

Therapeutic Options for Neonatal Acute Kidney Injury (AKI)

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Opinion statement

Acute kidney injury (AKI) occurs commonly in neonates and is associated with increased mortality. Recent advances in neonatal intensive care have resulted in improved patient survival, but this had not been paralleled by improved outcomes for neonates with AKI. Management of AKI remains supportive with no effective pharmacologic therapy to hasten the recovery process. Emphasis is placed on the prevention and minimization of further renal insults once AKI is established. Routine, regular assessments of renal function with identification of high risk patients and those with incipient AKI are essential so prevention strategies can be promptly initiated. Effective prevention strategies include prompt restoration/preservation of organ perfusion with fluid resuscitation to ensure an adequate effective circulating volume and inotropic support as needed to maintain hemodynamic stability while also avoiding/minimizing nephrotoxin exposure. In established AKI, efforts are focused on maintaining organ perfusion while closely monitoring cumulative fluid balance from admission and remaining cognizant of the need to minimize the degree of fluid overload as this has also been associated with poor outcomes. Continuous renal replacement therapy (CRRT) has become the preferred therapy for managing fluid overload and metabolic disturbances in critically ill children and adults but is still considered by many to be a heroic intervention for neonates due in large part to numerous technical challenges. The recent development of two miniaturized machines specifically designed to

deliver CRRT and hemodialysis (HD) to neonates will hopefully change this paradigm making it easier for nephrologists and intensivists to safely offer and provide this therapy to neonates. Prospective studies are needed to assess whether early initiation of RRT with correction of fluid imbalance results in improved patient survival and renal recovery.

Introduction

AKI epidemiology and definition

Acute kidney injury (AKI) is now recognized to be a complex syndrome ranging in severity from mild reversible renal dysfunction to severe, oligoanuric failure. It is associated with increased mortality in the acute setting as well as an increased risk for CKD amongst survivors [1–3]. Using contemporary definitions, the incidence of AKI in neonates has been estimated to range from 16 to 72 % based on the particular population studied (very-low-birth-weight infants, complex congenital heart disease, extracorporeal membrane oxygenation (ECMO), neonatal asphyxia) [4–8]. Conceptually, AKI signifies an abrupt decline in glomerular filtration accompanied by a loss of volume regulation and electrolyte/acid-base homeostasis as well as by an accumulation of nitrogenous waste products. Operationally, this has been much more challenging to define. Paradoxically, the incidence of AKI in critically ill patients has been increasing in the past few decades despite advances in critical care medicine and neonatology as these advances have resulted in improved patient survival but not in the development of effective treatments for AKI [9]. Care for patients with AKI remains supportive.

Research in the field of AKI has been hindered by lack of a consensus definition for AKI until relatively recently. In the past 15 years, three standardized working definitions for AKI (Risk, Injury, Failure, Loss, ESRD (RIFLE)/pediatric RIFLE (pRIFLE), Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO)) have been proposed and validated to clinical outcomes in adults, but not in children or neonates [1, 9–11, 12•]. All are based on an absolute or relative increase in serum creatinine from an established baseline or by the development of oliguria. The pitfalls of a serum creatinine-based definition for AKI are well recognized and include the (a) influence of non-glomerular filtration rate (GFR) determinants (e.g., muscle mass, diet, hydration status); (b) lack of sensitivity to acute, small changes in renal function; and (c) excretion, albeit limited, by routes other than filtration (proximal tubular secretion and bacterial degradation in the

gastrointestinal tract) [13, 14]. Use of a creatinine-based definition in neonates is further complicated by the unique physiology of neonates. Creatinine equilibrates across the placenta in utero which makes the serum creatinine at birth reflective of the mother's renal function not the infant's. Acute changes in volume status which happen over the first weeks of life affect the S_{Cr} measurement [15]. GFR at birth is low in newborns and increases during the first few weeks. In full-term infants, as the GFR increases, the serum creatinine gradually declines becoming reflective of the infant's renal function by 1 week of age as a new equilibrium is attained. In preterm infants, due to greater immaturity of the renal function, the serum creatinine will take weeks to reach its nadir [16, 17]. Further, preterm infants often experience an initial rise in serum creatinine during the first few days of life before peaking and progressively declining [18, 19].

