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Acute kidney injury in the fetus and neonate

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SUMMARY

Acute kidney injury (AKI) is an under-recognized morbidity of neonates; the incidence remains unclear due to the absence of a unified definition of AKI in this population and because previous studies have varied greatly in screening for AKI with serum creatinine and urine output assessments. Premature infants may be born with less than half of the nephrons compared with term neonates, predisposing them to chronic kidney disease (CKD) early on in life and as they age. AKI can also lead to CKD, and premature infants with AKI may be at very high risk for long-term kidney problems. AKI in neonates is often multifactorial and may result from prenatal, perinatal, or postnatal insults as well as any combination thereof. This review focuses on the causes of AKI, the importance of early detection, the management of AKI in neonates, and long-term sequela of AKI in neonates.

Keywords

Acute kidney injury; Neonate; Renal replacement therapy; Kidney adaptation

1. Postnatal kidney adaptation to extrauterine environment

Understanding the unique kidney adaptation that takes place early after birth is a crucial element in the prevention and management of neonatal AKI. There is great variability in nephron numbers at birth, ranging from 300,000 to 1.8 million nephrons per kidney. This variability is attributed to genetic and fetal environmental factors [1].

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Fetal urine production starts at 9–10 weeks. Fetal urine contributes to the amniotic fluid and increases with gestation [2]. During intrauterine life, fetal hemostasis is regulated by the placenta; however, the kidney is involved in critical functions including urine production, lung maturation, and hormonal production. Glomerular filtration rate (GFR), renal blood flow (RBF), and tubular functions progress with renal growth and nephrogenesis. In the near-term period, the fetal kidneys achieve sufficient glomerular and tubular development to allow the adaptation to extrauterine life [3].

Whereas adult RBF is about 20% of the cardiac output (COP), the fetal kidneys receive only 3–5% of COP and this reaches about 10% by first week of life and the adult level by age 2 years [4]. Similarly, GFR increases from about 5 to 40 mL/min/1.73 m^2 during the first week of life. It continues to increase to 65 mL/min/1.73 m^2 by two months of age and reaches the adult level of 120 mL/min/1.73 m^2 by two years of age [5]. The increase in GFR is attributed to increased RBF and decreased renal vascular resistance (RVR).

Renal vascular resistance is under the control of many vasoactive factors including angiotensin II, prostaglandins, nitric oxide (NO), and catecholamines [4]. Angiotensin II levels are higher in the newborn than in adults; levels decrease during the neonatal period and early childhood until reaching adult levels by 6–9 years of age [4,6]. Angiotensin II is a potent vasoconstrictor that increases RVR and subsequently contributes to decreased GFR [6]. This vasoconstrictor effect is opposed by the vasodilator effect of prostaglandins, especially on the afferent arterioles [7]. NO functions primarily as an afferent arteriole vasodilator. Endothelial NO synthase and angiotensin receptors are highly expressed in immature nephrons and downregulated at the end of nephrogenesis [3]. The renal sympathetic nervous system increases renal vascular tone in afferent and efferent arterioles. The upregulation of α2 receptors is associated with a downregulation of β2 receptors. Fetal renal vasculature is more sensitive to α2 receptor stimulation than in neonatal period [3].

The urinary flow rate increases 10-fold during fetal life from 6 mL/h at 20 weeks to 60 mL/h at 40 weeks of gestational age. Fetal urine is hypotonic (range: 100–250 mOsm/kg H_2O) [3]. The maximum urine concentration capacity of the full-term fetus (700 mOsm) does not reach adult levels (1400 mOsm) until 6–12 months of age [8]. This blunted concentration capacity is attributed to reduced tonicity of the medullary interstitium, low expression of aquaporins, and a relative tubular insensitivity to antidiuretic hormone (ADH). Higher production of prostaglandin E_2 in neonates may inhibit the tubular effect of ADH [9].

Electrolyte regulation also evolves during transition to extrauterine life. Excretion of sodium is higher during fetal life than in the newborn and adults. This high rate of sodium excretion may be related to high circulating concentrations, high sensitivity to natriuretic factors, a large extracellular fluid volume, relative insensitivity to aldosterone, and immaturity of tubular sodium reabsorption. In contrast to adult physiology, sodium is mainly reabsorbed in the distal portion of the immature tubules in the fetus [10]. Sodium excretion decreases with increasing gestational age [6].

