HHS Public Access

Author manuscript

Lancet Child Adolesc Health. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Lancet Child Adolesc Health. 2017 November ; 1(3): 184–194. doi:10.1016/S2352-4642(17)30069-X.

*Corresponding Author: David J Askenazi, MD, MsPH, Department of Pediatrics — Division of Pediatric Nephrology, University of Alabama at Birmingham, daskenazi@peds.uab.edu, Phone: +1–205–638–9781, Fax: +1–205–996–7590, Postal address: ACC 516, 1600 7TH Avenue South, Birmingham, AL 35233, USA.

**NKC Contributors

The following individuals served as collaborators and site investigators for the AWAKEN study. They collaborated in protocol development and review, local IRB submission, data collection, and participated in drafting or review of the manuscript:

David T. Selewski, MD, Subrata Sarkar, MD — C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, Michigan, USA.

Alison Kent, MD, Jeffery Fletcher, PhD — Centenary Hospital for Women and Children, Canberra Hospital, Australian National University Medical School, Canberra, Australia.

Carolyn L Abitbol, MD, Marissa DeFreitas, MD, Shahnaz Duara, MD — Holtz Children's Hospital, University of Miami, Miami, Florida, USA.

Jennifer R. Charlton, MD — University of Virginia Children's Hospital, Charlottesville, Virginia, USA.

Ronnie Guillet, MD, Carl D'Angio, MD, Ayesa Mian, MD, Erin Rademacher, MD — Golisano Children's Hospital, University of Rochester, Rochester, New York, USA.

Maroun J. Mhanna, MD, Rupesh Raina, MD, Deepak Kumar, MD — MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio, USA.

Namasivayam Ambalavanan, MD — Children's of Alabama, University of Alabama at Birmingham, Birmingham, Alabama, USA.

Ayse Akcan Arikan, MD, Christopher J. Rhee, MD — Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, USA.

Stuart L. Goldstein, MD, Amy T. Nathan, MD — Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

Alok Bhutada, MD, Shantanu Rastogi, MD — Maimonides Medical Center, Brooklyn, New York, USA.

Elizabeth Bonachea, MD, Susan Ingraham, MD, John Mahan, MD; Arwa Nada, MBBCH — Nationwide Children's Hospital, Columbus, Ohio, USA.

Patrick D. Brophy, MD, Tarah T. Colaizy, MD, Jonathan M. Klein, MD — University of Iowa Children's Hospital, Iowa City, Iowa, USA.

F. Sessions Cole, MD, T. Keefe Davis, MD — Washington University, St. Louis, Missouri, USA. Joshua Dower, BS, Lawrence Milner, MD, Alexandra Smith, MD — Tufts University School of Medicine, Boston, Massachusetts, USA.

Mamta Fuloria, MD, Kimberly Reidy, MD, Frederick J. Kaskel, MD — The Children's Hospital at Montefiore, Bronx, New York, USA

Jason Gien, MD, Katja M. Gist, DO — University of Colorado, Children's Hospital Colorado, Aurora, Colorado, USA.

Mina H. Hanna, MD — University of Kentucky, Lexington, Kentucky, USA.

Sangeeta Hingorani, MD, Michelle Starr, MD — University of Washington, Seattle Children's Hospital, Seattle, Washington, USA.

Catherine Joseph, MD, Tara DuPont, MD, Robin Ohls, MD, Amy Staples, MD — University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA.

Surender Khokhar, MD — Apollo Cradle, Gurgaon, Haryana, India.

Sofia Perazzo, MD, Patricio E. Ray, Mary Revenis, MD — Children's National Medical Center, George Washington University School of Medicine and the Health Sciences, Washington DC, USA.

Anne Synnes, MDCM — British Columbia Children's Hospital, Vancouver, British Columbia, Canada.

Pia Wintermark, MD, Michael Zappitelli, MD — Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada

Ethics Committee Approval

The University of Alabama at Birmingham Institutional Review Board (IRB) approved this collaborative study, and each center received approval from their respective IRBs.

Authors' contributions:

The authors have made the following contributions to this manuscript:

1. Substantial contributions to the conception or design of this work (DJA, JGJ, CM, CSW); or the acquisition (DJA, JGJ, SKS, SW, SR, ASC, RW, CM, JRS, SS), analysis (DA, LJB, RG), or interpretation of data (DJA, JGJ, LJB, SKS, SW, SR, DES, ASC, RW, CM, JRS, SS, CSW, JCK, RLG) for the work; AND

2. Drafting the work (DJA, JGJ, LJB) or revising it critically for important intellectual content (DJA, JGJ, LJB, SKS, SW, SR, DES, ASC, RW, CM, JRS, SS, CSW, JCK, RLG); AND

3. Final approval of the version to be published (DJA, JGJ, LJB, SKS, SW, SR, DES, ASC, RW, CM, JRS, SS, CSW, JCK, RLG); AND

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (DJA, JGJ, LJB, SKS, SW, SR, DES, ASC, RW, CM, JRS, SS, CSW, JCK, RLG).

Role of funding sources

Funding sources for this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflict of interest disclosures

All authors declare no real or perceived conflicts of interest that could affect the study design, collection, analysis and interpretation of data, writing of the report, or the decision to submit for publication.

Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study

Jennifer G. Jetton, MD[1], **Louis J. Boohaker, MPH**[2], **Sidharth K. Sethi, MD**[3], **Sanjay Wazir, MD**[4], **Smriti Rohatgi, MD**[5], **Danielle E. Soranno, MD**[6], **Aftab S. Chishti, MD**[7], **Robert Woroniecki, MD**[8], **Cherry Mammen, MD**[9], **Jonathan R. Swanson, MD**[10], **Shanty Sridhar, MD**[11], **Craig S. Wong, MD**[12], **Juan C. Kupferman, MD**[13], **Russell L. Griffin, PhD**[14], and **David J. Askenazi, MD**[15,*] **on behalf of the Neonatal Kidney Collaborative (NKC)**[**]

[1]Department of Pediatrics — Division of Nephrology, Dialysis and Transplantation, University of Iowa Stead Family Children's Hospital, Iowa City, Iowa, USA

[2]Department of Pediatrics — Pediatric Nephrology, University of Alabama at Birmingham

[3]Kidney and Urology Institute. Medanta The Medicity, Gurgaon, India

[4]Neonatology, Cloudnine Hospital, Gurgaon, Haryana, India

[5]Medanta, The Medicity, Gurgaon, Haryana, India

[6]Department of Pediatrics — Pediatric Nephrology. University of Colorado and Children's Hospital of Colorado, Aurora, Colorado, USA