Recently, neonatologists and pediatric nephrologists have formed an international collaborative, the Neonatal Kidney Collaborative (NKC), to foster the conduction of well-designed studies which will advance our knowledge about the epidemiology, prevention, therapy, and outcomes of neonatal AKI. One of the first aims of the group is to develop and validate a uniform definition for neonatal AKI. The collaborative has proposed a working definition for AKI based on modifications to the KDIGO AKI definition Table 1 [5, 20••].

Etiology and management overview

Hypoperfusion is by far the leading cause of neonatal AKI occurring secondary to hypovolemia (e.g., placental abruption, excessive third spacing, insufficient fluid replacement), hypotension (e.g., vasodilation from sepsis), and hypoxemia (e.g., chronic lung disease, fluid overload, abruption). Prolonged hypoperfusion can result in parenchymal damage and acute tubular necrosis (ATN). Intrinsic renal injury can also result from infection (e.g., pyelonephritis), vascular insults (e.g., thrombosis), and exposure to nephrotoxins (e.g., NSAIDs/aminoglycosides/contrast dye). Post-renal causes are much less common but crucial to recognize early as

Table 1. Neonatal AKI KDIGO classification

Stage	SCr	Urine output
0	No change in SCr or rise <0.3 mg/Ll	≥0.5 mg/kg/h
1	SCr rise ≥0.3 mg/dL within 48 h or SCr rise ≥1.5–1.9 × reference SCr ^a within 7 days	<0.5 ml/kg/h for 6 to 12 h
2	SCr rise ≥2.0–2.9 × reference SCr ^a	<0.5 ml/kg/h for ≥12 h
3	SCr rise ≥3 × reference SCr ^a or SCr ≥ 2.5 mg/dL ^b or receipt of dialysis	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

Differences between the proposed neonatal AKI definition and KDIGO include the following (adapted from Koralkar et al. [5]):
 SCr serum creatinine concentration
^aReference SCr will be defined as the lowest previous SCr value
^bSCr value of 2.5 mg/dL represents <10 ml/min/1.73 m²

the cornerstone of therapy is relief of the obstruction. Post-renal causes of neonatal renal failure include congenital anomalies of the urinary tract (e.g., posterior urethral valves, ureteropelvic or ureterovesicle junction obstruction), neurogenic or medication-related urinary retention, and acquired obstructions such as fungal bezoars and nephrolithiasis.

Given the lack of effective therapy, and limited support options with current renal replacement therapies, emphasis is placed on (a) early recognition of high risk patients as well as those with incipient AKI and on (b) strategies to prevent or minimize progression of incipient AKI. Supportive care measures for developing or established AKI include the following:

- (a) Treatment of the underlying process (e.g., antibiotics for sepsis, relief of obstruction);
- (b) Fluid therapy to correct hypovolemia and vasopressors, as needed, to maintain adequate blood pressure and ensure tissue perfusion;
- (c) Careful attention to fluid balance with use of fluid restriction, diuretics, and/or renal replacement therapy to minimize/manage fluid overload;
- (d) Electrolyte supplementation and/or binders to restore electrolyte and acid-base homeostasis;
- (e) Provision of adequate nutrition to promote healing;
- (f) Avoidance of further renal insults including exposure to nephrotoxins (medications/contrast dye), development of intravascular volume depletion especially during recovery phase of acute

tubular necrosis (ATN), as well as the development of significant cumulative fluid overload;

- (g) Dose adjustment for medications which are nephrotoxic and for those which are eliminated by the kidney;
- (h) Renal replacement therapy to prevent further fluid accumulation, restore euvolemia and metabolic balance, as well as to allow provision of adequate nutrition/blood products/medications.

Medical management of AKI

Fluid and vasopressor therapy

Preventive strategies for AKI begin with early identification of high risk patients coupled with careful attention to correction of hypovolemia, if present, and maintenance of hemodynamic stability. Early assessment for cardiogenic shock in the neonate is critical and necessitates the initiation of a prostaglandin E₁ (PGE₁) infusion to maintain ductal patency pending evaluation for complex duct-dependent congenital heart disease. In contrast, neonates with hypovolemic or septic shock require rapid fluid resuscitation to re-establish and/or preserve organ perfusion and function. Fluid and medications to increase blood pressure need to be aggressively but judiciously administered to achieve specific physiologic endpoints (mean arterial pressure, CVP, oxygen saturation, urine output) while minimizing significant cumulative fluid overload. Implementation of protocol-driven early-goal-directed therapy has been associated

with improved patient survival as well as a lower incidence of AKI [21, 22].

