Acute Kidney Injury in Premature, Very Low-Birth-Weight Infants

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Abstract

The epidemiology of neonatal acute kidney injury (AKI) is not well established, partly due to lack of a consensus definition. Preterm neonates are likely especially vulnerable to AKI. We performed a retrospective review to assess the incidence of and risk factors for AKI in very low-birth-weight (VLBW), premature infants admitted to a level 4 NICU (2006–2007). AKI was classified using a standardized definition based on changes in serum creatinine (SCr). AKI incidence varied inversely with gestational age (GA): 65% (22–25 weeks), 25% (26–28 weeks), 9% (29–32 weeks) as did severity ($p < 0.001$). Stage 1 AKI was most common in each cohort. Stages 2 and 3 AKI comprised approximately 60% of AKI in the 22- to 25-week cohort but 20% or less in the older cohorts. By univariate analysis, factors associated with AKI included younger GA, lower BW, lower Apgar scores, hypotension, more frequent treatment with nephrotoxic antimicrobials, longer-duration mechanical ventilation, and higher incidence of patent ductus arteriosus (PDA) requiring treatment. By multiple logistic regression analysis, only GA, hypotension, PDA, and longer duration of mechanical ventilation were independently associated with AKI. AKI was not independently associated with risk of death. Our study suggests that small increases (≥ 0.3 mg/dL) in SCr occur frequently in premature, VLBW infants, and are associated with increased morbidity but not mortality. AKI incidence and severity were highest in the youngest GA cohort. Understanding the epidemiology, risk factors, and impact of neonatal AKI is crucial as long-term premature infant survival continues to improve.

Keywords

- neonatal acute kidney injury
- creatinine
- patent ductus arteriosus

Introduction

The epidemiology and impact of acute kidney injury (AKI) in the neonatal period are not well established. This has become an area of increasing research interest as advances in neonatal medicine have led to improved survival of critically ill newborns and as recent studies in both adults and children

suggest AKI is an independent risk factor for the development of chronic kidney disease (CKD).^{1–6} Research involving neonatal AKI has faced some of the same limitations as AKI research in other populations, namely lack of a consensus definition. Earlier studies in neonates, often using oliguria or a serum creatinine (SCr) 1.5 mg/dL or greater to define AKI, reported an incidence of AKI ranging from 8 to 24% depending

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on the population studied (developed vs. underdeveloped countries, asphyxiated newborns, premature infants, etc.).⁷ In recent years, two standardized classification schemes for AKI based on relative increases in SCr and/or decreases in urine output—RIFLE (Risk, Injury, Failure, Loss, ESRD) and AKIN (Acute Kidney Injury Network)—have been developed and validated for adults.⁸ Both classification schemes have been adapted for use in the pediatric population⁹ and more recently, modifications to both have been proposed for the study of neonatal AKI.^{10–15} Studies in both adults and children suggest that a relatively small increase in SCr of 0.3 mg/dL or greater is associated with increased mortality.^{16,17}

Defining AKI in the neonate is especially challenging due to the unique physiology of the newborn. Both RIFLE- and AKIN-based definitions of AKI involve elevation of SCr above a baseline value. This baseline is exceedingly difficult, if not impossible, to define in neonates particularly within the first few days of life—a time when newborns are especially vulnerable to renal injury. As SCr freely equilibrates across the placenta, the infant's creatinine at birth is reflective of the mother's renal function, not the infant's. Schwartz et al demonstrated that in full-term infants, the maternal SCr load gradually decreases over the first week of life at which time the SCr becomes reflective of the infant's renal function/glomerular filtration rate (GFR).¹⁸ Premature infants born prior to the completion of nephrogenesis at 36 weeks' gestation have significantly lower GFR at birth compared to full-term infants and therefore experience a more gradual excretion of the maternal creatinine load. SCr therefore may not reflect the premature infant's GFR until after 1 week of age.¹⁹ The assessment of renal function in premature infants during the first few days of life is further complicated by the observation of an initial rise in SCr, typically between days 1 and 4.^{19,20}

The aim of this study is to assess the incidence of AKI amongst very low-birth-weight (VLBW) infants born prior to 32 weeks' gestation in a quaternary level neonatal intensive care unit (NICU) using a modified AKIN definition and to identify risk factors associated with the development of AKI in this setting. We hypothesized that the most premature infants would be at highest risk for developing AKI.