[7]Department of Pediatrics, University of Kentucky, Lexington, Kentucky, USA

[8]Department of Pediatrics — Pediatric Nephrology. Stony Brook School of Medicine, Stony Brook, NY, USA

[9]Department of Pediatrics — Division of Nephrology, University of British Columbia

[10]Department of Pediatrics — Division of Neonatology, University of Virginia Children's Hospital, Charlottesville, Virginia, USA

[11]Department of Pediatrics — Neonatology. Stony Brook School of Medicine, Stony Brook, NY, USA

[12]Department of Pediatrics — Division of Nephrology, University of New Mexico, Albuquerque, New Mexico, USA

For full disclosure, we provide here an additional list of other author's commitments and funding sources that are not directly related to this study: David J Askenazi serves on the speaker board for Baxter (Baxter, USA), and the Acute Kidney Injury (AKI) Foundation (Cincinnati, OH, USA); he also receives grant funding for studies not related to this manuscript from National Institutes of Health — National Institutes of Diabetes and Digestive and Kidney Diseases (NIH-NIDDK, R01 DK103608 and NIH-FDA (R01 FD005092). Jennifer G Jetton is supported by the University of Iowa Institute for Clinical and Translational Sciences NIH U54TR001356. Juan C. Kupferman is on the speaker's Bureau and consultant for Alexion Pharmaceuticals. Robert Woroniecki is supported by the Department of Pediatrics at Stony Brook Children's hospital (NY, USA). AWAKEN investigators at the Canberra Hospital were supported by the Canberra Hospital Private Practice fund, and investigators at University of Virginia Children's Hospital were supported by a 100 Women Who Care Grant (100 Women Charitable Foundation, CA, USA).

[13]Department of Pediatrics — Pediatric Nephrology, Maimonides Medical Center, Albert Einstein College of Medicine, Brooklyn, New York, USA

[14]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, USA

[15]Department of Pediatrics — Division of Pediatric Nephrology, University of Alabama at Birmingham, Birmingham, USA

Abstract

Background—Single-center studies suggest that neonatal acute kidney injury (AKI) is associated with poor outcomes. However, inferences regarding the association between AKI, mortality, and hospital length of stay are limited due to the small sample size of those studies. In order to determine whether neonatal AKI is independently associated with increased mortality and longer hospital stay, we analyzed the Assessment of Worldwide Acute Kidney Epidemiology in Neonates (AWAKEN) database.

Methods—All neonates admitted to 24 participating neonatal intensive care units from four countries (Australia, Canada, India, United States) between January 1 and March 31, 2014, were screened. Of 4273 neonates screened, 2022 (47·3%) met study criteria. Exclusion criteria included: no intravenous fluids ≥48 hours, admission ≥14 days of life, congenital heart disease requiring surgical repair at <7 days of life, lethal chromosomal anomaly, death within 48 hours, inability to determine AKI status or severe congenital kidney abnormalities. AKI was defined using a standardized definition —i.e., serum creatinine rise of ≥0.3 mg/dL (26.5 mcmol/L) or ≥50% from previous lowest value, and/or if urine output was <1 mL/kg/h on postnatal days 2 to 7.

Findings—Incidence of AKI was 605/2022 (29·9%). Rates varied by gestational age groups (i.e., ≥22 to <29 weeks =47·9%; ≥29 to <36 weeks =18·3%; and ≥36 weeks =36·7%). Even after adjusting for multiple potential confounding factors, infants with AKI had higher mortality compared to those without AKI [(59/605 (9·7%) vs. 20/1417 (1·4%); p< 0.001; adjusted OR=4·6 (95% CI=2·5–8·3); p=<0·0001], and longer hospital stay [adjusted parameter estimate 8·8 days (95% CI=6·1–11·5); p<0·0001].

Interpretation—Neonatal AKI is a common and independent risk factor for mortality and longer hospital stay. These data suggest that neonates may be impacted by AKI in a manner similar to pediatric and adult patients.

Funding—US National Institutes of Health, University of Alabama at Birmingham, Cincinnati Children's, University of New Mexico.

Introduction

While the study of acute kidney injury (AKI) in critically ill neonates has lagged behind that in older populations, the last five years have seen an intensification of research in this area. Small, single center studies in neonates with congenital heart disease,[1–3] sepsis,[4–6] hypoxic ischemic injury,[6–8] infants who receive extracorporeal membrane oxygenation,[9–10] and very low birth weight infants,[11–15] suggest that AKI is common and that those with AKI have worse outcomes.

Although provocative, study that uses a contemporary definition, is multi-center and encorporates larger sample size are needed to adjustment for multiple potential confounders and allow for generalizeability. Moreover, studies that encompass the entire neonatal intensive care unit (NICU) population may offer comparative insights across different gestational age (GA) groups.

The AWAKEN (Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates) study, was a 3–month retrospective cohort analysis of critically ill neonates from 24 centers who make up the Neonatal Kidney Collaborative (NKC).[16] The primary hypothesis of AWAKEN is that neonatal AKI is associated with increased mortality and longer NICU length of stay (LOS), independent of demographics, co-morbidities and severity of illness.

Methods

Complete description of the formation of the NKC, and methods for developing the AWAKEN database have been published elsewhere.[16] The University of Alabama at Birmingham Institutional Review Board (IRB) approved this collaborative study, and each center received approval from their respective IRBs. The study was registered at ClinicalTrials.gov NCT02443389.

Study population

Medical records for all neonates admitted to 24 level 2–4 NICUs from four countries (Australia, Canada, India and the United States) between January 1 and March 31, 2014, were reviewed. Inclusion criteria included: 1) admission within the study period, and 2) receipt of intravenous fluids (IV) for at least 48 hours. Exclusion criteria included: 1) admission at ≥14 days of life, 2) congenital heart disease requiring surgical repair at <7 days of life, 3) lethal chromosomal anomaly, 4) death within 48 hours of NICU admission, and 5) severe congenital kidney and urinary tract abnormalities. These criteria were selected in order to enroll infants who were most likely to have serial serum creatinine (SCr) and urine output (UOP) measurements. Babies admitted to the NICU without need for IV fluids are generally only mildly ill (i.e. transient tachypnea of the newborn, transient hypoglycemia, advancement of feeds) and have limited time receiving intensive care.

Data collection

The variables extracted were chosen based on their relevance to the study of neonatal AKI. All data, including frequency of laboratory monitoring, reflect local standards of care and were dictated by the treating clinicians. All data was entered and stored in MediData Rave™ a web–based database.

Detailed description of data collection for AWAKEN has been previously published.[16] Briefly, data were organized in five components: baseline demographics, daily information for week 1, weekly “snapshots” for the remainder of the hospitalization, discharge data (captured at discharge or 120 days of age, whichever came first), and prolonged LOS data for those who were hospitalized longer than 120 days.