Aside from the scenario of acute blood loss with hemorrhagic shock, KDIGO AKI guidelines recommend isotonic crystalloid solutions over colloid solutions for rapid volume expansion. Use of balanced crystalloid solutions simulating plasma (e.g., Lactated Ringer's, PlasmaLyte) may be preferable to unbalanced crystalloid solutions (NS) for volume resuscitation in adults with sepsis as the hyperchloremic metabolic acidosis resulting from aggressive resuscitation with NS has been associated with greater renal dysfunction; however, it is unclear whether use of buffered solutions results in improved outcomes [23, 24]. Insufficient data exist to make any recommendation regarding choice of crystalloid solution for volume resuscitation in children and neonates.

Vasoactive support is indicated if hypotension persists despite correction of hypovolemia and initiation of PGE₁ infusion in the case of duct-dependent congenital heart disease with cardiogenic shock. The KDIGO AKI guidelines emphasize that vasoactive support should not be withheld in volume-resuscitated patients due to concerns that vasoconstriction will reduce renal perfusion. In the volume replete patient, mean arterial pressure and perfusion increase with inotropic support [25••]. Insufficient data exist to suggest superiority of one vasopressor over another in the prevention/management of AKI. Dopamine and dobutamine are commonly used in neonates. At low doses (5 mcg/kg), dopamine binds to dopaminergic receptors in the kidney resulting in vasodilatation and improved blood flow. In the past, low-dose dopamine was frequently used with the belief that it offered some renoprotection. However, several randomized, double-blind, placebo controlled trials in adults/children have failed to show any renal benefit from dopamine and some studies have shown it may be harmful. The use of low-dose dopamine to prevent or treat AKI is therefore not recommended in children/adults [25••, 26]. At higher doses, dopamine has inotropic and alpha adrenergic effects resulting in increased cardiac output and vasoconstriction. Epinephrine is used for fluid refractory-dopamine-resistant shock. The 2007 Updated Clinical Practice Parameters for hemodynamic support of neonatal shock provides details regarding pressor/inotrope support [21].

Despite aggressive efforts to improve hemodynamic status, prerenal AKI may still progress to intrinsic AKI/acute tubular necrosis. Accurate serial volume

assessments are essential for fluid management in AKI. In a recent review, Goldstein outlined the three phases of fluid management in AKI: resuscitation, maintenance, and recovery [27••]. The goal in phase 1, fluid resuscitation, is the prompt administration of fluid to restore effective circulating volume and re-establish/maintain organ perfusion as well as function. Phase 1 may overlap with phase 2, the maintenance phase, as the hypovolemia due to capillary leak from sepsis may persist for several days. In phase 2, the focus shifts to the maintenance of fluid balance allowing for the provision of needed therapies (medications/blood products/and adequate nutrition) while simultaneously minimizing cumulative fluid overload. This requires careful attention to daily weights, total input (including flushes), and total output (insensible water losses, urine output, gastrointestinal losses, other losses such as chest tube, etc). Daily assessments of fluid balance as well as cumulative fluid balance from admission should be monitored. Cumulative fluid overload exceeding 10 % has been associated with significantly higher mortality in adults and children [28–31]. In the oliguric patient, strategies to maintain fluid balance include fluid restriction, diuretic therapy, and renal replacement therapy. In neonates, fluid restriction is often implemented when diuretics fail as renal replacement therapy is much more challenging to provide to this group of patients and still often considered heroic.

However, advances in the past decade have made renal replacement therapy (RRT) much more feasible for neonates. (See “Renal support therapies” section) In phase 3, the recovery phase, attention is directed towards fluid removal balancing the competing goals of rapid diuresis to optimize pulmonary status and weaning off the ventilator with the goal of preventing further renal ischemic insults secondary to overaggressive diuresis. Early initiation of RRT with the use of inotropes to maintain hemodynamic stability has been hypothesized to improve outcomes [30].

Finally, it is also important to remember that AKI in neonates is often non-oliguric, which often hides its presence to the clinician. High-output renal failure is also often seen during the polyuric phase of ATN, following relief of a urinary tract obstruction (post-obstructive diuresis), and in those with nephrotoxin injury (e.g., aminoglycosides). Meticulous attention to fluid balance is again essential with recognition that protocolized fluid administration based on gestational age and weight often requires readjustment. Development of intravascular volume depletion at this time can hinder

renal recovery and potentially result in another episode of AKI.