Materials and Methods

Patient Selection

The NICU at the Golisano Children's Hospital at Strong (GCHaS) is a level 4 NICU serving the Finger Lakes Region in upstate NY. The NICU has 1,100 to 1,200 admissions per year of which approximately 150 to 180 are VLBW premature infants. We performed a retrospective chart review of the GCHaS Neonatology database (NeoData NICU Patient Data System, Isoprime Corporation) for admission of all infants born between January 1, 2006 and December 31, 2007 with gestational age (GA) 32 weeks or less and birth weight (BW) less than 1,500 g. The study was approved by the University of Rochester IRB with a waiver of consent. Infants were included if they met the following criteria: (a) admitted/transferred to GCHaS NICU within 24 hours of birth; (b) survived 48 hours or

more; and (c) remained inpatient in GCHaS NICU until discharge, death, or postmenstrual age (PMA) 36 weeks or more if transferred. Infants were excluded if they did not meet all of these criteria and/or if they had complex cardiac or urologic disease (complex congenital heart disease or congenital urologic disease—posterior urethral valves, dysplasia, cystic disease, high-grade hydronephrosis, or vesicoureteral reflux grade 4 or 5).

Data Collection

Data on all admissions to the NICU at the GCHaS has been collected in NeoData since 1991. For this study, data were collected from birth until PMA 36 weeks and included patient demographics; small for gestational age (SGA); Apgar scores; SCr; survival; exposure to nephrotoxic medications (indomethacin, ibuprofen, aminoglycosides, vancomycin, amphotericin); as well as certain comorbid conditions including (a) infection requiring treatment with nephrotoxic intravenous antibiotics for 6 days or more, (b) hypotension defined as treatment with pressors and/or fluid boluses, (c) patent ductus arteriosus (PDA), and (d) respiratory failure requiring mechanical ventilation. Data regarding nonsteroidal anti-inflammatory drug (NSAID) exposure included prenatal exposure (indomethacin) when given for tocolysis, postnatal exposure (indomethacin) for intraventricular hemorrhage (IVH) prophylaxis, and postnatal exposure (indomethacin or ibuprofen) for treatment of PDA. Since 1997 it has been standard protocol in our NICU to administer indomethacin for IVH prophylaxis to AGA neonates with BW 1,000 g or less and GA 28 weeks or less. Indomethacin dosing for IVH prophylaxis is 0.1 mg/kg/dose IV every 24 hours for three doses unless not tolerated (creatinine > 1.4 mg/dL, urine output < 0.5 mg/kg/h, platelets < 50,000, bleeding, necrotizing enterocolitis) whereas the dosing for treatment of a PDA is 0.2 mg/kg/dose IV every 12 hours for three doses unless not tolerated. Infants could receive up to three rounds of indomethacin as clinically indicated. A minority of infants during the study period received ibuprofen for closure of PDA (10 mg/kg followed at 24-hour intervals by two doses of 5 mg/kg).

Definition for Acute Kidney Injury

The AKIN definition²¹ for AKI was modified for use in this study to reflect solely changes in SCr (► **Table 1**).

The criteria that the absolute rise in SCr occur within a 48-hour period were also modified given the retrospective

Table 1 Defining AKI in neonates

Stage of AKI	AKIN definition modified for neonates
I	↑ in SCr ≥ 0.3 mg/dL (occurring after DOL 4) from lowest previous SCr obtained after 24 h of age or an ↑ in SCr of ≥ 150–200%
II	↑ in SCr > 200–300% occurring after DOL 4
III	↑ in SCr > 300% occurring after DOL 4

Abbreviations: AKI, acute kidney injury; DOL, day of life; SCr, serum creatinine.

nature of the study and because SCr values were not obtained on a daily or regular basis. The criteria for a euvolemic patient were also not applied as it was difficult to retrospectively discern the volume status of the patient. Transdermal fluid losses in the extremely premature infant during the first postnatal week are not quantifiable and greatly affect urine output and thus calculated fluid balance. Finally, the criteria for decreased urine output were also not applied because neonatal renal failure is often nonoliguric making urine output an insensitive marker for renal dysfunction.