Acute kidney injury definition

All SCr values obtained during the study period were recorded. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup AKI definition — [17] modifed for neonates as previously published in neonatal studies[18–21] (see e-table 1). This definiton differs from KDIGO in three ways. First, UOP is reported in 24 hour increments rather than in 6–12 hour blocks, as most centers did not record UOP on an hourly basis. Second, to classify a patient with AKI^{SCr}, each SCr measurement was compared with the lowest prior SCr measurement to detect both an absolute and a percent rise from baseline. Comparison to the lowest prior SCr value is necessary because SCr values normally decline over the first weeks after birth such that the "baseline" SCr is constantly changing. Third, a SCr cutoff of 2·5 mg/dL (221 μmol/L) — instead of the 4.0 mg/dL (353.6 μmol/L) used in adults— was used for stage 3, since the cut-off of 2.5 mg/dL yields a GFR <10 mL/min/1·73 m^2.

When an infant had less than two SCr measurements assessed during hospitalization, it was considered that data was not sufficient for AKI^{SCr} classification. UOP threshold for AKI was set at ≤1 mL/kg/h averaged over 24 hours on days 2 to 7 after birth. If an infant did not have at least one day with quantifiable UOP in the medical record, it was considered to not have sufficient data to define AKI^{UOP}. Either diaper or catheter urine collection was acceptable as long as the UOP was quantifiable. Infants were classified as having AKI if they met either the SCr (AKI^{SCr}) and/or UOP (AKI^{UOP}). AKI max stage was classified as the highest of either SCr or UOP criteria. AKI severity was classified into one of three stages using traditional KDIGO methods (e-table 1).

Severity of illness score

The clinic risk index for babies II (CRIB II) score[22] was used to assess severity of illness for infants in the ≥22 and <29-week GA cohort in outcome analyses. This risk adjustment tool for assessing the probability of mortality incorporates five variables: sex, birthweight, GA, temperature at admission (°C), and base excess (mmol/L). This scoring system was validated in infants ≤32 weeks GA, therefore it was incorporated in the models for the smallest GA cohort only. There are no available, validated severity of illness scores for infants with GA ≥ 32 weeks.

Statistical analysis

Categorical variables were analyzed by proportional differences with the Chi-square test or Fisher exact test (where appropriate). All continuous variables were tested for normality using the Shapiro-Wilk Test. For normally distributed continuous variables the mean ± standard deviation (SD) were reported and analyzed using a Student t-test. For non-normally distributed variables, the median and interquartile range (IQR) were reported, and groups were compared using the Wilcoxon Signed Ranks test. Logistic regression was used to calculate crude odds ratios (ORs) and associated 95% confidence intervals (CIs) for the association between AKI and likelihood of death. To evaluate the association between AKI and LOS, linear regression was used to calculate the crude parameter estimates and associated 95% CI's. Multivariable logistic and linear regression models were run to account for potential confounding variables, and findings are reported as adjusted OR and adjusted

parameter estimate, respectively. Adjusted regression models were constructed using a backwards selection procedure with a significance level to stay <0·2. Separate regression models were created for the whole cohort as well as cohorts stratified by gestational age (GA) groups (GA ≥22 to <29 weeks; GA >29 to <36 weeks, and GA ≥36 weeks).

Time-to-event analysis for survival by AKI status and maximum AKI stage was performed using Kaplan-Meier curves for the entire cohort as well as for each GA category. In all analyses, a p-value <0·05 was considered statistically significant. SAS 9·4 (Cary, North Carolina) was used for all analyses.

Sensitivity analysis

The design of this study did not allow for standardized assessment for SCr values and/or UOP values. We were unable to decipher the AKI status in 140 infants. To determine whether these infants would have affected our results significantly, we performed a best-case/worst case sensitivity analysis for the incidence of AKI, hospital survival and hospital LOS. Similarly, we performed a sensitivity analysis to determine differences between infants born at centers that measured SCr more often (median SCr values ≥ 5) vs. less often (median SCr <5).

Results

Enrollment

A total of 4273 patients were admitted to NICUs at the 24 participating centers between January 1 and March 31, 2014. Of these, 2111 met one or more exclusion criteria or did not fulfill all inclusion criteria, and therefore, they were not enrolled in the study. Thus, we collected data from 2162/4273 (50·6%) of the potential subjects. In addition, 140 neonates were removed due to lack of adequate data to determine either a SCr or a UOP AKI status thus yielding a final sample of 2022 neonates. Figure 1 shows the enrolled and non-enrolled patients including reasons for exclusion. The distribution of GA within the cohort was 14%, 45%, and 41% for the three stratified groups (see figure 2).

Incidence of acute kidney injury

Table 1 shows the incidence of AKI by SCr vs. UOP criteria. There were 701/2162 (32·4%) patients who had fewer than two SCr measurements, and 383/2162 (17·7%) patients who did not have quantifiable UOP data for the first week of life. Of these, there were 140/2162 (6·5%) neonates who had insufficient UOP data as well as fewer than two SCr values, and therefore, could not receive any AKI classification and were excluded from the analysis. Of the remaining sample, 281/2022 (13·9%) had AKI^{UOP}, and 380/2022 (18·8%) had AKI^{SCr}. Only 56/2022 (2·8%) infants had both AKI^{SCr} and AKI^{UOP}. The incidence of AKI by either SCr or UOP criteria was 605/2022 (29·9%). e-Table-2 shows AKI status by SCr vs. UOP for AKI Stages 0–3. When classified according to highest AKI stage, 281/2022 (13·9%) reached AKI stage 1, 143/2022 (7·1%) reached AKI stage 2, and 181/2022 (8·9%) reached AKI stage 3. The incidence of AKI within each GA group is depicted in figure 2. AKI varied considerably between GA groups: 47·9% in the GA ≥22 to <29 weeks group, 18·3% in the ≥29 to <36 weeks group, and 36·7% in the ≥36 weeks group.

Patient characteristics

Characteristics of the entire cohort include: 56·5% were male infants; the majority (56·4%) were white, and 17·7% of admissions were of multiple gestation. The most common reasons for NICU admission were prematurity <35 weeks (52·1%), respiratory failure (46·1%), and sepsis evaluation (50·2%). Most infants (77·1%) were discharged home prior to 120 days of age, 79 infants (3·9%) died in the hospital, and 81 infants (4·0%) were in the hospital ≥120 days.