The fetus requires a positive potassium balance for normal growth. In preterm infants, hyperkalemia is usually evident due the immaturity of the distal tubules. The peritubular and

luminal permeability of potassium may be contributing to the physiologic positive balance. In premature infants immediately following birth, there is a shift of potassium from the intracellular to the extracellular compartment [11]. Once the kidney adapts to the extrauterine environment, there is the onset of diuresis which facilitates potassium excretion and the regulation of serum potassium levels. Finally, the newborn infant has a diminished threshold for renal bicarbonate excretion.

Neonatal kidneys are unique; studies in human [12] and non-human primates [13] showed that although no new nephrons are formed after birth in term infants, nephrogenesis continues in preterm babies after birth (until about 36 weeks of gestational age. Using human autopsy samples Faa et al. [14] showed that kidney maturation continues after birth in preterm babies. Thus, nephrogenesis is a process not restricted to the intrauterine life, but may be an ongoing process. Some studies suggest that the extrauterine environment and AKI are detrimental to optimal nephrogenesis [15,16].

2. Definition and incidence of AKI

2.1. Challenging diagnosis in a challenging population

In spite of all the limitations of using serum creatinine levels to define AKI in the neonate, it is still the most widely used marker. Creatinine levels change in even healthy newborns in the first days to weeks of life [17]. Neonatal serum creatinine levels initially reflect maternal creatinine and take several days to reach equilibrium. As such, neonates' serum creatinine decreases over the first weeks of life, with the rate of decline dependent on gestational age at birth [18]. In infants born at term, there is a rapid rise in both glomerular and tubular function during the immediate postnatal period; however, this abrupt increase is dampened in preterm infants with a gestational age less than 34 weeks [19,20]. In very low birth weight infants with a GA <30 weeks, renal function has been shown to rise very slowly during the first two months of life [21]. This difference between preterm and term infants has been attributed to the immaturity of the kidney at birth and to delayed adaptation to extrauterine life in preterm infants [17,19,21]. In addition, it is important to consider that creatinine is a marker of kidney function and its rise lags after the onset of kidney damage. Serum creatinine may not increase until 25–50% of renal function is lost [22]. As such, serum creatinine is not an ideal biomarker for the early detection of AKI in neonates; nonethless, we know that small changes in SCr are independently associated with poor outcomes.

2.2. Towards a working definition of neonatal AKI

Defining AKI in neonates remains a challenging dilemma for both neonatologist and nephrologist. Historically, neonatal AKI was defined in terms of absolute serum creatinine levels. More recently, proposed definitions are based upon the degree of increase in serum creatinine levels rather than a single absolute cut-off value. These definitions may have more biological plausibility but do require serial creatinine measurements; this may be of concern in preterm babies who are especially susceptible to anemia from iatrogenic blood losses.

In 2000 Gouyon and Guignard defined renal insufficiency of very preterm babies as a daily increase in serum creatinine of >0.50 mg/dL from day 0 to 1 and 0.30 mg/dL/24 h during the

remainder of the first week of life [23]. Oliguria was defined as urine volume of <1 mL/kg/h over a period of 24 h; severe oliguria was defined as urine volume of <0.5 mL/kg/h. Subsequent AKI definitions have also used varying combinations of rising serum creatinine, oliguria, and elevated blood urea nitrogen (BUN) levels [24,25], with the most widely used definition between 1995 and 2005 as an absolute SCr of ≥1.5 mg/dL.

In 2013, the question about which definition of neonatal AKI should be used was discussed with a panel of experts at an National Institutes of Health-sponsored workshop and concluded that the categorical modified Kidney Diseases: Improving Global Outcomes (KDIGO) definition which is being used in pediatric and adults studies is as good as any other proposed. Importantly, although large studies to validate their use in neonates are lacking, the definition does seem to be able to predict clinical outcomes, independent of potential confounders. Work to validate this defintion, and to perhaps tailor it to neonates, as well as the potential role of urine protein biomarkers to detect kidney damage are an area of active investigation. This neonatal KDIGO definition (Table I) relies on the lowest previous serum creatine to act as the baseline value to compare subsequent serum creatinine. Further research will be needed to determine whether it predicts clinical outcomes and whether modifications to this definition are necessary.