Subjects were classified as not having AKI if they did not demonstrate an increase in SCr 0.3 mg/dL or greater or if they did not have creatinine checked.

Infants experiencing a rise in SCr of 0.3 mg/dL or greater within the first 4 days of life were not considered to have had AKI unless the peak in SCr at that time was 1.5 mg/dL or greater or unless the creatinine did not decrease by greater than 0.2 mg/dL prior to discharge.^{19,20}

During 2006–2007, SCr at our institution was measured using an enzymatic assay and the Siemens Advia 2400 (Tokyo, Japan) analyzer.

Statistical Analysis

The analyses were performed using version 9.3 of the SAS System for Windows (SAS institute Inc., Cary, North Carolina, United States). Student *t*-test was used to compare continuous variables between groups if the data were approximately normally distributed; otherwise, Wilcoxon-Rank Sum test was used. Chi-square or Fisher's exact test was used to compare categorical variables. All tests were two sided and a $p < 0.05$ was considered statistically significant.

Multiple logistic regression analyses were performed to evaluate the association between AKI and clinical risk factors, such as GA at birth, Apgar 5, presence of a PDA, hypotension, SGA, aminoglycoside therapy for 6 days or more, and days on mechanical ventilation. Variables identified to be associated with AKI ($p < 0.15$) were considered potential confounders. Collinearity diagnostics were performed before being included in the final regression model. Logistic Regression model with death as dependent variable was also fitted to evaluate the association between AKI and mortality after controlling for clinical confounders.

Results

Demographics

Between January 1, 2006 and December 31, 2007, 445 VLBW infants born with GA 32 weeks or less and BW less than 1,500 g were admitted to the GCHaS NICU (► Fig. 1). Approximately 25% of the infants were excluded, the majority of whom were transferred either into our NICU after 24 hours of age or from our NICU to another facility prior to PMA 36 weeks resulting in incomplete data collection. Four infants were excluded due to significant urologic disease (grade 4 hydronephrosis or grades 4–5 vesicoureteral reflux). Two hundred and sixty-six infants met the inclusion criteria. These infants were subdivided into three GA categories (group 1: GA 23–25 weeks, $n = 54$; group 2:

Fig. 1 Patient enrollment. BW, birth weight; GA, gestational age; PMA, postmenstrual age; VLBW, very low birth weight.

GA 26–28 weeks, $n = 99$; group 3: GA 29–32 weeks, $n = 113$) for subgroup analysis.

Acute Kidney Injury Incidence, Severity, and Risk Factors

The overall incidence of AKI in VLBW infants born 32 or less weeks' gestation in our NICU was 26%. ► **Table 2** compares the characteristics of those diagnosed with and without AKI. Infants with AKI were younger GA (26.2 ± 1.7 vs. 29.0 ± 2.1 weeks) and had lower BW (0.84 ± 0.23 kg vs. 1.13 ± 0.24 kg) than those without AKI. Though infants with AKI had lower birth weight, there was no difference in the incidence of SGA between the two groups. Sex, race, and single versus multiple gestational births were also not significantly different between the groups. Infants who developed AKI were more depressed at birth (lower Apgar scores at 1 and 5 minutes) had a greater need for pressor support, required mechanical ventilation for a longer period of time, more frequently needed prolonged courses (≥ 6 days) of aminoglycosides and other nephrotoxic medications (vancomycin and amphotericin), and had a higher incidence of PDA with subsequent need for treatment with NSAIDs or surgical ligation.

Multiple logistic regression analyses predicting AKI showed that GA at birth (odds ratio [OR] 0.63; 95% confidence interval [CI] 0.48–0.83), hypotension (OR 3.24; 95% CI 1.34–7.83), presence of a PDA (OR 8.9; 95% CI 3.62–21.99), and a longer need for mechanical ventilation (OR 1.03; 95% CI 1.00–1.06) were independently associated with the development of AKI. AKI was not found to be independently associated with the risk of death in our population (OR 1.82; 95% CI 0.61–5.44).

