

## Neonatal Acute Kidney Injury: Diagnostic and Therapeutic Challenges

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### ABSTRACT

Acute kidney injury (AKI) affects more than 30% of hospitalized neonates with increased rates of mortality and longer hospital admission. While research in neonatal AKI has increased over the last few years, advances in clinical recognition, diagnosis, and supportive care for AKI in this specific age group, have lagged behind advances in pediatric patient groups. The lack of a standardized definition of AKI in neonates similar to those used in adult and pediatric patients in addition, the unique renal physiology of preterm and term infants create challenges for the use of serum creatinine as an AKI biomarker in these patients creating a challenge in diagnosis, management and even research concerning neonatal AKI. In addition nutrition as a

critical item in neonatal care, the special precautions regarding drugs use in neonates and renal replacement therapy in neonates which is not only technically difficult, but also associated with high rates of complications all yields AKI management in neonates to be a great challenge.

**Key words:** Neonate; Acute kidney injury

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### INTRODUCTION

The primitive antenatal kidney appears at 3rd week of gestation<sup>[1]</sup>, while the permanent kidney begins to form after the 30th day of gestation<sup>[2]</sup>. Fetal kidneys produce diluted urine forming a significant proportion of amniotic fluid<sup>[3]</sup>. Fetal urine output (UOP) rises from 15 ml/kg/hr to 50 ml/kg/hr at 40 weeks of gestation<sup>[4]</sup>. After birth, serum creatinine reflects the maternal renal function up to 72 hours of life<sup>[5]</sup>. Glomerular filtration rate (GFR) and effective renal plasma flow are low in term and preterm infants, due to high vascular resistance in renal vessels as a result of vasoconstrictive and vasodilator renal forces, and also due to marked drop of systemic vascular resistance resulting from redistribution of blood flow at birth<sup>[6]</sup>. GFR slowly increases daily, doubles at the age of 2 weeks and reaches full maturity by age of 2 years (Table 1). The neonatal kidneys work hardly in the first few days of life to reduce the extracellular fluid content with UOP up to 10 ml/kg/hr and also to manage the large water load from breast feeding. Urine flow is regulated by tubular reabsorption in presence of low GFR and high UOP giving a picture similar to polyuric phase of acute kidney injury (AKI)<sup>[7]</sup>.

### INCIDENCE, RISK FACTOR AND ETIOLOGY OF AKI IN NEONATES

The incidence of AKI in children is highly variable (25.1-82%) among pediatric intensive care unit (PICU) reports from different

countries due to various inclusion criteria and profile of patients admitted to the PICU<sup>[10-15]</sup>. The incidence of neonatal AKI is also variable. Table 2 shows AKI Incidence in various neonatal populations and the AKI definition used for diagnosis. Very low birth weight, a low 5 minute APGAR score, maternal drug administration, intubation at birth, respiratory distress syndrome, patent ductus arteriosus, sepsis, phototherapy and neonatal medications (Non-steroidal anti inflammatory drugs, Antibiotics, diuretics) are the most commonly reported factor predisposing to AKI in neonates<sup>[16]</sup>. Hypernatremic dehydration is a rarer cause of AKI in neonates that may occur as a result of inadequate milk intake<sup>[17,18]</sup>. Congenital renal malformations may presents as AKI, with progressive deterioration of kidney functions. Autosomal recessive poly- cystic kidney disease may cause renal failure in the neonatal period, but only in a small proportion of patients<sup>[19]</sup>.

## DIAGNOSTIC AND CLASSIFICATION CRITERIA FOR NEONATAL ACUTE KIDNEY INJURY

Before 2005, the majority of neonatal AKI studies used a definition of AKI defined by a serum creatinine concentration (SCr)  $\geq 1.5$  mg/dl. In 2012, Jetton and Askenazi<sup>[21]</sup> proposed a standardized neonatal AKI definition based on the kidney disease improving global outcome. (KDIGO) definition for adults and children (Table 3). Ackan arikan slightly modified the RIFLE criteria used for classification of adult AKI (Table 4) definition to enhance it is applicability in children, by specially assessing the change in serum creatinine and UOP. Base line serum creatinine estimation is challenging in neonates since serum creatinine rapidly decrease in the first week of life as the function of nephron mature and the lessened exposure to maternal creatinine level. UOP is the earliest clinical sign of AKI and it is the simplest method of diagnosis AKI in neonates so oligourea is considered a sensitive highly specific marker of AKI in neonates. Table 4 compares pediatric and neonatal RIFLE criteria<sup>[12]</sup>.