2.3. Incidence of AKI

The lack of a standard definition of neonatal AKI limits our ability to study this condition, particularly where epidemiology is concerned. The reported incidence of AKI in neonates is higher than in many other critically ill nephrology populations [26]. During the first postnatal days, newborns are at higher risk of developing AKI because they are born with high renal vascular resistance, low GFR, high plasma renin activity, decreased intercortical perfusion, and decreased reabsorption of sodium in the proximal tubules [27,28]. Available epidemiological data estimating AKI in neonates should be interpreted cautiously as different studies have used different definitions, and vary in the number of serum creatinine values ascertained; nonetheless, recent studies suggest a high incidence of AKI along with significant increases in morbidity and mortality among neonates with AKI as compared with age- and illness-matched controls. Andreoli [29] estimated the incidence of AKI (in a review of single-center studies that used a serum creatinine cut-off of 1.5 mg/dL) in critically ill neonates at between 8% and 24%, with mortality rates between 10% and 61% Using more contemporary definitions (an absolute rise of 0.3 mg/dL or 50% rise from lowest previous SCr), studies suggest an incidence of 19–40% in very low birth weight infants [30,31], and 38% in term neonates with perinatal asphyxia [32].

3. Groups at high risk of developing AKI in the neonatal period

Certain factors may place neonates at higher risk for developing AKI. Low birth weight is one such risk factor for AKI. Arcinue et al. reported an estimated 26% prevalence of AKI among extremely low birth weight (ELBW) newborns over a period of 10 years [33]. Furthermore, the mortality rate of infants with AKI in this cohort was more than double that in infants without AKI, 54% compared with 20%. Another report described an incidence of AKI of 26% among ELBW infants [34]. A cohort study of 229 very low birth weight (<1500

g) infants reported that those infants who experienced AKI during the NICU stay had lower birth weights and higher mortality than those without AKI [30]. As previously described, prematurity itself is an independent risk factor for AKI as a result of incomplete nephrogenesis and low nephron number [35–37]. Certain neonatal morbidities are also strongly associated with AKI. One such condition is perinatal asphyxia. Selewski et al. found the incidence of AKI among asphyxiated newborns who underwent therapeutic hypothermia to be 38% [32]. Kaur et al. [38] reported an AKI incidence of 41.7% in asphyxiated neonates, with an incidence of 9.1% in infants with moderate asphyxia and 56% among infants with severe asphyxia. Other studies support the correlation of AKI incidence with advancing severity of hypoxic ischemic encephalopathy [39,40] (Table 2). Newborns with congenital heart diseases affecting systemic circulation, and especially those undergoing cardiopulmonary bypass, also have higher incidences of AKI than the baseline neonatal population [41,42].

4. Etiology of neonatal AKI

Neonatal AKI may result from insults during the prenatal, perinatal, or postnatal periods. Generally, causes of AKI may be subdivided into three main categories; prerenal, renal, and postrenal. AKI in neonates is most often multifactorial.

4.1. Prerenal AKI

Prerenal AKI represents a functional change (rise in SCr and drop in UOP) without actual kidney damage. It is generally due to decreased renal blood flow. This is the most frequent cause of AKI in neonates, accounting for 85% of cases [35,43]. Diminished renal blood flow resulting from decreased intravascular volume may be seen in a myriad of states such as compromised placental blood flow (e.g. placental abruption), excessive gastrointestinal losses, and increased insensible losses, especially in premature neonates with skin immaturity. Prerenal AKI may also result from increased capillary permeability, as seen in sepsis, or decreased oncotic pressure from hypoalbuminemia. Renal blood flow may also be directly impaired in states of hypotension and compromised cardiac output. Renal blood flow may also be compromised in abdominal compartment syndrome and may result in prerenal AKI.

Neonatal exposure to certain medications may also cause prerenal AKI; this exposure may occur prenatally as a result of maternal exposure or postnatally as a neonatal exposure. Non-steroidal anti-inflammatory drugs (NSAIDs) may cause renal vasoconstriction via blockage of cyclooxygenases and prostaglandin synthase. NSAIDs given to pregnant women do cross the placenta and, as such, should be avoided during pregnancy. However, indomethacin may be used in the peripartum management of women with threatened preterm delivery as a form of tocolysis. Adverse effects on fetal renal function have been most extensively studied for indomethacin but have also been described after antenatal exposure to ibuprofen and ketoprofen [44]. A marked decline in fetal urine output has been observed within 5 h of indomethacin treatment and oligohydramnios developed in 70–82% of pregnancies during the first week of treatment, but disappeared after discontinuation of the drug. Development of oligohydramnios has been shown to be dose dependent [44]. Transient anuria but also

persistent fetal anuria in neonates exposed to indomethacin within 24 h of delivery has been reported [45].