Theophylline

AKI is a common complication of infants experiencing severe perinatal asphyxia with incidence rates of over 50 % reported in several studies [32–34]. During acute hypoxemia, adenosine levels increase as ATP hydrolysis exceeds synthesis resulting in intrarenal vasoconstriction and a fall in GFR. Four randomized controlled trials of severely asphyxiated neonates, three involving term and one involving preterm infants, found that a single prophylactic dose of theophylline, an adenosine receptor antagonist, administered within 1 h of birth had a renoprotective effect [35–38, 39•]. Theophylline treatment was associated with a significantly higher GFR and urine output as well as less cumulative fluid overload. KDIGO AKI guidelines for the management of AKI suggest that a single dose of theophylline can be considered in severely asphyxiated infants at high risk for AKI [25••]. Potential long-term renal and neurodevelopmental sequelae associated with the use of theophylline in this setting, however, have not been well studied. Additionally, the effect of prophylactic theophylline in the setting of therapeutic hypothermia, now the standard treatment for severely asphyxiated infants, has not been studied. Therefore, prophylactic theophylline should be used cautiously.

Therapeutic hypothermia is also thought to potentially offer some renoprotection by reducing metabolic demand and oxygen consumption. In adults experiencing out-of-hospital cardiac arrests, use of therapeutic hypothermia has been associated with decreased neurologic morbidity and mortality [40]. However, the impact of hypothermia on renal function in severely asphyxiated neonates has not been prospectively studied. In a recent retrospective review of severely asphyxiated newborns treated with therapeutic hypothermia, Selewski et al. reported an AKI incidence of 38 %, somewhat lower than that reported in historical studies performed before therapeutic hypothermia became the standard care [8].

Medication management

Nephrotoxic medication exposure

Avoidance/minimization of nephrotoxin exposure is another cornerstone in the prevention of AKI. Rhone et al.

reported an overall high rate of nephrotoxic medication exposure in very-low-birth-weight (VLBW) infants with 87 % receiving one or more nephrotoxic medications and 26 % developing AKI. Further, those with AKI were treated with more nephrotoxic medications per day than those without AKI [41•]. The most common exposures included aminoglycosides (86 %), indomethacin (50 %), and vancomycin (29 %). Risk factors for aminoglycoside nephrotoxicity included concurrent use of other nephrotoxic medications, high drug levels, prolonged treatment courses, and repeated treatment courses within a short time period. Intravascular volume depletion and pre-existing renal dysfunction may be additional risk factors. KDIGO guidelines for AKI management now recommend aminoglycosides not to be used unless appropriate, less nephrotoxic alternatives do not exist [25••]. Drug levels should be monitored when aminoglycoside therapy is necessary for more than 24 h with multiple daily dosing and 48 h with single daily dosing.

Indomethacin is another common exposure for preterm infants. Exposure may begin prenatally when used for tocolysis or postnatally when used for intraventricular hemorrhage prophylaxis or treatment of symptomatic patent ductus arteriosus (PDA). Management of the hemodynamically significant PDA poses a clinical conundrum as AKI can result from treatment for the PDA as well as from the PDA itself as blood is shunted away from the kidneys. Following fluid restriction, first line treatment for a persistent hemodynamically significant PDA includes indomethacin or ibuprofen, the latter reported to be less nephrotoxic [42, 43]. Both are contraindicated in moderate to severe AKI but can be administered when mild AKI exists. Although the treatment can be nephrotoxic, it can paradoxically improve renal perfusion and function by promoting ductal closure. Studies that explore the use of these medications for PDA closure should include short- and long-term kidney outcomes in these infants.

Recently, there has been increased interest in the use of acetaminophen as an alternative therapy for medical closure of PDA, particularly in neonates for whom NSAIDs are contraindicated. Acetaminophen is hypothesized to constrict the ductus by inhibiting the peroxidase portion of the prostaglandin synthase enzyme. Although a recent meta-analysis suggests acetaminophen is as effective as ibuprofen for ductal closure, the majority of included studies were uncontrolled and not of high

quality [44]. Randomized controlled trials as well as additional safety and efficacy data are needed before this therapy can be recommended.