Table 2 Patient characteristics: demographics, comorbidities, exposures, death ($n = 266$)

	AKI $n = 70$	No AKI $n = 196$	p value
<i>Demographics</i>			
Gestational age (wk) (mean $\pm$ SD)	26.2 $\pm$ 1.7	29 $\pm$ 2.1	< 0.001
BW (kg) (mean $\pm$ SD)	0.84 $\pm$ 0.23	1.13 $\pm$ 0.24	< 0.001
SGA n (%)	10 (14%)	43 (22%)	0.190
Gestation—singleton n (%)	51 (73%)	141 (72%)	0.883
Sex (M) n (%)	44 (62%)	105 (53%)	0.179
Race (white) n (%)	39 (56%)	98 (50%)	0.124
Apgar 1 median (range)	3 (0–9)	6 (1–9)	< 0.001 ^a
Apgar 5 median (range)	6.5 (1–9)	8 (1–9)	< 0.001 ^a
<i>Comorbidities</i>			
Hypotension (pressor support) n (%)	52 (74%)	37 (19%)	< 0.001
Respiratory failure (days of mechanical ventilation) n (%)	30.3 $\pm$ 20.4	8.1 $\pm$ 13.6	< 0.001 ^a
PDA n (%)	52 (74%)	32 (16%)	< 0.001
<i>Nephrotoxic medication exposure</i>			
Aminoglycoside therapy ≥ 6 d n (%)	53 (76%)	102 (52%)	< 0.001
Other nephrotoxic meds ≥ 6 d n (%)	27 (39%)	40 (20%)	0.003
NSAID (tocolysis/IVH ppx/or PDA treatment) n (%)	68 (96%)	77 (39%)	< 0.001
<i>PDA management</i>			
NSAID PDA treatment (indomethacin/ibuprofen) n (%)	49 (70%)	27 (14%)	< 0.001
> 1 course NSAID n (%)	33 (47%)	5 (3%)	< 0.001
Ligation n (%)	15 (21%)	1 (0.5%)	< 0.001 ^b
<i>Disposition</i>			
Death in NICU n (%)	16 (23%)	15 (8%)	< 0.001

Abbreviations: AKI, acute kidney injury; BW, birth weight; IVH, intraventricular hemorrhage; M, male; NICU, neonatal intensive care unit; NSAID, nonsteroidal anti-inflammatory drug; PDA, patent ductus arteriosus; ppx, prophylaxis; SD, standard deviation; SGA, small for gestational age.

^a p Values were based on Wilcoxon Rank Sum test due to skewed data distribution.

^b p Values were based on Fisher's exact test.

Remainder of p values were based on t -test (continuous variables) and Chi-square test (categorical variables).

Seventy four percent of the infants in the study were classified as not having had AKI. Approximately one-third of these infants did not have a SCr checked. To test the hypothesis that infants who did not have a creatinine checked likely did not have AKI, we compared the characteristics of these infants with those who had creatinine checked but did not meet the criteria for AKI.

Among infants classified as not having AKI, those who did not have creatinine checked were older and larger with higher Apgar scores, lower incidence of PDA, less frequent exposure to indomethacin and other nephrotoxins, and less need for mechanical ventilation and pressor support compared to those who did have creatinine checked. The death rate was not significantly different between groups. As a group, infants who did not have a creatinine checked were healthier than those who had creatinine checked. It therefore seems plausible to assume that those without a creatinine checked also did not have significant renal disease/AKI (**Table 3**).

Subgroup analysis revealed that the incidence and severity of AKI are inversely correlated with GA ($p < 0.001$). One-half of all cases of AKI occurred in the youngest GA cohort (22–25 weeks) in whom the incidence of AKI was 65%. This contrasts with an AKI incidence of 25% in the 26- to 28-week cohort and 9% in the 29- to 32-week cohort. Stage I AKI was the most common stage of AKI in all three cohorts accounting for nearly 40% of AKI cases in the youngest cohort but over 75% of cases in the older two cohorts. Stages II and III AKI occurred more frequently in the youngest cohort with approximately 30% of patients in this group each experiencing stage II or III AKI (**Table 4**).