The use of indomethacin and/or ibuprofen therapy in neonates is most often directed towards therapy for patent ductus arteriosus (PDA), in which the same vasoconstrictive effects are used to promote ductal closure. Inhibition of cyclooxygenase within the neonatal kidney results in decreased prostaglandin synthesis and consequent reduction in renal perfusion. AKI developed in 24% of neontaes receiving indomethacin for PDA closure [46]. Ibuprofen is considered less nephrotoxic than indomethacin, but it may not be exempt from causing adverse renal effects [47].

Angiotensin-converting enzyme (ACE) inhibitors inhibit the synthesis of angiotensin II and subsequently vasodilation of the renal efferent vessels with a subsequent fall in GFR. Maternal exposure to ACE inhibitors and angiotensin type 1 receptor (AT1-R) antagonists can affect the development and function of perinatal kidney. It may lead to renal papillary atrophy with impaired urinary concentrating ability [48]. Other features of intrauterine exposure to ACE inhibitors include oligohydramnios, pulmonary hypoplasia, and renal failure [49].

4.2. Renal AKI

Acute kidney injury due to intrinsic injury of the renal parenchyma is the second most frequent cause of AKI in neonate with an incidence of 11% [35,41]. On a histological basis, AKI due to renal causes is characterized by the presence of acute tubular necrosis (ATN). Persistent functional changes that are not adequately corrected may lead to true kidney damage and ATN. Renal AKI may be due to vascular compromise, as may be seen in bilateral renal vein thrombosis [50] or renal artery thrombosis seen with umbilical artery catheter malposition [51], and renal infarct. Some antimicrobial medications are well-known causes of AKI. Aminoglycosides have a direct toxic effect on the tubular epithelium through inhibition of lysosomal phospholipase, leading to cell death. They may also cause intrarenal vasoconstriction and local glomerular and mesangial cell contraction [52]. Gentamicin was the second most frequently administered medication in a large national database of NICUs in the USA [53]. Antenatal maternal administration of ampicillin and aminoglycosides reduces nephron number (range, 20–30%) and induces hypertension in adult rat offspring. Reduced nephron number results in a defect in ureteric bud ranching morphogenesis affecting the first branching division [54]. Current animal data suggest that vancomycin has oxidative effects on cells of the proximal renal tubule [55] by changing the energy-dependent renal reabsorption function of the proximal tubule cells and altering mitochondrial function [56]. The mechanism of amphotericin-induced nephrotoxicity is incompletely understood. It has been proposed that both tubular injury and renal vasoconstriction play an important role [57]. Amphotericin B inserts into cell membranes, resulting in the creation of pores that increase membrane permeability [57]. It also increases the permeability of the macula densa cells to sodium chloride. This may inappropriately activate the tubuloglomerular feedback system and lead to excessive afferent arteriolar vasoconstriction and a fall in GFR [58]. In addition to this direct effect, in-vitro studies suggest that approximately one-half of the tubular toxicity of amphotericin B may be

mediated by deoxycholate, a detergent used as a solubilizing agent for the drug [57]. Acyclovir nephrotoxicity is due to intratubular deposition of crystals; the nephron becomes obstructed leading to increased resistance to renal blood flow and subsequent elevation of the serum creatinine [59]. Intravenous immunoglobulin (IVIG) is another medication that may cause nephrotoxicity, attributed to osmotic insult caused by the high sucrose contents of most forms of IVIG [60]. Radiocontrast agents may also cause AKI and, although the exact mechanism is unknown, animal studies suggested that hypoxic medullary injury plays a critical role in contrast-induced nephropathy [61].

4.3. Postrenal AKI

AKI due to postrenal causes is less frequent and accounts for about 3% of cases of neonatal AKI [35,43]. Postrenal AKI may be caused by intrinsic obstructions, such as fungal balls, extrinsic compression, such as seen with tumors, and may also be due to congenital causes of urinary tract obstruction. These lesions include posterior urethral valves, triad syndrome, bilateral ureteropelvic junction obstruction or unilateral obstruction in single kidney (these conditions may present as AKI but then lead to chronic kidney disease). Postnatal causes of postrenal AKI may include urethral strictures due to traumatic bladder catheterization, and malfunctioning indwelling urinary catheters. Ultrasound is the mainstay of evaluation when postrenal etiologies are suspected. Relief of the obstruction generally results in improvement in renal function.