## NEW BIOMARKERS

Traditionally used biomarkers such as blood urea nitrogen (BUN) and creatinine are insensitive, non-specific and do not adequately differentiate between the different stages of AKI especially in neonates. A delay in diagnosis prevents appropriate timely patient management decisions. Early biomarkers of AKI such as Cystatin C and Beta 2 microglobulin (B2M) facilitate earlier diagnosis and specific preventative and therapeutic strategies, thus resulting in fewer complications and improved outcomes which was proved in many studies in pediatric population<sup>[23,24]</sup>. The superiority of these biomarkers to creatinine was replicated in many neonatal studies<sup>[25-27]</sup>.

## MANAGEMENT OF AKI IN NEONATES

### Non-dialytic management of AKI in the newborn

Identification and management of reversible causes is crucial element in management of neonatal AKI. If urinary tract obstruction is identified, it should be relieved and urological consultation should be sought for further management<sup>[28]</sup>. Treatment of the metabolic complications of AKI involves appropriate management of fluid (This includes body weight recorded at least twice daily to facilitate early detection of fluid overload), electrolytes, and acid- base balance; provision of good nutrition; and initiation of renal replacement therapy (RRT) if conventional therapy fails. Although, newborns are

**Table 1** Normal GFR in neonates, Children and Adolescents[8,9].

Age	Mean GFR +/- SD (ml/min/1.73m <sup>2</sup> )
29-34 weeks GA- 1 week postnatal age	15+/- 5.6
29-34 weeks GA- 2-8 week postnatal age	28.7+/- 13.8
29-34 weeks GA- above 8 week postnatal age	51.4
1 week term males and females	41+/-15
2-8 weeks term males and females	66+/-25
Above 8 weeks term males and females	96+/-22
2-12 years (males and females)	133+/-27
13-21 years (males)	140+/-30
13-21 years (females)	126+/-22

GFR: glomerular filtration rate, SD: standard deviation, GA: gestational age.

**Table 2** Acute kidney injury Incidence in various neonatal populations and the definition used for diagnosis[20].

Population	AKI incidence	AKI Definition
Pre-term VLBW	18%	Modified KDIGO
Pre-term ELBW	12.50%	Modified KDIGO
Sick near-term/ term	18%	Modified KDIGO
Asphyxiated newborn	38%	Modified KDIGO
ECMO	71%	RIFLE criteria
Cardiac surgery	62%	AKIN criteria

AKI: Acute kidney injury, VLBW: very low birth weight, ELBW: extremely low birth weight, ECMO: extracorporeal membrane oxygenation, KDIGO: kidney disease improving global outcome. RIFLE: risk, injury, failure, loss, end stage. AKIN: acute kidney injury neonate.

**Table 3** Neonatal acute kidney injury Kidney Disease Improving Global Outcomes(KDIGO) classification[21].

Stage	Serum creatinine	Urine output
0	No change in sCr or rise less than 0.3 mg/dl	$\geq 1$ ml/kg/h
1	sCr rise $\geq 0.3$ mg/dl within 48 h or sCr rise $\geq 1.5-1.9$ x reference sCr within 7 days	$\geq 0.5$ ml/kg/h and less than 1 ml/kg/h
2	sCr rise $\geq 2-2.9$ reference sCr	$\geq 0.3$ ml/kg/h and less than 0.5 ml/kg/h
3	sCr rise $\geq 3$ x 3 reference sCr or sCr $\geq 2.5$ mg/dl or receipt dialysis	Less than 0.3 ml/kg/h

sCr: Serum creatinine.

able to tolerate potassium levels up to 6.5mmol/L, higher levels are characteristic of AKI<sup>[29]</sup>. Bicarbonate therapy for correction of acidosis should be restricted to severe life threatening conditions. There is disagreement on the role of rapid infusion of sodium bicarbonate in intraventricular hemorrhage in neonates by causing episodic increase in the cerebral blood flow by causing high arterial CO<sub>2</sub> leading to cerebral vasodilation<sup>[30]</sup>.