Table 2 depicts differences between those with and without AKI. Infants with AKI were more likely to belong to the highest birthweight category [302/605 (50·2%); p<0.05), were more likely to have been born outside the participating hospitals (i.e., "outborn"), and more likely to be admitted for hypoxic ischemic encephalopathy, seizures, congenital heart disease, necrotizing enterocolitis, and need for surgical evaluation; they were less likely to be admitted for prematurity and sepsis evaluation (all p<0·05). Polyhydramnios was more frequent in the AKI group compared with the No-AKI group (5.6% vs. 2.8%; p=0·002). There was no difference between the two groups in terms of rates of oligohydramnios, intrauterine growth restriction (IUGR), and gender. Mothers of infants with AKI were less likely to have chronic hypertension (6.3% vs. 9.9%; p< 0.01), pre-eclampsia (11.1% vs. 15.5%; p< 0.01), received steroids (28.6% vs. 39.7%; p< 0.001) or anti-hypertensives (7.4% vs 12.1%; p< 0.002). There was no difference in maternal history of eclampsia, kidney disease, illicit drug exposure or intrapartum complications between the AKI and No-AKI groups.

Center characteristics

Clinical care of critically ill neonates and frequency of kidney function monitoring reflect local standards of care. e-Table 3 summarizes the SCr count, rates of AKI, country, type of SCr assay, and mortality outcomes by center. The median and IQR of SCr counts per patient varied from 1(1,1) to 11 (3,26). The incidence of AKI by center varied from 2·5 to 74·1%. with the higher incidence of AKI noted in the centers with more SCr counts per patients. Survival rates varied from 77·8% to 100%, with only one US center having <90% survival rate.

Timing of first AKI event

Timing of the first AKI event for the entire cohort, and for each GA group, is shown in e-figure 1. First AKI events occurred most often during the first week after birth for the entire cohort as well as for the two older GA groups. Infants with GA ≥22 to <29 weeks had proportionally more AKI events after the first week than the other two GA groups.

Outcomes

Infants with either AKI^{SCr} or AKI^{UOP} criteria had higher mortality rate than those without AKI — i.e., 59/605 (9·7%) vs. 20/1417 (1·4%) p<0·0001. When stratified by AKI stage, mortality for infants with stage 3 had higher mortality rates than stage 2 or stage 1 (both p<0·001). Infants with AKI also had longer hospital LOS than those without AKI — i.e., median 23 days (IQR 10–61) vs. 19 days (IQR 9–36); p<0·0001. Infants with higher stages of AKI (stages 2 and 3) had longer LOS than those with No-AKI (p<0·0001). See table 3.

Table 4 shows the crude and adjusted associations between AKI and outcomes (mortality and LOS) for the entire cohort, while e-Tables 4–6 show analysis for each of the stratified groups. When the entire cohort was considered, AKI was significantly associated with increased mortality (crude OR=7·5 (95% CI=4·5–12·7); p<0·0001], and hospital LOS [crude beta parameter estimate =14·9 days (95% CI= 11·6–18·1); p<0·0001]. Even after adjusting for multiple demographic characteristics, interventions, and co-morbidities; those with AKI had over four-fold increased odds of death [adjusted OR= 4·6 (95% CI=2·5–8·3); p=<0·0001], and longer hospital LOS [adjusted parameter estimate 8·8 days (95% CI=6·1–11·5); p<0·0001]. Survivors with AKI had longer LOS than those without AKI [median 23 days (IQR 11, 64) vs. 19 days (IQR = 9–36) p<0.0001]. Non-survivors with AKI had similar LOS than those without AKI [median 13 (IQR 5–21) vs. 15 (IQR 5, 33) p=0.38]. Evaluation of the stratifed GA groups showed that after controlling for potential confounders, AKI status was independently associated with an increased adjusted odds of death (OR 3·7, 95% CI 1·4–9·7) for the ≥22 to <29 GA group; however, there was no observed adjusted association between AKI and LOS (see e-Table 4). For the ≥29 to <36-week GA group, AKI was independently associated with an increased adjusted odds of death (OR 5·1, 95% CI 1·6–16·5) and longer LOS (beta parameter estimate 9·6, 95% CI 5·4–13·8) (see e-Table 5). Among those with a GA ≥36 weeks, those with AKI had increased adjusted odds of death (OR 3·9, 95% CI 1·2–13·2) and longer LOS (beta parameter estimate 11·0, 95% CI 8·0–14·0) (see e-Table 6).

The mortality rate of the 140 infants who could not be given an AKI classification due to insufficient SCr/UOP data was similar to that of infants in the No-AKI group — i.e., 4/140 (2·9%) vs 20/1417 (1·4%), p=0.18.

Kaplan-Meier analysis

Kaplan-Meier survival curves for the entire cohort by any AKI and by stages of AKI are shown in figure 3, while curves for each GA group are shown in e-figure 2a–f. The majority of deaths took place within the first 50 days of hospitalization. When evaluating the entire cohort, survival was worse for infants with AKI compared to those without AKI. When the entire cohort was stratified according to AKI stage, infants with stage 3 had worse survival outcomes than infants with stage 2, stage 1, or no AKI. Interestingly, the AKI stage 1 group had worse survival than the AKI stage 2 group (p<0.001). Similar findings were seen when the survival curves were stratified by GA categories for any AKI as well as for stages of AKI.

Sensitivity Analysis

In the worst case scenario (140 subjects with missing data have AKI), the incidence of AKI in the AWAKEN cohort is 745/2162 (34·5%). AKI was significantly associated with mortality [crude OR=6·4 (95% CI=3·9–10·7); p<0.0001], and hospital LOS [crude parameter estimate 8·7 days (95% CI=5·7–11·6); p<0.0001]. After adjusting, those with AKI had higher adjusted odds of death [adjusted OR=4·2 (95% CI=2·3–7·6); p<0.0001], and longer hospital LOS [adjusted parameter estimate 5·3 days (95% CI=2·9–7·8); p<0.0001]. In the best case scenario (140 subjects with missing data do not have AKI), the prevalence of AKI in the AWAKEN cohort is 605/2162 (28%). AKI was significantly associated with

mortality [crude OR=6·9 (95% CI=4·2–11·2); p<0.0001], and hospital LOS [crude parameter estimate 16·5 days (95% CI=13·4–19·6); p<0.0001]. After adjusting, those with AKI had higher adjusted odds of death [adjusted OR=3·6 (95% CI=2·0–6·2); p<0.0001], and longer hospital LOS [adjusted parameter estimate 9·6 days (95% CI=7·0–12·2); p<0.0001]. Therefore, we conclude by this sensitivity analysis that not being able to provide the 140 infants with an AKI classification does not substantially affect our results

As expected, the incidence of AKI in the centers that measured SCr often (median SCr ≥ 5/infant) was higher than the incidence of AKI in centers that measured SCr less often (median SCr <5/infant) (347/840 (41.3%) vs. 258/182 (21.8%); p< 0.0001). Regardless of whether infants were in centers that checked SCr often or not, infants with AKI had higher adjusted odds of death and LOS, than infants without AKI. Specifically, in centers that performed SCr checks often, the adjusted OR for death was 3.1 (1.3 – 7.4) (p<0.01), and adjusted LOS was 13 (8.2 – 17.7) (p<0.001). In centers that performed SCr checks less often, the adjusted OR for death was 6.1 (2.5 – 14.6) (p<0.001) and adjusted LOS was 4.4 (1.2 – 7.7) (p<0.01).

