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Special Articles

Developing a neonatal acute kidney injury research definition: a report from the NIDDK neonatal AKI workshop

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Critically ill patients are at highest risk for acute kidney injury (AKI), or abrupt renal dysfunction. Before 2004, most pediatric AKI literature reported on the technical feasibility and outcomes of renal replacement therapy treatment for AKI. The field of AKI has evolved markedly; AKI is no longer an "all or nothing" event (renal replacement therapy vs. not) but an organ injury whereby increasing injury is associated with worsening outcomes. In the past, the definition of AKI in the literature was inconsistent, leading to a lack of standardized AKI research and knowledge on epidemiology and outcomes. The publication of internationally standardized AKI definitions has promoted AKI classification into mild, moderate, and severe categories, providing a definable disease to evaluate the impact of AKI on outcomes and an operational outcome for studies aiming to reduce AKI incidence. Many studies have now shown that AKI is an important risk factor for both short-term outcomes (e.g., hospital mortality) and long-term outcomes (including mortality and chronic kidney disease) in adults and children (1–6).

The research on the definition of AKI has largely excluded neonates. It is unclear whether pediatric AKI definitions (7) are applicable to neonates, leading to inconsistency in defining neonatal AKI within the literature and significant lags in AKI research. In 2013, an NIDDK-sponsored workshop with neonatologists, pediatric nephrologists, and NIH representatives was conducted (8), including an AKI definition workshop. This report summarizes this discussion, and aimed toward the following: (i) identify challenges and potential solutions to neonatal AKI definition; (ii) evaluate current AKI definitions; and (iii) provide recommendations for the development of a neonatal AKI definition.

NEONATAL AKI EPIDEMIOLOGY, RISK FACTORS, AND OUTCOMES

Most data on neonatal AKI pertain to neonates in the neonatal intensive care unit or those undergoing surgical repair for congenital heart disease. Several reviews report neonatal intensive care unit–AKI incidence to be 8–40%, depending on the definition used (9–11). As high as >60% of neonates undergoing congenital heart disease surgery develop postoperative AKI (11,12). Renal replacement therapy-requiring AKI incidence in the neonatal intensive care unit is ≤1% (refs 13,14) and ranges from <1 to 10% after neonatal congenital heart disease repair (15,16). Mortality in neonates with AKI is as high as 60%, including data from studies using non-renal replacement therapy-AKI definitions (10,11). As detailed in several reviews, risk factors and etiology of neonatal AKI are often multifactorial, including conditions leading to intravascular volume depletion (e.g., hypovolemia, sepsis with capillary leak), ischemia (e.g., low cardiac output, vasopressors), nephrotoxic medication, and multiple organ dysfunction (9–11,17). Neonates have additional unique conditions predisposing to and causing AKI, including prenatal/perinatal events (e.g., maternal medications during pregnancy; prematurity; placental blood loss at birth; and perinatal asphyxia with renal ischemia) and postnatal events (e.g., infection susceptibility; excessive fluid skin losses; and umbilical catheter-associated renal vessel thrombosis) (9–11,17). As described below, neonatal renal

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physiologic changes contribute to the challenge of developing a neonatal AKI definition. Appreciating these issues will lend to developing a neonatal-specific AKI definition, with a goal of performing rigorous research on epidemiology and outcomes (hospital and long-term outcomes), identifying consistent AKI risk factors, and ultimately research aimed at reducing AKI incidence and improving outcomes.

Neonatal Developmental Physiology Considerations

Nephrogenesis begins at the 5th week of gestational age (GA), with urine production beginning at 9–10 weeks' GA. As fetal serum creatinine (SCr) concentration is that of the mother, neonatal SCr at birth reflects maternal SCr (10,11). After birth, glomerular filtration rate (GFR) increases markedly, with increasing proportion of cardiac output contributing to renal blood flow and complex neuroendocrine-mediated decrease in renal vascular resistance (10,18). Consequently, postnatal SCr decreases abruptly over days and then slowly over weeks and months, as GFR attains full maturity by 1–2 years (refs 19,20). Tubular function also matures progressively throughout fetal life and postnatally. Of most relevance is the fact that urinary concentration function (water reabsorption) is lower at birth, reaching healthy child concentration ability by about 1 year of age (10,21). Contemporary AKI definition relies on documenting SCr change or decreasing urine output (7). Early-life renal physiologic events cause these parameters to change independently of AKI; thus, neonatal physiology must be considered to most validly apply such criteria, at least until different renal injury markers are available.

Neonatal AKI Definition

A standardized neonatal AKI definition will promote a uniform approach to framing research and developing clinical benchmarks. An ideal AKI definition should allow identification of risk for worse outcomes (including hospital and long-term outcomes such as poor growth or chronic kidney disease), and allow detection early enough to trigger conservative strategies to prevent further renal injury and worsening AKI severity. With careful thought and consideration to neonatal renal physiology, it may be feasible to maximize the validity of SCr and urine output as criteria for defining neonatal AKI.