Osmotic diuretics should be avoided due to risk of intraventricular hemorrhage<sup>[28]</sup>. Loop diuretics have also been proclaimed to be renal protective due to their effects on the redistribution of the renal blood flow resulting from the changes in the prostaglandin synthesis. Loop diuretics should be used with caution due to their ototoxic potential (although reversible) and the risk of renal calculi with long-term use<sup>[31]</sup>.

Dopamine is a safe and effective vasopressor agent commonly used in neonates as a first line therapy for hypotension. Dopamine also improves UOP and serum creatinine in neonates transiently<sup>[32]</sup>.

Theophyllin appears to have an important therapeutic effect in the prophylaxis of AKI in the post-asphyxial neonate. Theophyllin, by antagonizing the adenosine receptors, is capable of contrasting renal va-

**Table 4** Pediatric and neonatal RIFLE criteria[22].

	Creatinine criteria		Urine out put criteria	
	pRIFLE	n RIFLE	p RIFLE	nRIFLE
Risk	eCCL decrease by 25%	?	UOP < 0.5 ml/kg/hrx8hr	UOP < 1.5 ml/kg/hr for 24 hr
Injury	e CCLdecrease by50%	?	UOP < 0.5 ml/kg/hrx16hr	UOP < 1.0 ml/kg/hr for 24 hr
Failure	eCCL decrease by 75% or eCCL < 35ml/min/1.73m <sup>2</sup>	?	UOP < 0.3 ml/kg/hrx24hr or anuric for 12hr.	UOP < 0.7 ml/kg/hr for 24 hr or anuric for 12 hr
Loss of function	Persistent failure > 4 weeks	Persistent failure > 4 weeks	Persistent failure > 4 weeks	Persistent failure > 4 weeks
End stage	Persistent failure > 3 month	Persistent failure > 3 month	Persistent failure > 3 month	Persistent failure > 3 month

eCCL: estimated creatinine Clearance.UOP: urine output. Hr: hour, Question mark ('?') is intended to mean uncertain thresholds, RIFLE: risk, injury, failure, loss. pRIFLE: pediatric RIFLE. nRIFLE: neonatal RIFLE

**Table 5** Advantages and Disadvantages of Different Dialysis Modalities[40].

Modality	Advantages	Disadvantages
Peritoneal dialysis	No need for vascular access or blood prime; No systemic heparinization; Slow, continuous; Less risk of hemodynamic instability	Slower correction of metabolic parameters; Risk of peritonitis; Contraindicated in patients who have severe pulmonary disease and intra-abdominal processes
Hemodialysis	Rapid correction of metabolic abnormalities ; Rapid removal of fluid or toxins; Initial modality of choice in metabolic; disorders such as hyperammonemia	Vascular access; Blood prime; Risk of hemodynamic instability; Systemic heparinization; Reverse osmosis system required; Dialysis disequilibrium; Relative contraindications: severe; hemorrhage or hemodynamic instability
Hemofiltration with or without dialysis	Slow, continuous without dialysis; Less risk of hemodynamic instability; Citrate-based anticoagulation available at some centers; Removal of toxins, cytokines	Vascular access; Blood prime; Hypotension initially with bradykinin release syndrome; Systemic heparinization in some institutions

soconstriction both preventively and during AKI (thus limiting injury and allowing a faster recovery)<sup>[33-35]</sup>. Despite the many and promising studies theophillin still does not have an official role in the guidelines for the treatment of AKI and its use requires further research<sup>[36]</sup>.

Nutritional support is highly important during AKI management in neonate. Protein intake should be adjusted at least to meet the basal growth requirements (1-2 g/kg/day) while keeping the BUN below the threshold for causing increase in the serum osmolarity<sup>[37]</sup>.

#### Dialysis modalities in neonates with AKI

The main indications for initiating dialysis in neonates with AKI includes: severe oligoanuria (decrease in hourly urine out put to less than 0.5 mL/kg for more than 12 hours) despite fluid therapy, diuretics, and inotropic support; hypervolemia (physical evidence of total body fluid overload, edema); hyperuricemia ( $\geq 13$  mg/dL); severe metabolic acidosis despite bicarbonate therapy and azotemia<sup>[38]</sup>.