Given the high incidence of AKI in the 22- to 25-week GA subgroup, further analysis was performed in this group (**Table 5**). Those who developed AKI had lower birth weight, more frequent need for pressor support, longer periods of mechanical ventilation, and higher incidence of PDA with subsequent greater exposure to NSAIDs for treatment of PDA. Surgical ligation of the PDA was required in

Table 3 Characteristics of patients classified as not having AKI ($n = 196$)

	No AKI with creatinine $n = 133$	No AKI, no creatinine $n = 63$	p value
<i>Demographics</i>			
Gestational age (wk) (mean $\pm$ SD)	28.3 $\pm$ 2	30.4 $\pm$ 1.6	< 0.001
BW (kg) (mean $\pm$ SD)	1.07 $\pm$ 0.24	1.26 $\pm$ 0.18	< 0.001
SGA n (%)	24 (18%)	19 (30%)	0.070
Gestation—singleton n (%)	99 (74%)	42 (67%)	0.258
Sex (M) n (%)	72 (54%)	33 (52%)	0.818
Race (white) n (%)	68 (51%)	30 (48%)	0.013
Apgar 1 median (range)	5 (1–9)	7.5 (1–9)	< 0.001 ^a
Apgar 5 median (range)	8 (1–9)	9 (3–9)	0.006 ^a
<i>Comorbidities</i>			
Hypotension (pressor support) n (%)	37 (28%)	0	< 0.001
Respiratory failure (days of mechanical ventilation) n (%)	11.4 $\pm$ 15.4	1.3 $\pm$ 2.5	< 0.001 ^a
PDA n (%)	32 (24%)	0	< 0.001
<i>Nephrotoxic medication exposure</i>			
Aminoglycoside therapy $\geq$ 6 d n (%)	80 (60%)	22 (35%)	0.001
Other nephrotoxic meds $\geq$ 6 days n (%)	35 (26%)	5 (8%)	0.003
NSAID (tocolysis/IVH ppx/or PDA treatment) n (%)	73 (55%)	4 (6%)	< 0.001
<i>PDA management</i>			
NSAID PDA treatment (indomethacin/ibuprofen) n (%)	27 (20%)	0	0.001
> 1 course NSAID n (%)	5 (4%)	0	0.178
Ligation n (%)	1 (1%)	0	> 0.999 ^b
<i>Disposition</i>			
Death in NICU n (%)	12 (9%)	3 (5%)	0.395

Abbreviations: AKI, acute kidney injury; BW, birth weight; IVH, intraventricular hemorrhage; M, male; NICU, neonatal intensive care unit; NSAID, nonsteroidal anti-inflammatory drug; PDA, patent ductus arteriosus; ppx, prophylaxis; SD, standard deviation; SGA, small for gestational age.

^a p Values were based on Wilcoxon Rank Sum test due to skewed data distribution.

^b p Values were based on Fisher's exact test.

Remainder of p values were based on t -test (continuous variables) and Chi-square test (categorical variables).

eight infants, all of whom were in the group who developed AKI. Notably, in this subgroup of 22- to 25-week infants, AKI did not appear to be associated with SGA, sex, race, Apgar scores at 1 or 5 minutes, intrauterine exposure to indomethacin for tocolysis or postnatal exposure for IVH prophylaxis, and prolonged courses of aminoglycosides or

other nephrotoxic antimicrobials. AKI was also not associated with death.

Among infants born with GA 22 to 28 weeks who also developed a PDA ($n = 68$), the incidence of AKI was 65%. This risk was notably higher in infants receiving two or more courses of NSAIDs. Surgical ligation of the PDA was

Table 4 Spectrum of AKI and severity of AKI by gestational age^a

	Gestational age (wk)		
	22–25 wk ($n = 54$)	26–28 wk ($n = 99$)	29–32 wk ($n = 113$)
No AKI	19 (35%)	74 (75%)	103 (91%)
Stage I AKI	15 (28%)	21 (21%)	8 (7%)
Stage II AKI	10 (18.5%)	4 (4%)	1 (1%)
Stage III AKI	10 (18.5%)	0	1 (1%)

Abbreviation: AKI, acute kidney injury.