Medication dosing

Medication dosing in critically ill neonates with AKI can be challenging. Nephrotoxic medications as well as those eliminated by the kidney may require dose reductions. On the other hand, hydrophilic medications may need to be dose adjusted upwards if there is significant fluid overload or decreased protein binding as both of these can increase the volume of distribution. Drugs with low protein binding and low volume of distribution will get cleared with dialysis. Monitoring drug levels when available can help guide dosing as serum creatinine does not accurately reflect renal function when not in a steady state [45].

Diuretics

Loop diuretics are frequently administered in the setting of oliguric AKI in hopes of converting to non-oliguric AKI which may, in turn, be misconstrued as an improvement in renal function. The increase in urine output resulting from administration of loop diuretics results from inhibition of sodium and water transport in the ascending limb of the loop of Henle and not from improvement in glomerular filtration. Loop diuretics continue to be administered commonly in clinical practice and may make fluid and electrolyte management easier thereby reducing the degree of fluid retention. However, no clinical studies unequivocally demonstrate an improvement in clinical outcomes (e.g., higher patient or renal survival, time to renal replacement therapy) to support the ongoing use of loop diuretics in this setting [46]. Indeed, there is some data to suggest it may even be harmful [47].

In neonates with AKI, the volume requirements for even maximally concentrated meds, blood products, and adequate nutrition often surpass what the infant is able to excrete making fluid restriction impractical in many situations. Diuretics are commonly prescribed in neonatal AKI despite the lack of evidence showing improved outcomes. The technical challenges for providing renal replacement therapy to neonates, especially premature, extremely low birth-weight (ELBW) infants, along with physician bias and experience, often make renal replacement therapy a “last resort” consideration. However, newer technology designed to specifically support neonates with minimal complications will soon be available to assist with fluid management in the NICU.

Furosemide is used most frequently and can be administered in a bolus or continuous fashion. It is highly protein bound and actively secreted by organic acid transporters in the proximal tubule. Once it gains entrance to the urinary space, it acts on the Na-K-Cl cotransporter located on the luminal surface of cells in the ascending limb of the loop of Henle where it inhibits sodium and water reabsorption. Decreased binding of loop diuretics to albumin, as can occur with hypoalbuminemia, hyperbilirubinemia, and/or co-administration of other medications which are highly protein bound, can decrease the effectiveness of the loop diuretics by impeding their delivery to the urinary space. Bumetanide is considered more potent than furosemide and enters the urinary space by proximal tubular secretion as well as by diffusion across tubular cell membranes because it is lipid soluble. In a recent study of oliguric AKI in preterm infants, Oliveros et al. found bumetanide more effective than furosemide for increasing urine output [48], but the results may have been biased by use of non-equivalent doses of furosemide and bumetanide [49]. Merheb et al. similarly found that bumetanide effectively increased urine output in ELBW infants, but this was associated with an increase in serum creatinine [50]. Although the use of diuretics cannot be justified in terms of improved patient or renal survival, they can be helpful for fluid management if oliguric AKI can be converted to non-oliguric AKI. This must be done cautiously however as aggressive use of diuretics can result in intravascular volume depletion with subsequent re-injury to the kidney.

Renal support therapies

The optimal modality, dosing, and timing for initiation of renal replacement therapy are unknown. The choice of modality—peritoneal dialysis (PD), hemodialysis (HD), or continuous renal replacement therapy (CRRT)—is often based on physician experience and preference as well as institutional resources.

Peritoneal dialysis

PD has generally been the preferred form of RRT for neonates as it is technically easier to establish and maintain dialysis access and it does not require anticoagulation, specialized machinery, or specialized nursing. The gradual ultrafiltration and metabolic clearance make it well tolerated but less suited for urgent situations such as hyperkalemia or pulmonary edema. PD efficiency can also be limited by the patient's

peritoneal membrane transport characteristics as well as the proportionally larger tubing dead space relative to the fill volume in neonates. The immature skin and paucity of subcutaneous tissue place the preterm infant at increased risk for exit site leakage which, if it occurs, not only renders PD futile but also increases the risk for infection. Finally, PD is contraindicated in the presence of conditions which compromise the integrity of the abdominal wall such as omphalocele or recent abdominal surgery.

Performing PD in infants can be laborious as the small fill volume required often precludes the use of automated cyclers necessitating the use of closed-circuit manual setups (e.g., Gesco Dially-Nate®). The Baxter Home Choice® cycler is reported to deliver fill volumes as small as 60 ml, but in practice, alarms are frequently experienced with fill volumes less than 100 ml.