5. Management of AKI in the neonate

Where possible, prevention of AKI should be the primary goal of management. When AKI does occur, early recognition and mitigation are crucial. Avoidance of further nephrotoxic insults may decrease the risk for progression of AKI and further deterioration in renal function.

5.1. Fluids: the delicate balance

More important than the quantity of fluid intake provided, or the quantity of output, close attention to fluid balance (including flushes) is vital. The goal of fluid management in the neonate is to provide necessary hydration, nutrition, medications, and blood products, while still achieving fluid homeostasis and avoiding dehydration as well as progressive fluid overload. Excessive, unreplaced fluid losses may contribute to prerenal AKI; appropriate fluid resuscitation would be needed to restore kidney function. Special attention to insensible water loss (IWL) is crucial in this population, especially in early preterm babies. In an animal model of preterm infants, Agren et al. showed that IWL was inversely proportional to gestational age and was attributed to the expression and cellular localization of the aquaporins that might contribute to the high losses of water through the immature skin [62]. IWL is typically 180–310 mL/m^2/day (15–25 mL/kg/day), of which about 60% is transepidermal [63] and 40% respiratory [64].

Whereas AKI in neonates is more usually non-oliguric, some newborns may develop oliguric/anuric renal failure with subsequent fluid overload [65]. Overwhelmingly, studies in critically ill children and adults have shown how fluid overload has a determinental impact

on morbidity and mortality independent of severity of illness and co-morbidities. For example, in a retrospective chart review of 80 children with mean ages 58.7 ± 73 months with respiratory failure, Arikan et al. found that fluid overload of ≥15% was independently associated with longer hospital stay, longer duration of ventilation, and worse oxygenation index [66]. A recent retrospective study analyzed data from 435 neonates who underwent cardiac surgery with cardiopulmonary bypass and found that fluid overload of ≥16% was an independent risk factor for worse outcomes [67].

There are no specific guidelines regarding the use of diuretics in neonates with AKI. There are also no comparative studies between the use of intermittent doses of diuretics versus continuous infusion in neonate. Nonetheless, standard practice includes a trial of diuretic therapy, often with furosemide, in oliguric neonates with AKI. Minimizing fluid intake, while still maintaining adequate hydration and nutrition, can help prevent or minimize fluid overload. Patients with AKI who do not make urine after 1–1.5 mg/kg/dose of furosemide are unlikely to improve and have a high rate of progressive AKI. Further management with diuretics carries a higher risk of toxicity (ototoxicity for example) with few potential benefits. Those patients who are not responsive to furosemide challenge should be considered for renal replacement therapy (RRT) early in the disease state [68,69].

5.2. Electrolyte disturbances

Neonates have lower serum sodium levels due to negative sodium balance, and this finding is proportional to gestational age [70]. Hyponatremia in the setting of AKI, however, is often due to dilution factors and is best treated with fluid restriction rather than with sodium supplementation.

Hyperkalemia is a life-threatening complication of AKI. Neonatal potassium levels are often checked by capillary samples from heel sticks; as such, they are often hemolyzed and serum potassium may be falsely elevated. When possible, a free-flowing venous or arterial sample with prompt processing is preferable. Measuring free plasma hemoglobin and using the following formula may also be helpful in correction of serum potassium levels in the setting of hemolysis:

Correction factor of 0.00319 × free plasma hemoglobin [71].

Management of acute hyperkalemia should begin with cardiac stabilization using calcium chloride or calcium gluconate to increase the threshold of resting membrane potential at which excitation occurs [72]. Exogenous potassium administration from intravenous fluids or parenteral nutrition should be immediately discontinued in the acute setting. Potassium can be shifted to the intracellular compartment by the administration of glucose with insulin, sodium bicarbonate, or administration of β2-adrenergic agonists [73]. Excretion of potassium can also be promoted using loop diuretics. Loop diuretics prevent reabsorption of sodium and potassium in the loop of Henle and directly increase urinary potassium excretion.