^a $p < 0.001$ (Cochran-Mantel-Haenszel Statistics used to evaluate the association between stage of AKI and gestational age groups).

Table 5 Patient characteristics for infants 22–25 wk gestation: demographics, comorbidities, exposures, death ($n = 54$)

	AKI $n = 35$	No AKI $n = 19$	p value
<i>Demographics</i>			
Gestational age (wk) (mean $\pm$ SD)	25.0 $\pm$ 0.6	25.2 $\pm$ 0.5	0.145
BW (kg) (mean $\pm$ SD)	0.71 $\pm$ 0.12	0.79 $\pm$ 0.12	0.030
SGA n (%)	4 (11%)	2 (10%)	> 0.999
Gestation—singleton n (%)	26 (74%)	14 (74%)	0.999
Sex (M) n (%)	18 (51%)	10 (53%)	0.933
Race (white) n (%)	22 (63%)	7 (37%)	0.169
Apgar 1 median (range)	3.5 (0–9)	5 (1–9)	0.146 ^a
Apgar 5 median (range)	6 (1–9)	7.5 (2–9)	0.094 ^a
<i>Comorbidities</i>			
Hypotension (pressor support) n (%)	32 (91%)	10 (53%)	0.002
Respiratory failure (days of mechanical ventilation) n (%)	39.7 $\pm$ 19.8	22.2 $\pm$ 17.4	0.003 ^a
PDA n (%)	26 (74%)	5 (26%)	< 0.001
<i>Nephrotoxic medication exposure</i>			
Aminoglycoside therapy $\geq$ 6 d n (%)	30 (86%)	12 (63%)	0.087
Other nephrotoxic meds $\geq$ 6 d n (%)	18 (51%)	5 (26%)	0.075
NSAID (tocolysis/IVH ppx/or PDA treatment) n (%)	35 (100%)	18 (95%)	0.352
<i>PDA management</i>			
NSAID PDA treatment (indomethacin/ibuprofen) n (%)	25 (71%)	4 (21%)	< 0.001
> 1 course NSAID n (%)	19 (54%)	1 (5%)	< 0.001
Ligation n (%)	8 (23%)	0 (0%)	0.040 ^b
<i>Disposition</i>			
Death in NICU n (%)	12 (34%)	4 (21%)	0.309

Abbreviations: AKI, acute kidney injury; BW, birth weight; IVH, intraventricular hemorrhage; M, male; NICU, neonatal intensive care unit; NSAID, nonsteroidal anti-inflammatory drug; PDA, patent ductus arteriosus; ppx, prophylaxis; SD, standard deviation; SGA, small for gestational age.

^a p Values were based on Wilcoxon Rank Sum test due to skewed data distribution.

^b p Values were based on Fisher's exact test.

Remainder of p values were based on t -test (continuous variables) and Chi-square test (categorical variables).

performed in 15 of the 68 infants. All of the infants who underwent surgical ligation were in the AKI group. Thirteen of the 15 infants requiring surgical ligation received two or more courses of NSAIDs prior to ligation. Only one infant underwent surgical ligation without a trial of NSAID therapy as it was contraindicated (**►Table 6**).

Discussion

Neonates born prematurely prior to the completion of nephrogenesis are suspected to be particularly vulnerable to AKI, the short- and long-term consequences of which have not been studied. Research in this area has been challenging

Table 6 Risk of patients with a PDA developing AKI based on NSAID exposure

	AKI ($n = 44$)	No AKI ($n = 24$)	p value
NSAID courses			< 0.001 ^a
No NSAID for treatment of PDA	3 (7%)	4 (17%)	
1 course NSAID	11 (25%)	15 (62%)	
> 1 course NSAID	30 (68%)	5 (21%)	
Ligation	15 (34%)	0	0.001

Abbreviations: AKI, acute kidney injury; NSAID, nonsteroidal anti-inflammatory drug; PDA, patent ductus arteriosus.