Alparslan et al. in 2012 described their experience providing PD to preterm and term neonates (GA 27–41 weeks; weight 1000–3800 g) using an Baxter Home Choice® cycler adapted for very low fill volumes and using a single cuffed Tenckhoff neonatal straight catheter placed percutaneously with one or two sutures closing the skin [51]. The Baxter Home Choice® cycler was adapted with an infusion pump to allow delivery of fill volumes less than 60 ml, the smallest fill volume which the cycler can deliver. Similar to other published reports, they experienced high complication (~26 %) and mortality rates (~59 %).

As improvements in neonatal intensive care have resulted in improved survival of ELBW infants, the limits of RRT are continually challenged. The overall incidence of AKI in preterm infants is high and appears to be inversely correlated to gestational age and birth weight [5]. In recent years, pediatric nephrologists, neonatologists, and pediatric surgeons have developed innovative strategies using available equipment and technology to manage AKI in these vulnerable patients. Commercially available PD catheters are generally too large for ELBW infants leading practitioners to improvise dialysis access with the use of non-traditional catheters such as IV cannulas, silicone drains, and vascular catheters [52–54]. Angiocaths are attractive because they do not require a stylet for placement thereby reducing the risk of visceral injury. However, the flexibility of angiocaths makes them more prone to kinking with subsequent catheter malfunction.

Harshman et al. [55] described their successful experience providing cycling PD to an ELBW infant (BW 830 g) for 3 weeks using a standard 8 cm temporary

PD catheter placed in a non-traditional location—the left upper quadrant. The higher insertion allowed effective placement given the catheter length relative to the infant's torso length. To prevent leakage, the catheter was secured with a purse-string suture at the posterior rectus sheath with running sutures used to close the subcutaneous tissue and skin.

Assuming access can be achieved, the efficiency of continuous cycling PD (CCPD) is still low compared to HD or CRRT. Use of low initial fill volumes helps reduce the chances for leakage but also limits the clearance and ultrafiltration achieved. To improve the efficiency of PD, Raaijmakers et al. performed continuous flow peritoneal dialysis (CFPD) in neonates and children with AKI [56]. First introduced in the 1950s for adults, CFPD theoretically can improve the efficiency of PD by providing a continuous flow of dialysate through the peritoneal cavity. The continuous flow of dialysate provides a high concentration and osmotic gradient between the plasma and dialysate thereby maximizing solute mass transfer and ultrafiltration. Elimination of the catheter dead space associated with cyclical PD also theoretically helps improve the efficiency of PD for patients requiring small fill volumes. CFPD can be performed using two peritoneal catheters, one for continuous inflow of fresh dialysate and the other for drainage of used dialysate. Careful attention is required when placing the two catheters to allow sufficient distance between them so as to minimize recirculation. In a small study of six infants/toddlers ranging in age from 11 days to 2.5 years, the authors report significantly higher clearance and ultrafiltration with CFPD compared to conventional cycling PD. Mean urea clearance 15 ml/min/1.73 m² vs 5 ml/min/1.73 m²; mean ultrafiltration (UF) 1.8 ml/1.73 m² vs 0.2 ml/1.73 m². The authors report no major complications but did experience some issues with inflow and nutrient loss [56].

Hemodialysis and CRRT

Intermittent HD and CRRT are more efficient than peritoneal dialysis and allow for more predictable fluid removal.

CRRT is preferred over HD for critically ill, hemodynamically unstable patients as it allows gradual, adjustable fluid, solute, and waste product removal.

However, use of both are limited in neonates due to the challenges of establishing vascular access as well as the technical and safety limitations of currently available machines. Achieving and maintaining a well-functioning vascular access is paramount for both HD

and CRRT. Small double lumen catheters (5 Fr) are available but may not adequately support CRRT. In the prospective pediatric CRRT (ppCRRT) registry, when CRRT was provided using 5-Fr catheters, circuit lifespan was less than 20 h even with anticoagulation [55]. Seven Fr double lumen catheters, particularly when placed in the internal jugular vein, have been used successfully [57•, 58]. Ultrasound can be used to assess blood vessel caliber and aid in the selection of an appropriate-sized catheter. Placement of an overly large diameter catheter can be associated with vascular occlusion, thrombosis, and stenosis, which may have long-term implications for future dialysis access. El Masri et al. describe their experience successfully providing CRRT in neonates with cardiac disease and limited vascular options by use of two single lumen catheters (hemostasis valve sheaths) placed in two separate central veins. The valve sheaths provided adequate blood flow for CRRT, but the thin walls of the sheath were prone to kinking with subsequent introduction of air into the circuit. The authors propose the use of two 5-Fr single lumen continuous arteriovenous hemofiltration (CAVH) catheters which have more sturdy walls [59].