Using cation exchange resins may prevent further increase of serum potassium. Two forms of cation exchange resins are available: sodium polystyrene sulfonate and calcium polystyrene sulfonate. The mechanism of action of these agents is based on binding

potassium in the intestine in exchange for sodium or calcium. Each gram of resin can potentially bind up to 0.5–1 mEq of potassium. While these agents are classically administered via the enteral route, the use of potassium-binding resins in preterm infants has been associated with the development of necrotizing enterocolitis [74,75]. As such, the practice of decanting milk with these resins rather than direct administration may be preferred. In lower acuity settings, hyperkalemia can be addressed by decreasing potassium intake. Breast milk is usually low in potassium and phosphorous compared with standard neonatal formulas but may also be decanted as needed. For formula-fed infants, low potassium formulas can be utilized.

Hyperphosphatemia can be treated initially with dietary phosphate restriction. Formula-fed newborns may be transitioned to low phosphate renal formulas [76]. Calcium carbonate can be used as a temporary measure to prevent further increases in serum phosphorus. Added to feeds, calcium carbonate acts as a phosphate binder, rendering it insoluble and subsequently decreasing its intestinal absorption.

Acidosis may be temporized by the use of intravenous or oral sodium bicarbonate supplementation. In newborns receiving intravenous fluids or parenteral nutrition, acetate may be favored over chloride to help address metabolic acidosis.

5.3. Renal replacement therapy (RRT) in neonatal AKI

When medical management of AKI fails, renal replacement therapy (RRT) is considered. Indications for RRT are not well described in neonates, and RRT is often delayed until no other plausible alternatives exist to address life-threatening complications such as hyperkalemia. Nonetheless, many infants, such as those with volume overload interfering with ventilation and those with poor nutrition owing to volume restriction, may benefit from earlier initiation of RRT [23]. Waiting too long to refer an infant with fluid overload for RRT may be catastrophic, as excess fluid accumulation might make RRT access imposible to attain.

There are three main modalities of RRT in neonates: peritoneal dialysis, intermittent hemodialysis and continuous renal replacement therapy. The choice of the modality of RRT largely depends on the center experience, availability of access, and the presence of certain contraindications to a particular modality.

Acute peritoneal dialysis (PD) has historically been the mainstay of RRT for neonates given its relative ease of access and technical simplicity [23,77]. Acute PD may easily be performed in units with no HD expertise, and it is effective for the management of AKI and metabolic disturbances in children of all ages, including newborns and preterm infants [78]. Limitations to PD in the neonatal population include certain congenital defects involving the abdominal wall and organs and intraperitoneal surgeries.

Whereas HD has been the preferred modality for the treatment of severe hyperammonemia in neonates, it is generally not the preferred method of RRT in neonates with AKI. This is especially true if the primary indication for therapy is volume overload; if significant fluid

removal is needed, neonates are susceptible to hemodynamic instability owing to the relatively large extracorporeal circuit volume.

Continuous renal replacement therapy (CRRT) is effective for patients with high ultrafiltration needs. The use of CRRT in neonates has been limited by the currently available technology, with circuits generally only approved for older children who weigh >20 kg. Nonetheless, CRRT has been performed on hundreds of patients with machinery adapted for the smaller patient. Whereas the blood volume of a 4 kg full-term neonate is about 320 mL, the smallest CRRT circuit used currently in the USA with the Prismaflex filter M60 is 100 mL. M60 also carries the risk of bradykinin release because of the AN-69 membrane, which has pushed some centers to use the HF1000 polysulfone membrane with a total circuit volume of about 170 mL. If the circuit volume is >10% of the patient's blood volume, blood-priming the circuit is advisable to avoid acute hemorrhagic shock. Strategies to limit the risk of hypotension during blood priming include giving intravenous calcium to limit hypocalcemia due to the chelating effect of citrate preservative in the blood as well as buffering the blood with sodium bicarbonate to counteract acidic pH of blood products. Other risks of blood primes (especially when multiple circuits are needed or in those with a high extracorporeal volume) include hyperkalemia and bleeding diathesis, as blood primes do not include platelets or coagulation factors found in whole blood.