Difficulties with SCr to Define Neonatal AKI

Baseline SCr determination. Current AKI definitions require measuring the magnitude of SCr rise from "baseline" steady-state SCr. There is no baseline steady-state SCr in neonates, as SCr should be physiologically decreasing postnatally.

Several strategies were discussed. It was agreed that using maternal SCr as a baseline is inappropriate, because of the rapid postnatal SCr drop occurring within hours and frequent unavailability of this parameter. One proposed method was considering the lack of or less than expected SCr decrease as an AKI criterion. This may be appropriate in early postnatal life (week 1), when rapid SCr decrease is expected. However, this criterion may be inappropriate in premature infants, or later in the first month of postnatal life when rapid early postnatal GFR rise has occurred. Moreover, there is interindividual and GA-related variability in postnatal SCr decrease (19,22). Incorporating this criterion to define AKI would require evaluating thresholds and time frames for a "lack of SCr drop" across GA and term vs. preterm groups.

Another method defines baseline SCr as the lowest SCr before a given day's SCr. For example, the lowest SCr before postnatal day 6 would serve as "baseline" for postnatal day 6 (ref. 18). This method relies on having regularly measured SCr values and may overestimate baseline SCr in early postnatal life when GFR is rapidly increasing.

Other neonate-specific non-renal factors affecting SCr. SCr concentration is affected by volume status, exacerbated by physiologically decreasing extracellular fluid volume postnatally. There is a likely variability in SCr generation associated with GA, muscle mass, and nutrition, affecting SCr concentration independent of renal function. As alluded to above, it is unknown whether SCr-based AKI definition criteria should differ depending on gestational or postnatal age.

Change in estimated GFR. Perinatal GFR-estimating equations have not been developed, and GFR equations derived in older children have not been validated in neonates. GFR change as an AKI criterion is thus inappropriate.

SCr rise threshold. No studies have explicitly examined whether SCr rise thresholds (e.g., 50% rise from baseline) used in pediatric AKI definition are the most appropriate for use in neonates, thus representing an important research area. In older children, SCr doubling from baseline (i.e., stage 2 AKI) is consistently associated with increased mortality and morbidity (1,2). Until the most ideal SCr rise thresholds for neonatal AKI definition have been identified, it is advisable that SCr doubling from baseline be included in neonatal AKI definition for clinical trials or long-term outcome studies.

Urine output change for defining neonatal AKI

Current pediatric AKI definition includes classification of increasingly severe decrease in urine output per unit time (shown in Table 1). Several neonate-specific challenges with the use of urine output criteria to define AKI were discussed.

Logistical challenges. Indwelling urinary catheters are seldom used in neonates. Measuring urine output using weighed diapers may be inaccurate because of radiant warmers causing urine evaporation, thereby increasing the measurement challenge. It has been proposed that urine output measurement using weighed diapers should be performed every 3 h, which may improve accuracy and reduce the significance of evaporative losses (21,23). Whether this leads to a difference in AKI ascertainment has not been elucidated.

Staging urine output decrease in neonates. The urine output threshold for the current pediatric AKI definition was empirically derived, with urine output <0.5 ml/kg/h for at least 8 h being considered abnormal (1,21). For reasons described above, especially relating to lower urinary concentration ability in neonates and variability across GA, defining thresholds for low neonatal urine output is challenging. Authors of a single-center neonatal intensive care unit study proposed that the low urine output threshold in neonates should be higher than that in older children (<1.5 ml/kg/h for 24 h) based on their analysis of different urine output thresholds for predicting mortality (23). This outcome-based threshold determination is more valid than empirically derived threshold definitions and deserves further research to either validate their findings or determine the most ideal urine output threshold for global neonatal AKI definition.

It was proposed that fluid overload (or fluid balance) may more appropriately reflect renal water excretion function than does urine output. However, fluid overload (expressed in the literature either as cumulative fluid balance divided by weight or as percent change in daily weight) (24,25) is shown to be associated with poor hospital outcomes in critically ill children (24–30). Research should specifically evaluate fluid overload or fluid balance severity staging, rather than, or together with, urine output decrease, in neonatal AKI definition.

Other serum and urine biomarkers for AKI definition

This discussion was limited at the meeting and will not be reviewed in this report. However, many new AKI diagnostic biomarkers (including alternative GFR biomarkers (6,31), and traditional and novel biomarkers of renal tubular injury (32–35)) are being studied. There is recent expert consensus that there is a need to define AKI not only with functional markers (i.e., SCr, and urine output) but also with structural markers of renal tissue injury (i.e., mainly markers of renal tubular injury) (36). Including tissue injury markers in neonatal AKI definition is appealing, as they represent actual renal tubular injury, when functional markers (SCr and urine output) are especially challenging to interpret. Data on novel AKI biomarkers are emerging in neonates, but more research is needed to understand the factors affecting these biomarkers (e.g., necrotizing enterocolitis and neonatal-specific conditions), their validity to identify neonatal renal injury, and how to incorporate them into a practical and operational AKI definition.