Renal Replacement Therapy (RRT)

RRT was performed on 25/605 (4·1%) of neonates with AKI, which accounts for 25/2022 (1·2%) of neonates enrolled in the study, and 25/4273 (0·5%) of neonates admitted to the NICU during the 3 months period. The types of RRT included peritoneal dialysis alone (N = 9), continuous renal replacement therapy (CRRT) (N = 4), CRRT + ECMO (n=11) and peritoneal dialysis + CRRT (n=1). No infants were dialyzed with intermittent hemodialysis or slow low efficiency dialysis. Of those who received RRT, 19/25 (76%) survived. Infants with AKI who had RRT had lower survival than infants with AKI who did not have RRT [19/25 (76%) vs. 527/580 (90·9%) p < 0·01]. Neonates with AKI who received RRT tended to have longer LOS than infants with AKI who did not have RRT although this was not statistically significant [median 43 days (IQR 22–103) vs. 22 (10–61); p= 0.07].

Discussion

The overall incidence of AKI in the AWAKEN study was 29·9%, and those with AKI had > 4-fold higher independent odds of death and longer independent hospital LOS. This data supports findings from other critically ill neonates, children, and adults that show AKI is associated with poor outcomes, even after controlling for numerous confounders. The large sample size highlights practice variations in monitoring for neonatal AKI and shows differences in the incidence and outcomes across GA categories.

While the overall incidence of AKI in this cohort was 29·9%, the incidence by GA category showed a U-shaped distribution with the highest rates in the oldest (>36 weeks) and youngest (≥22 to <29 weeks). The incidence of AKI for the smallest GA groups was 47·9%, a finding in-line with published single center studies.[10–15] Similarly, the AKI rate in ≥36-week GA infants (i.e., 36·7%) is consistent with those in other studies of term infants.[6–8] The AKI incidence rates in the GA ≥29 to <36 group was 18·3%. AKI rates in the group have not been reported previously. Our data suggests that infants in this middle GA group are also at risk for AKI, but not to the same extent as other sick neonates. One possible

explanation may be that these infants are not as critically ill as the lowest and term GA groups. Compared to the middle GA group, those in the lowest GA group had more outborn deliveries, lower 1 and 5-minute APGAR scores, higher rates of respiratory failure, sepsis evaluation, HIE, NEC, and maternal vaginal bleeding. Those in the lowest GA category were less likely to be born SGA, and less likely born to mothers with pre-eclampsia. Infants who are delivered due to medical maternal conditions, such as pre-eclampsia, tend to be less ill compared to infants who are born premature for other reasons (i.e. chorioamnionitis). Compared to the middle GA group, infants in the term group were more likely to be outborn, had higher HIE, maternal infection, and meconium stained fluid during delivery.

We chose to use the KDIGO definition adapted for neonates for several reasons. First, a recent AKI workshop explored this definition and concluded that, while adjustments to the definition may be needed in the future as more data becomes available, this definition was a reasonable starting point for accruing epidemiology data on neonatal AKI.[23] Second, as this definition is the most widely accepted definition of AKI in pediatric and adult cohorts, it allows us to compare our data to other populations. Indeed, AWAKEN documents AKI rates in neonatal ICU patients similar to those in recently published multi-center studies of pediatric and adult ICU groups. For example, the Assessment of Worldwide AKI and Renal Angina Epidemiology (AWARE) study, a multi-national cohort of critically ill pediatric patients, demonstrated an AKI incidence of 26%.[24] Similarly, AKI-EPI, an adult multi-center study published in 2015,[25] showed an AKI incidence of 57%. AWAKEN, AWARE, and AKI-EPI all show that **a)** AKI is independently associated with clinical outcomes in ICU patients, **b)** higher stages of AKI portend worse outcomes, and **c)** including UOP in the definition of AKI identifies patients with renal injury who would not have been detected by SCr changes alone. Like the AWARE study, we found that most infants with AKI^{SCr} did not have AKI^{UOP} and vice versa. Despite these similarities, the AWAKEN study differs from the AWARE study in that the populations are different for the following reasons: a) AWARE excluded children < 3 months old, and b) the co-morbid conditions, stage of glomerular development, and baseline kidney function differ between neonates and children > 3 months. Nevertheless the conclusions remain similar — AKI is common and is independently associated with significant clinical outcomes. Thus, patients do not just die with AKI, rather, AKI is likely to be a critical component in the disease process.

We found that few infants met criteria for both types of AKI, which could be due to poor tubular function in premature infants, high rates of nephrotoxic medications which are known to cause non-oliguric AKI, or possibly due to ascertainment bias, as we only captured UOP data during the first week of life. Without measuring UOP, the incidence of AKI would have been reduced by approximately one third. Our findings suggest that quantification of UOP is an important part of evaluating for neonatal AKI. Given the difficulty in placing urinary catheters in some infants and efforts to minimize catheter-associated urinary tract infections in many institutions, the weighing of diapers may be a necessary and reasonable method (recognizing that this method may not be completely accurate, especially when urine is mixed with stool). To date, only a few studies have rigorously assessed oliguria as a measure of neonatal AKI.[2, 26] Due to the retrospective study design, we used cutoffs for UOP using 24-hour increments. A prospective study that documents UOP hourly and

accounts for factors that may affect urine output (e.g., use of diuretics) is greatly needed to delineate the most clinically significant threshold for oliguria in infants.

We found striking different kidney function surveillance patterns and AKI rates across centers. The median number of SCr checked per patient across all centers was 3 (IQR 1 to 8). The site with the lowest AKI rate (3%) also had the lowest number of SCr (median=1; IQR =1–1); while the site with the highest AKI rate (74·1%) was checked SCr much more often (median=8; IQR =5–15). Thus, it is possible that the incidence of neonatal AKI would have been even higher if more rigorous AKI surveillance protocols were implemented. Indeed, evidence-based guidelines that outline optimal parameters for monitoring kidney function in neonates are greatly needed.