Currently available HD and CRRT machines were designed for adults and modified for use with children but are not currently FDA approved for children under 20 kg. Machines can be set up with smaller circuits/filters, and roller pumps can be calibrated to provide blood flow rates as low as 30 ml/min. Ideally, the circuit volume should be less than 10 % of the patient's effective circulating volume to minimize hemodilution and hemodynamic instability. Even the smallest circuits currently available exceed this parameter for neonates necessitating the use of a blood prime which, in turn, is associated with the risks of infection, transfusion reaction, potassium and citrate load, sensitization due to HLA exposure, thrombocytopenia, hypocoagulability state, and the bradykinin release syndrome if an AN-69 hemofilter is used [60].

Finally, although HD and CRRT allow for programmable and more precise ultrafiltration control in adults and older children compared to PD, this does not hold true for neonates due to the relative imprecision of the scales for small volumes typical for neonates. For example, ultrafiltration accuracy may differ by ± 30 ml/h from the actual fluid removal with current machines. This imprecision represents ~ 1 % of the blood volume for a 70-kg adult in comparison to ~ 12 % for a 3-kg neonate.

Clearly, to safely provide HD and CRRT to neonates, there is a need for specialized equipment designed with low circuit volumes which run at slow blood flow rates

and which are associated with more precise UF scales. A small circuit ultrafiltration machine, Aquadex®, has been adapted to provide continuous venovenous hemofiltration (CVVH) in neonates. Collaboration between experts in the field of pediatric nephrology and industry within the past decade has also led to the exciting development of two miniaturized machines—Newcastle Infant Dialysis and Ultrafiltration System (NIDUS®) and Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM®)—capable of providing renal replacement therapy to neonates.

Askenazi et al. recently published a case series of CRRT on infants and small children performed by adapting the Aquadex® machine for CRRT. With this machine which has an extracorporeal volume of 33 ml, cardiovascular instability during CRRT initiation was minimal, even in severely critically ill patients [61••].

NIDUS® provides hemodialysis to infants as small as 800 g (range 800 g–8 kg). Unlike conventional HD machines which are driven by roller pumps, the NIDUS® is a syringe-driven machine which withdraws a small amount of blood (5–12.5 ml), passes it through a dialysis filter, and then returns it to the patient. The circuit volume has been reduced to less than 10 ml obviating the need for a blood prime. UF rates in the range of 0–60 ml/h can be achieved with microliter precision of UF control. Use of this innovative technology allows treatment to be performed using a single lumen central venous line for up to 24 h at a time. Conventional HD may not be well tolerated by neonates due to rapid fluid and electrolyte shifts within a short period. However, the NIDUS® machine allows treatment to continue for up to 24 h making metabolic clearance and ultrafiltration more gradual and potentially better tolerated. It has been successfully used to provide therapy to several infants [62••].

CARPEDIEM® is a pump-driven machine which was designed to provide multiple therapies, including CRRT, to infants 2.5–10 kg in size. Though it requires a double lumen catheter, it was developed for use with small catheters (4–4.5 Fr). The extracorporeal circuit volume has been reduced to 27 ml excluding the filter which may range in volume from 27.2 to 41.5 ml (three filters available with surface areas of 0.075, 0.15, and 0.25 m²). Blood flow rates ranging from 5 to 50 ml/min can be achieved with excellent accuracy (error < 10 %) using miniaturized roller pumps which reportedly cause little microhemolysis. Gravimetric control along with improved UF scale sensitivity to 1 g provides more accurate fluid balance. CARPEDIEM® was licensed in Italy in 2013 and as of February 2016, 45 infants have been

supported with CARPEDIEM® (verbal communication with Claudio Ronco). CARPEDIEM® has the additional advantage of being able to provide multiple extracorporeal therapies including continuous venovenous hemofiltration/continuous venovenous hemodialysis/continuous venovenous hemodiafiltration (CVVH/CVVHD/CVVHDF), plasma exchange, blood exchange, single pass albumin dialysis [63, 64••, 65].