Examining Currently Proposed Neonatal AKI Definitions

Recent attempts to modify and apply existing child AKI definitions to neonates have been made (17,18,21,23). **Table 1** compares some of these modifications. Few modifications to SCr criteria have been proposed. For stage 3 AKI, rather than including a criterion of SCr cutoff >4 mg/dl, this threshold was reduced to 2.5 mg/dl (**Table 1**). A modified "baseline" SCr definition has been proposed, where baseline SCr is the lowest SCr measured before a given day's SCr (described

Table 1. Proposed neonatal AKI definition modifications from KDIGO pediatric AKI definition, using SCr and urine output criteria

Stage	Serum creatinine criteria (in mg/dl)			Urine output criteria (in ml/kg/h)[a]		
	Pediatric definition	Neonatal modification: 2012	Neonatal modification: 2015–2016	Pediatric definition	Neonatal modification: 2013	Neonatal modification: 2016
1	≥ 0.3 Rise within 48 h or ≥ 1.5–1.9× rise from baseline[b] within 7 days	≥ 0.3 rise or ≥ 1.5–1.9× rise from baseline (defined as previous lowest/trough value)	≥ 0.3 rise within 48 h or ≥ 1.5–1.9× rise from baseline (previous lowest value) within 7 days	< 0.5 for 8 hours	< 1.5 for 24 h	≤ 1 for 24 h
2	≥ 2–2.9× rise from baseline	Unchanged	Unchanged	< 0.5 for ≥ 16 h	< 1 for 24 h	≤ 0.5 for 24 h
3	≥ 3× rise from baseline or ≥ 4.0 or eGFR < 35 ml/min per 1.73 m^2 or RRT initiation	≥ 3× rise from baseline or ≥ 2.5 or RRT initiation	≥ 3× rise from baseline or ≥ 2.5 or RRT initiation	< 0.3 for ≥ 24 h or anuria for ≥ 12 h	< 0.7 for 24 h or anuria for 12 h	≤ 0.3 for 24 h

AKI, acute kidney injury; eGFR, enhanced glomerular filtration rate; RRT, replacement therapy; SCr, serum creatinine concentration.
[a]The published KDIGO definition proposes timing cutoffs for low urine output to be >6 h for stage 1 (instead of >8 h) and >12 h for stage 2 (instead of >16 h). The pediatric literature to date has consistently utilized urine output decrease timing cutoffs as displayed in the table.
[b]Baseline SCr: no clear guideline on how to define pediatric baseline SCr. In the literature, baseline SCr has most commonly been defined as the lowest SCr measured in the previous 3 months.

Table 2. Research gaps and opportunities identified in neonatal acute kidney injury definition

SCr in neonatal AKI definition
1. Research is needed to focus on evaluating the validity and outcome associations of different methods of defining baseline SCr in neonates, which consider the physiological changes occurring in SCr in early neonatal life
2. Research is needed to develop SCr-based neonatal AKI definitions by studying newborn infants at varying gestational and postnatal ages, from the first few weeks of life, compared with older age groups
3. Studies evaluating neonatal AKI and long-term outcomes should be powered to evaluate the association between at least stage 2 AKI and outcomes
Use of urine output change as a criterion for defining AKI in newborn infants
4. Research is needed to further evaluate urine output-defined AKI in neonatal AKI studies, including comparison with SCr-AKI definition and outcome associations
5. Research is needed to define "volume overload" or "change in volume status/balance" by evaluating and comparing studies that precisely measured urine output and incorporating the findings in the definition of neonatal AKI
6. Urine output and/or volume overload-based neonatal AKI definitions need to be evaluated in neonates of varying gestational and postnatal ages, comparing the first week of life with later periods
Use of other serum and urine biomarkers for a neonatal AKI definition
7. Future studies need to evaluate novel AKI biomarkers in neonates for AKI diagnosis and prediction of short- and long-term neonatal outcomes
8. Studies are needed to elucidate neonatal clinical and physiologic factors that affect AKI biomarker concentrations independent of renal function

AKI, acute kidney injury; RRT, replacement therapy; SCr, serum creatinine concentration.

above). Proposed neonatal urine output criteria have been modified considerably, mainly to increase the low urine output threshold (Table 1, last two columns), which is reasonable, given the neonatal physiology issues described above. Each of these definition modifications requires extensive validation and evaluation in relevant neonatal subgroups.

Summary

Research on neonatal AKI definition is evolving and must consider physiology (e.g., developmental GFR increase) while allowing for flexibility to include future validated markers of structural/tissue injury. Neonatal AKI definitions will enable rigorous clinical and translational research. A summary of research recommendations and knowledge gaps is provided in Table 2. Multicenter studies (such as The Neonatal Kidney Collaborative group, formed subsequent to this NIH workshop) to address these knowledge gaps and determine definitions that are most feasible and best predict outcomes are needed (4). Until a widely accepted definition is available, researchers should strive to use rational, physiology-based SCr and urine output definition criteria and clearly describe methods used to define neonatal AKI, in published data, in order to move this field forward.

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