The preferential use of hemodialysis (HD) and hemofiltration by pediatric nephrologists is increasing, but those modalities are technically difficult procedures. The large extracorporeal circuit volumes, anticoagulation, and vascular access required are limiting factors, particularly in neonates. As a result, peritoneal dialysis (PD) is generally the most common form of RRT in young children, including neonates, the advantages being relative ease of access and technical simplicity<sup>[19]</sup>. A study by Bojan and colleagues stated that early initiation of PD in neonates and infants with AKI after cardiac surgery was associated with significantly lower mortality rates<sup>[39]</sup>.

Peritoneal dialysis is the optimal dialysis modality for neonates. PD facilitates the slow removal of fluids and solutes, while preventing hemodynamic instability. PD is technically a simple treatment modality, which can be continuously performed in neonates, hospitalized at neonatal intensive care units (NICUs)<sup>[40]</sup>. PD is generally performed after a failed conservative treatment. Indications for dialysis include decompensated metabolic acidosis, hyperkalemia and/or progressive azotemia, hyponatremia with symptomatic volume overload, hypocalcemia, hypophosphatemia and inability to provide adequate nutrition (due to oliguria or anuria), hyperammonemia and accumula-

tion of neurotoxic metabolites<sup>[41]</sup>. Table 5 compares advantages and disadvantages of different dialysis modalities in neonates<sup>[40]</sup>.

The first large series for neonatal HD described 33 infants weighing less than 5 kg received hemodialysis treatment between 1980-1991 in Children's hospital, Harvard medical school with 52% survival rate at end of dialysis treatment. In 27% of these cases dialysis was performed through two single lumen catheters in umbilical artery and vein<sup>[42]</sup>.

Hemodialysis is used if PD is contraindicated, failed or when rapid correction of volume overload is required, severe hyperkalemia, severe unremitting metabolic acidosis are present, and in the treatment of oxalosis and hyperammonemia. Most infants require hemodialysis four times weekly to avoid the fluid overload caused by their liquid nutrition. Neonatal blood lines have smaller internal luminal diameters. Even the pump header segment has a smaller internal luminal diameter, thus requiring a pump speed four times greater than the blood flow. Dialyzers that have smaller surface areas also are used. The surface area can be reduced by decreasing the length of the dialyzer and the number of hollow fibers within the dialyzer. Some dialyzers require a reduction in the volume of dialysate from 500 to 600 mL/min to 300 to 400 mL/min for the dialyzer/circuit set to work properly<sup>[43]</sup>.

Even with neonatal blood lines and small dialyzers, most neonates weighing less than 8 kg require at least occasional blood priming. If the hemoglobin level is maintained in the high range of normal or the patient is transfused concurrently during the start of dialysis, the infant may tolerate a crystalloid or 5% albumin prime. For many neonates, warming the dialysate is insufficient to maintain normal patient temperature; returning the blood via a warming device sometimes is needed. Increasing the overhead warmer temperature is also helpful<sup>[43]</sup>.

The most commonly used equations to determine the efficacy of dialysis are the Kt/V equation and peritoneal equilibration testing (PET). Studies evaluating dialysis adequacy have not been performed for neonates. PET has been used extensively in pediatric patients to determine the permeability of the peritoneal membrane. patients with

high-transport membranes have excellent Kt/V values because urea and creatinine diffuse well, but have poor ultrafiltration rates because the dextrose diffuses quickly across the membrane, thereby rapidly decreasing the osmolality gradient needed for ultrafiltration. Many neonates have high-transport membranes<sup>[40]</sup>.

### Prognosis of neonatal AKI

There are few studies on the long-term prognosis of neonatal AKI regarding long-term kidney disturbances, such as chronic renal insufficiency, hypertension and defect in renal concentration. Therefore, it is important to emphasize the need for a prolonged and careful follow-up of all neonates who suffered from AKI, especially preterm<sup>[44]</sup>. In general AKI with conserved diuresis has better survival and long term outcome while AKI with contracted diuresis has poor outcome specially in presence of multiple organ failure<sup>[36]</sup>.

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