^a $p < 0.001$ testing the distribution of NSAID courses (three categories) between AKI cases.

mainly due to lack of a consensus definition for AKI but also due to limitations of an accurate marker for renal function and “real-time” renal injury. Creatinine-based definitions remain the standard for diagnosing AKI in clinical practice despite its well-recognized flaws because SCr is simple, convenient, and practical to measure. SCr is an endogenous marker generated by muscle metabolism, which serves as a surrogate estimate of GFR because it is predominantly eliminated by glomerular filtration. However, factors other than glomerular filtration, such as muscle mass and diet, can affect its value. Additionally, although glomerular filtration is the main route of creatinine excretion, tubular secretion accounts for approximately 10% of its elimination.²² Therefore, as glomerular filtration decreases, the proportion of secreted to filtered creatinine increases resulting in an overestimation of GFR by SCr. Further, changes in SCr lag behind the renal injury, and therefore significant damage is incurred before becoming clinically detectable by a rise in SCr. The relationship between SCr and GFR is complex, but the parameter height/SCr is linearly related to GFR in the pediatric CKD population.^{23–25} Given the limited muscle mass that neonates have, variations in muscle mass are not likely to impact SCr much in this age group. However, hydration status and protein intake could.

Creatinine-based definitions also suffer from technical issues as the assay has not yet been standardized across labs. Creatinines measured using an enzymatic assay, as in our study, have now been standardized to IDMS creatinine standards, but nonenzymatic methods will be less accurate at low values.^{26,27}

The unique physiology of neonates during the first few days of life adds another level of complexity to the use of a creatinine-based definition. SCr is reflective of the mother's renal function at birth. Changes in intrarenal blood flow and vascular resistance ensue during the first few days of life resulting in a rapid increase in GFR. However, this increase in GFR is slower in premature infants and somewhat variable among infants born with the same GA. In full-term infants, the SCr begins to fall reaching a level reflective of the infant's renal function by approximately 1 week of age.¹⁸ However, in premature infants in whom glomerular and tubular function are both more immature, an initial rise in SCr is often observed during the first 4 days of life,²⁰ which is likely related to an imbalance between maternal load, rate of creatinine generation by the infant, volume status, and level of renal function maturation. With the rapid acceleration of GFR during the first few days of life, SCr begins to fall after around day 4 of life. Therefore, in addition to the typical “rise in SCr” used to define AKI, we expanded the definition of AKI in this population to include failure of the creatinine to fall by greater than 0.2 mg/dL prior to discharge.

The major limitations to our study include the retrospective nature of data collection and the variable number of creatinines available for review. SCr was obtained per clinical indication or per protocol (for IVH prophylaxis or PDA treatment with indomethacin), and therefore creatinines were not obtained with the same frequency in all patients. The youngest GA cohort had the most SCr data starting from birth as all

were screened for IVH prophylaxis with indomethacin. More frequent creatinine monitoring in this cohort could result in overdiagnosis of AKI as some increases in creatinine may have been transient (e.g., prerenal azotemia) and not clinically relevant for the long term. Less frequent creatinine monitoring in the oldest cohort born with GA 29 to 32 weeks could result in underdiagnosis of AKI as mild episodes of AKI may have gone unnoticed, thereby exaggerating the difference in AKI incidence to some extent between the different GA cohorts. The long-term clinical relevance of these episodes is also unknown.

Another weakness of the study is that we did not address maternal/prenatal factors (e.g., preeclampsia) that might influence the risk of developing postnatal AKI.

Using a modified AKIN definition for AKI, we found a relatively high incidence of AKI (26%) among premature infants born prior to 32 weeks' GA who were admitted to our quaternary care NICU. The incidence of AKI was inversely related to GA with a risk of nearly 40% in those born under 29 weeks' GA and exceeding 60% in those born under 26 weeks' GA. Given nearly 60% of nephrons developing during the third trimester, it would be anticipated that the infants born prior to 26 weeks' gestation had the highest incidence of AKI. Rodriguez et al have shown through an autopsy study that nephron development can continue postnatally in premature infants for a limited time (until ~ 32 weeks corrected GA), but this process is hindered by the development of neonatal AKI. Premature infants still ultimately had fewer nephrons compared to full-term infants.²⁸ Sutherland et al recently also confirmed that renal development continues postnatally in premature infants, but the glomeruli are morphologically abnormal.²⁹ In contrast to the findings by Rodriguez et al, they did not find a reduced number of glomerular generations in the premature infants who completed nephrogenesis.

