophysiology of systemic inflammatory response syndrome in critically ill patients [27, 59]. However, there is no concrete data that middle-molecule clearance shows a survival advantage in these patients [60–62].

Although there is no pediatric data on solute removal in PIRRT, it is helpful to understand the adult-based studies in this regard for prescribing PIRRT in critically ill children. An excellent study on kinetic modeling compared effective dose delivery by three acute dialysis therapies: CVVH, daily HD, and SLED [63]. A modified equivalent renal clearance (EKR) approach was used to account for the initial unsteady state during the dialysis. Effective small-solute clearance in CVVH was found to be 8% and 60% higher than in SLED and daily HD, respectively. Differences in favor of CVVH were more pronounced clearance for middle and large solute categories, likely due to a combination of convection and continuous operation. If one were to extrapolate from UKM data based on IHD and CRRT studies, PIRRT should provide at a minimum a weekly $StdKt/V_{urea}$ of 2 when compared to IHD,

or a weekly StdKt/V_{urea} of 6 when compared to CVVH [28]. It has been shown that undertaking PIRRT with Qd 350 ml/min, Qb 200 ml/min, hemofiltration 1 l/h and duration of 8 h/day for 6 days may be comparable to CRRT at 20 to 25 ml/kg/h [34]. From the study by Kielstein et al., it can be extrapolated that clearance obtained from 12 h of PIRRT is comparable to 23 h of CRRT [38]. They found a comparable urea reduction ratio between PIRRT and CVVH although the PIRRT patients were dialyzed for 11.7 ± 0.1 h compared with 23.3 ± 0.2 h for CRRT patients.

Monitoring during PIRRT

As PIRRT is most often used in ICUs on critically ill children, close monitoring of vital parameters is obviously an integral part. In ICUs, intra-arterial BP monitoring will be useful but for hemodynamically stable child non-invasive BP monitoring (such as with Dynamap) should suffice. PIRRT is very effective in solute removal because of its long duration and, unlike IHD, sometimes potassium, phosphate, and magnesium levels can dip, which can result in neuromuscular problems including difficulty in weaning off the ventilator. Hence, most of the PIRRT protocol includes the regular monitoring of phosphorous and magnesium in addition to the standard monitoring of urea, creatinine, and electrolytes, i.e., sodium, potassium, chloride, and calcium [21, 40, 41]. To factor in the risk of anticoagulation use, monitoring of APTT has been recommended in some studies, and the goal has ranged from 10 s above baseline to 1.5 times the normal value [21, 42, 64].

Outcomes

Even though there is a lack of robust evidence in favor of any specific dialysis modality for AKI [65–67], CVVH/D has been long held as the preferred choice for acutely ill patients and even KDIGO guidelines support its use [2, 66]. As mentioned above, evidence has been accumulating in favor of PIRRT as a viable alternative to CVVH/D.

Clearance/efficacy Using single-pool UKM, SLED has been shown to offer very effective small solute clearance (Kt/V 1.3–1.5) and lower small solute disequilibrium compared to IHD, and provides equally effective azotemia control compared to CVVH [63]. Further improvement in middle- and large-molecule clearance can be achieved by adding convection clearance, i.e., by the use of hemodiafiltration (e.g., Fresenius Genius, and 5008 and 5008 S machines), although this is still not approved in the United States. A recent meta-analysis showed that compared to CRRT, IHD showed a trend towards higher incidence of dialysis dependence, albeit this result was primarily seen in observational cohorts rather than in RCTs [67]. The increased incidence of non-recovery of renal function may be attributed to the higher rates of incidental hypotension in IHD. PIRRT, being a hybrid technique, should theoretically provide better hemodynamic stability than IHD while achieving comparable clearance. Clinically, this was demonstrated by Wu et al., where better hemodynamic stability resulted in a negative indirect effect on mortality rate [7]. In one of the largest RCTs involving PIRRT, Schwenger et al. randomized 232 surgical ICU patients to either CVVH (35 ml/kg/h) or SLED using single-pass batch dialysate (12 h of dialysis with a blood flow rate of 100 to 120 ml/min) [37]. In addition to the absence of any difference in hemodynamic stability during treatments, the SLED group required fewer days of mechanical ventilation, fewer blood transfusions and was associated with decreased cost and nursing time. The recent systematic review by Zhang et al. also showed similar results in favor of PIRRT [21].