The frequency of RRT use in NICU has not been previously described. Our data shows that RRT is used very sparingly in NICUs. Despite the limited use, the rates of survival in these cohorts are better than that reported in a large pediatric CRRT registry, which showed that survival in children < 5 kg was 44%.[27] Not surprisingly, compared to the entire cohort and to those with AKI who did not receive RRT, infants that receive RRT had higher mortality This is likely due to higher severity of illness and co-morbidies in those who receive RRT. We presume that without RRT, the survival in patients who received RRT would have been much worse. Having RRT devices available that were specifically designed for neonates likely would have increased the use of these devices in neonates with AKI, and presumably provided some of those with AKI a better chance for survival. The high incidence and mortality rates ascribed to AKI in NICU is justification for exploration of preventive and therapeutic strategies to limit the impact of AKI, and implementation of safer RRT devices designed specifically for neonates.[28]

The strengths of our study include the assembly of a large neonatal cohort, a multi-center approach, and successful collaboration between neonatology, pediatric nephrology, and epidemiology experts in neonatal AKI. These factors enabled a robust analysis adjusting for potential confounders using pre-specified contemporary definitions. Multi-disciplinary collaboration yields a more accurate interpretation of clinical data and events.

Despite these strengths, we acknowledge several important limitations. First, because this is a retrospective study, we had to rely on SCr and UOP data available in the medical records; therefore, we may have missed AKI cases. We tried to mitigate this issue by excluding patients with insufficient SCr and UOP data from outcomes analyses and performed a best case/worst case sensitivity analyses showing that the absence of data for the 140 patients did not alter our results significantly, as the associations with mortality and LOS remained significant in both scenarios. Second, we acknowledge that although the neonatal AKI definition used for this study has been vetted by an expert panel, the definition continues to be empiric. Findings from AWAKEN support the use of this definition in the future, although refinement may be necessary. Two groups for which the use of this definition requires additional clarification include infants whose SCr does not decline in the first week of life, and infants born with a very high SCr due to maternal kidney disease. In addition, future prospective studies should explore how different SCr/UOP cutoffs, and incorporation of other urine and serum biomarkers could improve the ability to reliably define AKI. Third,

we acknowledge that our inclusion/exclusion criteria did not allow for data collection on all neonates admitted to the NICU during the study period. As described in the methods section, selection criteria were chosen to identify sick infants who were most likely to have kidney function monitoring, and limit the number of infants admitted for mild or transient conditions requiring brief period of supportive care (i.e., transient tachypnea, transient hypoglycemia, or late prematurity). Given that infants who do not require intravenous fluids rarely have evaluations for SCr or quantified UOP data, limiting these types of patients reduced the number of infants without adequate data for analysis. Similarly, exclusion of infants who die within the first 48 hours of admission is justified as they do not always receive full medical support (e.g., if condition is felt to be lethal), and 48 hours is not ample time to see a SCr rise and thus be able to evaluate for AKI. Only 48/4273 (1.1%) of potential subjects were excluded because of death within 48 hours. Fourth, we acknowledge that in spite of the large sample size of our study, potential confounders between groups may have been missed. Finally, we did not assess or control for aspects of different health care systems, or seasons (AWAKEN enrolled infants born from January to March), that may have contributed to variation in antenatal care, mortality rates, and LOS.

In conclusion, this study provides substantial data depicting the epidemiology of neonatal AKI. We show differences in AKI incidence across GA groups and show the independent association between AKI and important clinical outcomes. Indeed, our findings are consistent with studies in other critically ill populations, highlighting that the kidney is not just an “innocent by-stander” in critical illness, but rather plays an important role in morbidity and mortality. Initiatives, such as the International Society of Nephrology 0 by 25 program[29], designed to reduce the incidence and sequelae of kidney injury need to also focus on critically ill neonates.. Growing evidence on the developmental origin of kidney disease,[30] highlights how neonates born premature, small for gestational age, and low birth weight are at risk of chronic kidney disease due to low nephron number at birth. Low nephron numbers may predispose infants to AKI as they may not have compensatory renal reserve at the time of stress. Furthermore, the impact by which AKI has on the optimal kidney growth in these infants may be substantial. For these reasons, improving our understanding of the global burden of neonatal AKI should be a priority for international agencies that advocate for neonates and for populations at risk for kidney disease.

The AWAKEN database will provide the ability to test additional questions that cannot be answered in the confines of one publication. Some of the analyses currently underway include evaluations of specific AKI risk factors, impact of fluid balance on outcomes, modifications to the neonatal AKI definition, the association of AKI with co-morbid neonatal conditions, and many others. Unfortunately, many questions about neonatal AKI cannot be addressed using this cohort due to the retrospective design of the study (i.e. cause of death, AKI epidemiology during specific events, the ability of urine biomarkers to diagnose AKI, and the long-term outcomes after AKI). To answer these and other questions, partnerships between neonatologists and nephrologists must continue. Carefully planned, adequately powered, prospective studies that monitor kidney injury and function data systematically, provide insights about AKI during high-risk events, capture the cause of death, and assess long-term renal recovery will be needed to further advance the field of neonatal AKI. Such studies will provide evidence to create guidelines for neonatologists,

pediatricians and pediatric nephrologists who care for these patients during and after discharge from the NICU.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Emma Perez-Costas, PhD (Department of Pediatrics, University of Alabama at Birmingham) performed the technical editing and proofreading of this manuscript.

The authors would also like to thank the outstanding work of the following clinical research personnel and colleagues for their involvement in AWAKEN: Ariana Aimani, Samantha Kronish, Ana Palijan, MD, Michael Pizzi — Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada; Laila Ajour, BS, Julia Wrona, BS — University of Colorado, Children's Hospital Colorado, Aurora, Colorado, USA; Melissa Bowman, RN — University of Rochester, Rochester, New York, USA; Teresa Cano, RN, Marta G. Galarza, MD, Wendy Glaberson, MD, Aura Arenas Morales, MD, Denisse Cristina Pareja Valarezo, MD — Holtz Children's Hospital, University of Miami, Miami, Florida, USA; Sarah Cashman, BS, Madeleine Stead, BS — University of Iowa Children's Hospital, Iowa City, Iowa, USA; Jonathan Davis, MD, Julie Nicoletta, MD — Floating Hospital for Children at Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA; Alanna DeMello — British Columbia Children's Hospital, Vancouver, British Columbia, Canada; Lynn Dill, RN — University of Alabama at Birmingham, Birmingham, Alabama, USA; Ellen Guthrie, RN — MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio, USA, Nicholas L. Harris, BS, Susan M. Hieber, MSQM — C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, Michigan, USA; Katherine Huang, Rosa Waters — University of Virginia Children's Hospital, Charlottesville, Virginia, USA; Judd Jacobs, Ryan Knox, BS, Hilary Pitner, MS, Tara Terrell — Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; Nilima Jawale, MD — Maimonides Medical Center, Brooklyn, New York, USA; Emily Kane — Australian National University, Canberra, Australia; Vijay Kher, DM, Puneet Sodhi, MBBS — Medanta Kidney Institute, The Medicity Hospital, Gurgaon, Haryana, India; Grace Mele — New York College of Osteopathic Medicine, Westbury, New York, USA; Patricia Mele, DNP — Stony Brook Children's Hospital, Stony Brook, New York, USA; Charity Njoku, Tennille Paulsen, Sadia Zubair — Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, USA; Emily Pao — University of Washington, Seattle Children's Hospital, Seattle, Washington, USA; Becky Selman RN, Michele Spear, CCRC — University of New Mexico Health Sciences Center Albuquerque, New Mexico, USA; Melissa Vega, PA-C — The Children's Hospital at Montefiore, Bronx, New York, USA); Leslie Walther RN — Washington University, St. Louis, Missouri, USA.