In our study, by univariate analysis, AKI was also found to be associated with lower birth weight, lower Apgar scores, clinical markers of increased illness severity (more frequent need for pressor support, longer duration of mechanical ventilation, more frequent exposure to treatment courses of nephrotoxic antibiotics), PDA, and NSAID exposure for treatment of PDA.

Epidemiologic studies have shown a clear association between low BW (< 2.5 kg), decreased nephron number and the development of CKD.³⁰ Low BW may occur secondary to prematurity and/or intrauterine growth restriction. One might hypothesize that infants born with fewer glomeruli that are also morphologically abnormal may be more susceptible to AKI. Although racial disparities in AKI incidence have been reported in adults with higher rates in African Americans, we did not find this association in our study.³¹ One might speculate that perhaps the influence of incomplete nephrogenesis overshadows the effect of race. However, our study is relatively small and larger studies are needed. We also did not find a gender association with AKI, which is not necessarily surprising given the major causes of neonatal AKI—renal hypoperfusion (secondary to hypoxic-ischemic injury, hypotension, and/or intravascular volume depletion) and

nephrotoxic medication exposure—would be anticipated to affect both sexes similarly.

Both PDA and its treatment with NSAIDs (indomethacin/ibuprofen) can independently result in renal injury by decreasing renal perfusion—the former by shunting blood away from the kidney and the latter by inhibiting intrarenal vasodilatation that is dependent on prostaglandin synthesis. In our population, infants may have been exposed to indomethacin prenatally when used for tocolysis, early postnatally for IVH prophylaxis, or during the neonatal period for treatment of a PDA. Unlike others, we did not find an association between AKI and indomethacin used for tocolysis.³² This may potentially relate to differences in dosing and timing of the tocolytic in relation to delivery; during the study period tocolysis with indomethacin was limited to 48 hours. Of the three potential exposures to indomethacin, treatment courses for PDA closure were associated with development of AKI in our group. In a subgroup analysis of patients who developed a PDA, we examined the relationship between AKI and the number of courses of indomethacin treatment. Seven patients who developed a PDA did not receive indomethacin treatment; of these, three developed AKI. Approximately 40% of patients who received one course of indomethacin developed AKI whereas over 80% of those receiving two or more courses of indomethacin developed AKI. The higher incidence of AKI among those requiring re-treatment may potentially be related to greater toxicity from higher indomethacin exposure or to the presence of a more hemodynamically compromising PDA that is harder to close. Though it is difficult to tease out the cause of the AKI, the data suggest that infants requiring re-treatment with NSAID for PDA are at higher risk for developing AKI. This group of infants may warrant closer monitoring of renal function, with particular attention to volume status and medication choices (avoiding nephrotoxins if a suitable alternative is available). We did not investigate the effect of younger GA at birth, chronologic age of patient when PDA developed, or antenatal exposure to indomethacin on the need for re-treatment for PDA closure.

Although AKI in our study was clearly associated with increased morbidity, using logistic regression, AKI did not independently predict death. This finding is in contrast to other recent studies of AKI.³³

Conclusion

Increases in SCr suggesting the development of AKI occur frequently in premature infants and are associated with increased morbidity. The highest incidence for AKI and the most severe cases were observed in the youngest GA cohort, suggesting that the most premature infants are the most vulnerable to developing AKI. Until recently, research in the field of neonatal AKI has been sparse and advances hindered by the lack of a uniform definition. As premature infant survival has dramatically improved over the past 20 years and as AKI is emerging as a risk factor for the development of CKD, it has become imperative for neonatologists and nephrologists to investigate the epidemi-

ology, risk factors, and short- and long-term renal consequences of premature birth and neonatal AKI. Despite advances in critical care, effective clinical interventions to treat AKI once established are still lacking. Therefore, understanding the epidemiology and risk factors for developing AKI is crucial as this may facilitate changes in clinical practice to prevent or minimize the risk for developing AKI.

Disclosures

None.

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