Recently smaller circuits have been employed to decrease the complications of RRT in newborns. The HF20 filter, with a surface area of 0.2 m^2, has been used for years across the world but has not been approved in the USA by the Food and Drug Administration (FDA). Fortunately, new devices specifically designed for newborns which employ smaller circuits are being tested. Two very promising new devices are the Newcastle Infant Dialysis Ultrafiltration System (NIDUS), with an extracorporeal volume of 6.5 mL for filters of 0.045 m^2, and Cardiac And Renal Pediatric Dialysis Emergency (CARPEDIEM™) that has available circuits of 27, 34, and 45 mL for filters of 0.075, 0.15, and 0.25 m^2 respectively [79,80]. These machines are not yet approved by the FDA for use in the USA. In a recent study, Askenazi et al. reported on a single-center experience of using the Aquadex™ for RRT in small children. They adapted this machine, originally designed for slow continuous ultrafiltration [81], to enable convective clearance of uremic toxins. In 12 critically ill children, with age range 4–1460 days and weight range of 2.7–12.4 kg, they report their experience of 261 days of therapy. Complications were infrequent and 58% of patients survived.

6. Prognosis and long-term complications of AKI

The prognosis of AKI in newborns is highly dependent on the etiology of the condition [29] and on gestational age [82]. Despite appropriate treatment, 25–50% of newborns with AKI die [83] and long-term problems appear in the survivors [84].

Over the past few years, a body of data from experimental animals as well as human studies has shown that AKI is not a limited insult and may result in permanent kidney damage [85,86]. In a prospective cohort study, Mammen et al. [87] followed 126 children with AKI for up to three years after the AKI episode. Overall, 10% of patients developed CKD and the

prevalence had a direct correlation with AKI severity; most of the patients who develop CKD had AKI stage 3 during their hospital course. Of the 30 patients with neonatal AKI, 16.6% developed CKD, suggesting that this population may be at higher risk of developing CKD after AKI. Menon et al. reported residual renal damage in 70% of children who developed AKI due to nephrotoxic medication at the six-month follow-up visit after their illness. This residual damage was in the form of reduced GFR, hyperfiltration, proteinuria, or hypertension [84]. In the only study specifically evaluating long-term sequelae of AKI in the newborn population, height was reduced in those with AKI after a two-year follow-up [88].

Studies evaluating CKD after AKI episodes in neonates specifically are lacking. More studies are needed to explore the long-term sequela of AKI in neonates in order to inform appropriate follow-up guidelines to promote the early detection and management of CKD, proteinuria, and hypertension.

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Conflict of interest statement

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Practice points

- There is no unified definition of AKI in neonates, but a working definition has been proposed.
- Neonatal AKI is frequent and is independently associated with mortality.
- Fluid overload is associated with poor outcomes, yet no specific guidelines exist for the use of diuretics or renal replacement therapy in this population.
- Close follow-up of all neonates with a history of AKI is crucial for early detection of long-term complications such as hypertension, proteinuria and progression to chronic kidney disease.

Research directions

- Identification of practical urinary biomarkers for early detection of AKI in neonates.
- Benefits of intermittent versus continuously infused diuretic therapy.
- Understanding which babies will benefit from RRT with novel devices designed to minimize the risk and maximize benefit for renal support.
- Understanding strategies to limit the short- and long-term morbidities of at-risk infants.

Table 1

Neonatal KDIGO (Kidney Diseases: Improving Global Outcomes) acute kidney injury definition.

Stage	Serum creatinine (SCr)	Urine output over 24 h
0	No change in serum creatinine or rise <0.3 mg/dL	>1 mL/kg/h
1	SCr rise ≥0.3 mg/dL within 48 h or SCr rise ≥1.5 to 1.9 × reference SCr[a] within 7 days	>0.5 and ≤1 mL/kg/h
2	SCr rise ≥2 to 2.9 × reference SCr[a]	>0.3 and ≤0.5 mL/kg/h
3	SCr rise ≥3 × reference SCr[a] or SCr ≥2.5 mg/dL[a] or Receipt of dialysis	≤0.3 mL/kg/h

[a]Reference SCr is the lowest prior SCr measurement.

Table 2

Incidence of acute kidney injury (AKI) in different stages of hypoxic–ischemic encephalopathy (HIE).

Study	Country	Population	Definition of AKI	Incidence of AKI		
				HIE stage I	HIE stage II	HIE stage III
Gopal et al. [39]	India	50 full-term newborns with an Apgar score of ≤7 at 5 min	Oliguria (urine output <0.5 mL/kg/h) and/or serum creatinine level >2 SD above the mean value for that particular gestational age or rising creatinine levels (0.3 mg/dL/day)	25%	88%	100%
Alaro et al. [40]	Nairobi	60 full-term newborns	Renal function was assessed by measuring serum creatinine on day 3 of life. AKI was defined by a level of creatinine >133 µmol/L.	4.6%	9.7%	42.9%