Funding sources

Cincinnati Children's Hospital Center for Acute Care Nephrology provided funding to create and maintain the AWAKEN Medidata Rave electronic database. The Pediatric and Infant Center for Acute Nephrology (PICAN) provided support for web meetings, for the NKC steering committee annual meeting at the University of Alabama at Birmingham (UAB), as well as support for some of the AWAKEN investigators at UAB (LBJ, RJG). PICAN is part of the Department of Pediatrics at the University of Alabama at Birmingham (UAB), and is funded by Children's of Alabama Hospital, the Department of Pediatrics, UAB School of Medicine, and UAB's Center for Clinical and Translational Sciences (CCTS, NIH grant UL1TR001417). Finally, the AWAKEN study at the University of New Mexico was supported by the Clinical and Translational Science Center (CTSC, NIH grant UL1TR001449) and by the University of Iowa Institute for Clinical and Translational Science (U54TR001356).

References

1. Taylor M, Carmona F, Thiaqarajan RR, et al. Mild postoperative acute kidney injury and outcomes after surgery for congenital heart disease. J Thorac Cardiovasc Surg. 2013; 146(1):146–152. [PubMed: 23040323]
2. Blinder JJ, Goldstein SL, Lee VV, et al. Congenital heart surgery in infants: effects of acute kidney injury on outcomes. J Thorac Cardiovasc Surg. 2012; 143(2):368–374. [PubMed: 21798562]
3. Wong JH, Selewski DT, Yu S, et al. Sever acute kidney injury following stage 1 Norwood palliation: effect on outcomes and risk of sever acute kidney injury at subsequent surgical states. Pediatr Crit Care Med. 2016; 17(7):615–623. [PubMed: 27099973]

4. Di Nardo M, Ficarella A, Ricci Z, et al. Impact of severe sepsis on serum and urinary biomarkers of acute kidney injury in critically ill children: an observational study. Blood Purif. 2013; 35(1–3): 172–176. [PubMed: 23428967]
5. Mathur NB, Agarwal HS, Maria A. Acute renal failure in neonatal sepsis. Indian J Pediatr. 2006; 73(6):499–502. [PubMed: 16816511]
6. Alaro D, Bashir A, Musoke R, Wanaiana L. Prevalence and outcomes of acute kidney injury in term neonates with perinatal asphyxia. Afr Health Sci. 2014; 14(3):682–688. [PubMed: 25352889]
7. Selewski DT, Jordan BK, Askenazi DJ, Dechert RE, Sarkar S. Acute kidney injury in asphyxiated newborns treated with therapeutic hypothermia. J Pediatr. 2013; 162(4):725–729. [PubMed: 23149172]
8. Askenazi DJ, Koralkar R, Hundley HE, Montesanti A, Patil N, Ambalavanan N. Fluid overload and mortality are associated with acute kidney injury in sick near-term/term neonate. Pediatr Nephrol. 2013; 28(4):661–666. [PubMed: 23224224]
9. Askenazi DJ, Ambalavanan N, Hamiton K, et al. Acute kidney injury and renal replacement therapy independently predict mortality in neonatal and pediatric noncardiac patients on extracorporeal membrane oxygenation. Pediatr Crit Care. 2011; 12(1):e1–6.
10. Fleming GM, Sahay R, Zappitelli M, et al. The incidence of acute kidney injury and its effect on neonatal and pediatric extracorporeal membrane oxygenation outcomes: A multicenter report from the Kidney Intervention During Extracorporeal Membrane Oxygenation Study Group. Pediatr Crit Care Med. 2016; 17(12):1157–1169. [PubMed: 27755398]
11. Koralkar R, Ambalavanan N, Levitan EB, McGwin G, Goldstein S, Askenazi D. Acute kidney injury reduces survival in very low birth weight infants. Pediatr Res. 2011; 69(4):354–358. [PubMed: 21178824]
12. Carmody JB, Swanson JR, Rhone ET, Charlton JR. Recognition and reporting of AKI in very low birth weight infants. Clin J Am Soc Nephrol. 2014; 9(12):2036–2043. [PubMed: 25280497]
13. Viswanathan S, Manyam B, Azhibekov T, Mhanna MJ. Risk factors associated with acute kidney injury in extremely low birth weight (ELBW) infants. Pediatr Nephrol. 2012; 27(2):303–311. [PubMed: 21809002]
14. Stojanovic V, Barisic N, Milanovic B, Doronjski A. Acute kidney injury in preterm infants admitted to a neonatal intensive care unit. Pediatr Nephrol. 2014; 29(11):2213–2220. [PubMed: 24839217]
15. Weintraub AS, Connors J, Carey A, Blanco V, Green RS. The spectrum of onset of acute kidney injury in premature infants less than 30 weeks gestation. J Perinatol. 2016; 36(6):474–480. [PubMed: 26796125]
16. Jetton JG, Guillet R, Askenazi DJ, et al. Assessment of worldwide acute kidney injury epidemiology in neonates: Design of a retrospective cohort study. Front Pediatr. 2016; 4:68. [PubMed: 27486571]
17. Kellum JA, Lameire N. KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013; 17(1):204. [PubMed: 23394211]
18. Jetton JG, Askenazi DJ. Acute kidney injury in the neonate. Clin Perinatol. 2014; 41(3):487–502. [PubMed: 25155722]
19. Stoops C, Sims B, Griffin R, Askenazi DJ. Neonatal acute kidney injury and the risk of intraventricular hemorrhage in the very low birth weight infant. Neonatology. 2016; 110(4):307–312. [PubMed: 27490643]
20. Askenazi D, Patil NR, Ambalavanan N, et al. Acute kidney injury is associated with bronchopulmonary dysplasia/mortality in premature infants. Pediatr Nephrol. 2015; 30(9):1511–1518. [PubMed: 25808019]
21. Sarkar S, Askenazi DJ, Jordan BK, et al. Relationship between acute kidney injury and brain MRI findings in asphyxiated newborns after therapeutic hypothermia. Pediatr Res. 2014; 75(3):431–435. [PubMed: 24296799]
22. Parry G, Tucker J, Tarnow-Mordi W. UK Neonatal Staffing Study Collaborative. CRIB ii: an update of the clinical risk index for babies score. Lancet. 2003; 361:1789–91. [PubMed: 12781540]