Mortality Similar mortality outcome has been described by most of the RCTs comparing PIRRT with CVVH. In the large RCT by Schwenger et al., the 90-day mortality was comparable in both arms: 49.6% in SLED compared to 55.6% among those who underwent CVVH [37]. Likewise, meta-analysis has also failed to show any mortality benefit of CVVH over PIRRT [16]. Interestingly, summation of observational studies identified in the systematic review has shown a reduction in mortality trends favoring PIRRT, which has been postulated to be related to the decreased need for anti-coagulation in PIRRT [16]. Importantly, irrespective of the type of study, i.e., RCT or observational, PIRRT was found to be similar in efficacy to CVVH for fluid removal, solute clearance (urea, creatinine, phosphate), need for escalating vasopressor and mortality, or renal outcomes.

Complications Serious complications on PIRRT have been reported to be low. A study by Caires et al. reported serious complications in only 0.7% ($n = 3$) sessions (arrhythmias and one death related to the procedure) in a total of 421 sessions [20]. Although this study excluded patients on epinephrine >0.2 mcg/kg/min or refractory hypotension, positive data have been reported even among more critically ill subjects. Ponce et al. observed serious complications (ventricular tachycardia or increase of nor-epinephrine dosage >1 mcg/kg/min) in only 1.4% of the sessions among a group of patients receiving nor-epinephrine (0.3 to 1 mcg/kg/min) [68]. The hemodynamic stability of PIRRT has been shown to have a stable effect on the mean arterial pressure [7] and this has been demonstrated to have a positive effect in a cohort of uremic patients with brain hemorrhage [13].

Cost-effectiveness A significant advantage of PIRRT over CVVH/D has been its cost-effectiveness which is likely to make it very useful in any resource-constrained facilities. Schwenger et al. clearly demonstrated that SLED requires

Table 6 Drug dosing in prolonged intermittent renal replacement therapy (PIRRT) in children. NB: The dosing suggested are based on adult studies as there are no pK studies for medication in pediatric PIRRT

Drug/dose used	Dialysis machine	SLED characteristics	Pharmacokinetics in SLED	Recommendations
Vancomycin Single dose of 15 mg/kg IV [73] Single dose of 1 g (adult) IV 12 h prior to dialysis [64]	Fresenius 2008H (Fresenius Medical Care)	Dialysate flow rate 100 ml/min and blood flow rate 200 ml/min. Dialysis duration 24 h	Mean half-life 43.1 h and mean clearance 24.3 ml/min. Mean volume of distribution 0.84 l/kg. Mean volume of distribution 0.84 ± 0.17 l/kg	Initial dose of 15 mg/kg and measurement of serum drug levels at 24 h
	Batch dialysis system (GENIUS, Fresenius Medical Care, Bad Homburg) with polysulphone high-flux dialyzer with surface area 1.3 m^2	Both dialysate and blood flow rate 160 ml/min. Dialysis duration 480 ± 6 min	Mean half-life 11.2 h. Mean clearance 2.1 l/h and 3.8 l/h based on analysis method. Mean volume of distribution 0.57 l/kg	Initial dose of 20–25 mg/kg and monitoring of drug levels for further dosing.
Gentamicin Single dose of 0.6 mg/kg IV post dialysis [70]	Fresenius Medical Care, high-flux polysulfone F50 filter with surface are 0.5 m^2	Blood flow rate 200 ml/min and dialysate flow rate 300 ml/min. Duration of dialysis 480 min	Mean half-life 3.7 ± 0.8 h. Mean clearance 75.9 ± 38.4 ml/min/1.73 m^2. Mean volume of distribution 0.28 l/kg	2–2.5 mg/kg after hemodialysis to maintain optimal peak and trough levels at 7.5 mcg/ml and 0.8 mcg/ml, respectively
Meropenem Single dose of 1 g (adult) IV 6 h prior to dialysis [64]	Batch dialysis system (GENIUS, Fresenius Medical Care, Bad Homburg) with polysulphone high-flux dialyzer with surface area 1.3 m^2	Both dialysate and blood flow rate 160 ml/min. Dialysis duration 480 ± 6 min	Mean half-life 3.7 h. Mean clearances 2.3 and 5.1 l/h based on analysis method. Mean volume of distribution 0.72 l/kg	0.5–1 g every 8 h
Ertapenem Single dose of 1 g IV [72] (adult)	Batch dialysis system (GENIUS, Fresenius Medical Care, Bad Homburg) with polysulphone high-flux dialyzer with surface area 1.3 m^2	Mean blood and dialysate flow 160 ml/min. Dialysis duration 480 min	Half-life 6.7 h. Mean clearance 49.5 ± 10.9 ml/min. Volume of distribution 15.9 ± 3.2 l	1 g/day
Linezolid Single dose of 600 mg (adult) IV before dialysis [67]	Fresenius Medical Care (low-flux polysulfone filters with 1.6 m^2 surface area)	Blood flow 200 ml/min and dialysate flow 100 ml/min. Dialysis duration 8–9 h	Half-life 5.88 h and clearance 33.3 ml/min. Volume of distribution 30.19 l	Drug should be administered towards the end of dialysis session
Moxifloxacin Single dose of 400 mg (adult) IV 8 h prior to dialysis [74]	GENIUS batch system (Fresenius Medical Care, Bad Homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	Mean blood and dialysate flow 161 ± 4 ml/min. Dialysis duration 481 ± 9 min	Mean half-life 6 h and mean clearances 2 l/h and 3.1 l/h based on analysis method. Mean volume of distribution 3.8 l/kg	Standard 400 mg/day irrespective of liver impairment
Levofloxacin Single dose of 250/500 mg (adult) IV 12 h prior to dialysis [74]	GENIUS batch system (Fresenius Medical Care, Bad Homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	Mean blood and dialysate flow 161 ± 4 ml/min. Dialysis duration 481 ± 9 min	Mean half-life 10.3 h and mean clearances 2.93 l/h and 3.12 l/h based on analysis method. Mean volume of distribution 1.71 l/kg	Dosage adjustment is necessary and drug should be given after dialysis
Ampicillin/ sulbactam	GENIUS batch system (Fresenius Medical	Mean blood and dialysate flow 162 ±	Mean volume of distribution for	