ECMO and CRRT

Critically ill neonates requiring ECMO often have multi-organ system failure including renal dysfunction. The incidence of AKI is high in this population, exceeding 50 % in several series [7, 66•, 67]. The systemic inflammatory response resulting from exposure of the blood to the extracorporeal circuit and the ensuing capillary leak contribute both to the development of AKI and fluid overload. Increasing cumulative fluid overload leads to visceral edema [68] and has been shown in several studies to be associated with a longer ECMO course as well as increased mortality [69, 70]. Improvements in fluid balance and reversal of fluid overload is associated with improved survival, better lung function, and shorter time to decannulation [70–72]. A more recent study by Selewski et al. confirms the association between the degree of fluid overload and mortality in children on ECMO but did not find that reducing the degree of fluid overload once established resulted in improved survival suggesting the timing and duration of fluid accumulation are critical [73•]. ELSO guidelines now recommend minimizing the degree of fluid overload and trying to maintain euvolemia. (Extracorporeal Life Support

Organization Guidelines. Available at <http://www.else.med.umich.edu/Guidelines.html>). Indeed, in a survey of ELSO centers, Askenazi et al. found that the most common indication for initiating RRT while on ECMO is fluid overload (43 % of centers) with another 16 % of centers starting RRT to prevent fluid overload [74••]. CRRT is used most frequently in conjunction with ECMO and can easily be performed by incorporation of either an in-line hemofilter or CRRT machine into the ECMO circuit. Refer to the review by Askenazi et al. for details regarding technical considerations (e.g., location of filter/machine placement) when combining these therapies [74••].

Aggressive fluid removal with CRRT during ECMO can be limited by the development of hypotension and/or excessive negative pressure in the venous limb of the ECMO circuit. Sasser et al. recently published their favorable experience adding PD to enhance fluid removal in post op cardiac neonates on ECMO who were already receiving CVVHF/CVVHD. The additional fluid removal by PD is thought to potentially be better tolerated because it is not directly lost from the macrocirculation but rather from the capillaries within the peritoneal membrane [75].

Diuretics, often employed during ECMO to minimize fluid overload, must be administered prudently as their use can increase the risk for prerenal AKI and ATN by masking oliguria secondary to intravascular volume depletion. In a recent study, loop diuretics were found to be an independent risk factor for AKI in children on ECMO receiving pre-emptive continuous hemofiltration [76].

Conclusion

Neonates are especially vulnerable to the development of AKI which, in turn, is associated with a high mortality. Despite advances in intensive care medicine, promising treatments to ameliorate AKI have not materialized. Although no specific pharmaceutical interventions are FDA approved for the treatment of AKI, the clinician can make important decisions that can ultimately impact outcomes. First, identification of patients at risk should be made by increasing provider awareness about AKI together with regular monitoring of renal function. Second, strategies to prevent poor outcomes in those at risk should be considered, including screening for sepsis, avoiding nephrotoxic medications, and optimizing hemodynamics. Close attention to hemodynamic status is critical and necessitates prompt, aggressive administration of fluids and pressors to restore/maintain visceral perfusion while simultaneously minimizing

cumulative fluid overload. If the patient cannot tolerate the fluid necessary for nutrition and medications, CRRT should be considered.

CRRT is increasingly being used to manage fluid overload and metabolic disturbances in critically ill children and adults with studies now focusing on outcomes based on the timing of CRRT initiation. Provision of CRRT to neonates, however, continues to lag due in large part to numerous technical challenges associated with use of existing machinery which was designed to provide therapy to adults. The dedication of our European colleagues addressing these technical concerns is laudable and has resulted in two miniaturized machines which have been successfully used to safely provide therapy to several neonates. However, these machines are not yet universally available and in the USA, practitioners continue to adapt existing machinery in an effort to provide this therapy to neonates. The community has a moral obligation to assure that safe and effective therapies are available for the smallest infants, and collaboration from regulatory bodies such as the FDA, industry, and academics (both pediatric nephrologists and neonatologists) will be vital. Prospective studies will be needed to determine which babies, at which time points, are most likely to benefit from the therapies. Such efforts will likely improve patient survival and renal recovery.

Compliance with Ethical Standards

Conflict of Interest

Ayesa N. Mian and Maroun J. Mhanna declare that they have no conflict of interest.

David J. Askenazi has received personal fees from Baxter, BTW, and the Acute Kidney Injury Foundation outside of the submitted work.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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