Table 6 (continued)

Drug/dose used	Dialysis machine	SLED characteristics	Pharmacokinetics in SLED	Recommendations
Single dose of 2 g/1 g (adult) IV 3 h prior to dialysis [66] Multiple doses of 2 g/1 g (adult) twice daily for 4 days [66]	Care, Bad Homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	6 ml/min. Dialysis duration 442 ± 77 min	ampicillin/sulbactam were 13.1 ± 11.1 l and 22 ± 21.8 l, respectively, mean half-life 2.8 ± 0.8 h and 3.5 ± 1.5 h, respectively, mean clearances 80.1 ± 7.7 ml/min and 83.3 ± 12.1 ml/min, respectively No significant drug toxicity with twice-daily dosing	Twice-daily dosing 2 g/1 g with one dose given after dialysis
Trimethoprim/sulfamethoxazole 15 mg/kg/day and 95 mg/kg/day IV [75]	GENIUS batch system (Fresenius Medical Care, Bad Homburg) with polysulfone high-flux dialyzer with surface area 1.3 m^2	Mean blood and dialysate flow 170 ± 41 ml/min. Dialysis duration 442 ± 101 min	Clearances 94 ± 20.2 ml/min and 51 ± 18.8 ml/min, respectively	Further studies are needed to establish dosing recommendations

less nursing time and is significantly cheaper compared to CVVH [37]. The RRT cost per day for SLED using high flux membrane was €63.2 compared to €209.3 for CVVH. In contrast to CVVH, PIRRT usually does not require a special circuit or fluid and neither does it require round-the-clock nursing support nor any add-on training for the nurses. In addition, initial set-up cost is also less, as PIRRT does not require ultrapure water and can often be done on the same HD machine being used for conventional HD. Obviously, addition of convection clearance increases the cost as one needs to ensure ultrapure water, as well as requiring more specialized machines.

Comparison with PD

In resource-constrained units, PD definitely offers a cost-effective viable option for children with AKI in the PICU. Although in the developed world the use of acute PD has waned following the report of premature termination of the RCT by Phu et al. [9] due to higher mortality among PD (47%) cohort in contrast to hemofiltration (15%), it remains an important (and often the only) option in the developing world [11, 13]. Recent studies primarily from Brazil have demonstrated that critically ill AKI patients can be successfully treated with PD using cycler therapy, flexible catheters and high volumes (HV) of fluid, and both adequate small solute clearances and ultrafiltration can be achieved [69–71]. In contrast to the various studies comparing PIRRT with IHD and CVVH, there are very few studies (even among adults) that have compared PIRRT with PD. Ponce et al. reported on a double-center RCT comparing extended HD (EHD), i.e., PIRRT, with high-volume PD (HVPD) for the treatment for AKI in the ICU. Four hundred and seven patients were randomized but only 143 patients were analyzed. Although no survival benefit or difference in hospital stay was demonstrated, EHD did show faster metabolic control, higher dialysis dose, and better ultrafiltration in comparison to HVPD [10].

Pediatric study

At the time of writing, of this review, only a single study had been published detailing pediatric experience on PIRRT [27]. Lee et al. reviewed their experience on SLED-f among 14 critically ill children totaling 60 sessions. The study concluded that in their cohort of sick children, SLED-f provided good hemodynamic tolerance and correction of fluid overload, pH, and electrolyte imbalance. In addition, they also showed a significant drop in inflammatory markers such as adiponectin, interleukin 17 A (IL-17A), and IL 16, post SLED-f session. Despite a relatively high PRISM score (16.8 ± 23.3), they reported an overall 28-day survival of 71.4%. In the absence of any comparator group in their study, they compared the outcomes with the prospective pediatric continuous renal replacement therapy (ppCRRT) registry cohort. Although the different nature of the ppCRRT cohort as well as

different time frame makes direct comparison difficult, they did show a superior survival rate in comparison to the ppCRRT group (100% survival for PRISM III score < 10 in comparison to 55% in the ppCRRT registry and 55.6% for PRISM III score > 10 vis-à-vis 47%) [3]. This survival benefit to some extent is in accordance with the meta-analysis of Zhang et al. [21] who postulated that lower need for heparin, lower incidence of circuit clot, and decreased rate of bio-film formation in PIRRT compared to CVVH might contribute towards the lower mortality, although it was not statistically significant. Lastly, SLED-f was found to be significantly cheaper, i.e., US$77 per day, as opposed to CVVH with an average expenditure of US $305.

Though the study was unique in being the first to analyze SLED-f in children, the small study population, selective cohort (excluded children less than 20 kg) and retrospective nature of the study did leave a lot of unanswered questions regarding its viability in young critically ill children who are more prone to hemodynamic instability, as well as in a non-selected prospective cohort. Additionally, it has to be emphasized that the cohort of Lee et al. underwent filtration along with dialysis. Although SLED can be undertaken without much addition to a standard HD unit, filtration requires ultrapure water, which may increase the initial set-up cost, making it difficult for resource-constrained facilities where the utility of SLED is likely to be most important vis-à-vis CRRT. Another major pitfall is assessing the adequacy of dialysis dose prescribed, as even the adult literature does not have robust data and pediatric data is non-existent. None of the major adult studies, like the Brazil RCT or the Hannover Dialysis Outcome study showed any significant survival advantage of intensified HD and hence the optimum dose of dialysis remains debatable [51, 72].

Drug-dosing adjustments during SLED

Despite the increasing reports of feasibility and usefulness of PIRRT, drug dosing remains a major concern. A lack of studies and an absence of a standard definition for PIRRT has made it challenging for pharmacists and nephrologists when it comes to antibiotic dosing in the setting of SLED in critically ill septic patients. A recent electronic survey done to check pharmacists' antibiotic dosing recommendations in SLED showed wide variations from 4- to 12-fold in dosing regimens across health facilities, and suggested monitoring of drug concentrations in blood and use of pharmacokinetic modeling techniques for appropriate dosing in SLED [73]. As pharmacokinetic studies for SLED in the pediatric population are lacking, we have to extrapolate from adult studies regarding any drug dosage adjustments. Unfortunately, even adult studies are few in number (Table 6), making robust recommendations difficult [74–86].

Conclusions

PIRRT provides a modality of RRT with excellent hemodynamic stability, acceptable biochemical clearance, and ease of use without the need for specialized equipment. It can be performed with a conventional dialysis machine used in a chronic maintenance dialysis program, and costs a small fraction of CVVH expenditure. Perhaps most importantly the flexible nature of this modality allows sufficient time for any ancillary procedures/treatments such as imaging or surgical intervention. Although we do not have very robust evidence supporting the superiority of PIRRT over CVVH, current evidence does support the outcomes of PIRRT being at least equivalent to CVVH. Similarly, while the use of cyclers and flexible catheters are likely to have made PD a more competitive option for children with AKI, effective fluid removal with PD remains an important concern, particularly in children with fluid overload. The availability of PIRRT in such a scenario is likely to be useful. Finally, it should be accepted that these therapeutic strategies may not necessarily be considered as competitors, but rather as alternatives, each of which might be applicable within the same unit and even the same patient, depending on the practical options at hand at a given time and on the metabolic or fluid balance needs of the patient. The definite advantage that PIRRT does have over CRRT is its cost-effectiveness, which is important in resource-constrained facilities, and its lesser requirement for anticoagulation. As initiating PIRRT in children poses challenges quite different to adults, one has to appreciate the current limitations, particularly adequacy, and dose modifications. In view of only a single pediatric study, further research is warranted to check for feasibility, tolerability, adequacy measurement, and drug-dose modifications in critically ill children on PIRRT.

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