23. Zappittelli M, Ambalavanan N, Askenazi DJ, et al. Developing a neonatal acuted kidney injury definition. A report form the NIDDK neonatal AKI workshop. Pediatr Res. 2017 in press.
24. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. AWARE Investigators. Epidemiology of acute kidney injury in critically ill children and young adults. N Engl J Med. 2017; 376(1):11–20. [PubMed: 27959707]
25. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI–EPI study. Intensive Care Med. 2015; 41(8):1411–1423. [PubMed: 26162677]
26. Bezerra CT, Vaz Cunha LC, Liborio AB. Defining reduced urine output in neonatal ICU: importance for mortality and acute kidney injury classification. Nephrol Dial Transplant. 2013; 28(4):901–909. [PubMed: 23348885]
27. Askenazi DJ, Goldstein SL, Koralkar R, et al. Continuous renal replacement therapy for children ≤ 10 kg: a report from the prospective pediatrics continuous renal replacement therapy registry. J Pediatr. 2013; 162(3):587–592. [PubMed: 23102589]
28. Ronco C, Garzotto F, Brendolan A, et al. Continuous renal replacement therapy in neonates and small infants: development and first-in human use of a miniaturized machine (CARPEDIEM). Lancet. 2014; 383(9931):1807–1813. [PubMed: 24856026]
29. Mehta RL, Burdmann EA, Cerda J, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 global snapshot: a multinational cross-sectional study. Lancet. 2016; 387(10032):2017–2025. [PubMed: 27086173]
30. Luyckx VA, Perico N, Somaschini M, et al. A developmental approach to the prevention of hypertension and kidney disease: a report from the low birth weight and nephron number working group. Lancet. 2017 S0140-6736(17)30576–30577.

Research in context

Evidence before this study

Prior to undertaking this project in 2014, we searched PubMed (no date restrictions) for all studies of acute kidney injury (AKI) in neonates using the following search terms: neonatal, neonate, infant, kidney injury, acute kidney injury, renal failure, acute renal failure. Reference lists for each study obtained through PubMed were reviewed in order to identify additional studies not previously identified. The multi-disciplinary nature of the Neonatal Kidney Collaborative allowed for input from members familiar with the neonatology as well as pediatric nephrology literature. All studies identified include either retrospective or prospective observational data from single centers with small sample sizes. Most studies are limited to select subsets of patients such as very low birth weight infants, infants with perinatal asphyxia, sepsis, or receipt of extracorporeal membrane oxygenation. Only one study included urine output criteria in the definition of AKI; the rest use only SCr-based definitions. In addition, multiple different serum creatinine-based AKI definitions have been used, making it difficult to compare data across studies.

The incidence of neonatal AKI based on published studies ranges from 3–71%, a wide range that reflects heterogeneity in patient selection, frequency and type of monitoring, and the AKI definition used. Most of these studies show that AKI is associated with poor outcomes, but are limited by small sample size when controlling for potential confounders.

Added value of this study

AWAKEN (Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates) is the largest neonatal AKI study to date. It is the first multi-center, multi-national project and the first to include infants hospitalized in the neonatal intensive care unit across the gestation age spectrum, allowing us to make comparisons across gestational age groups. This study documents that approximately 30% of sick neonates admitted to the NICU develop AKI, and that neonatal AKI is associated with morbidity and mortality independent of multiple potential confounders. The use of a standardized AKI definition modified from one that is widely accepted for use in pediatric and adult cohorts allows for comparison of this data to that from adult and pediatric intensive care unit populations. This study will help move the field forward toward the establishment of a common framework for neonatal AKI research.

Implications of all the available evidence

This work improves our understanding of the incidence of AKI in the NICU and its association with important clinical outcomes in these patients. AKI affects neonates of all gestational ages. Consistent with studies in other critically ill populations, neonatal AKI is not simply an incidental finding but a key event that impacts mortality and hospital length of stay. Future studies that capture AKI systematically during high-risk events are greatly needed. With AWAKEN as a foundation, additional studies will provide data needed to support the development of evidence-based monitoring guidelines for use by

neonatologists, pediatricians and pediatric nephrologists as they care for patients with AKI in the NICU as well as those at risk for chronic kidney disease in the future. Strategies designed to prevent AKI and therapies to reduce the burden of AKI, including renal support devices designed for neonates, are greatly needed to improve the outcomes of these vulnerable infants.

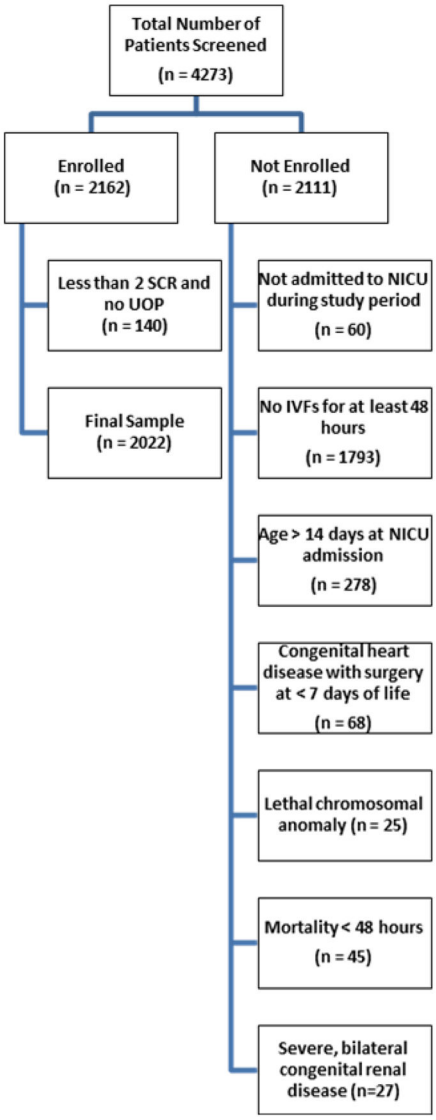

Figure 1. Flow chart of patients enrolled and not enrolled

UOP, urine output; IVFs, intravenous fluids; SCr, serum creatinine.

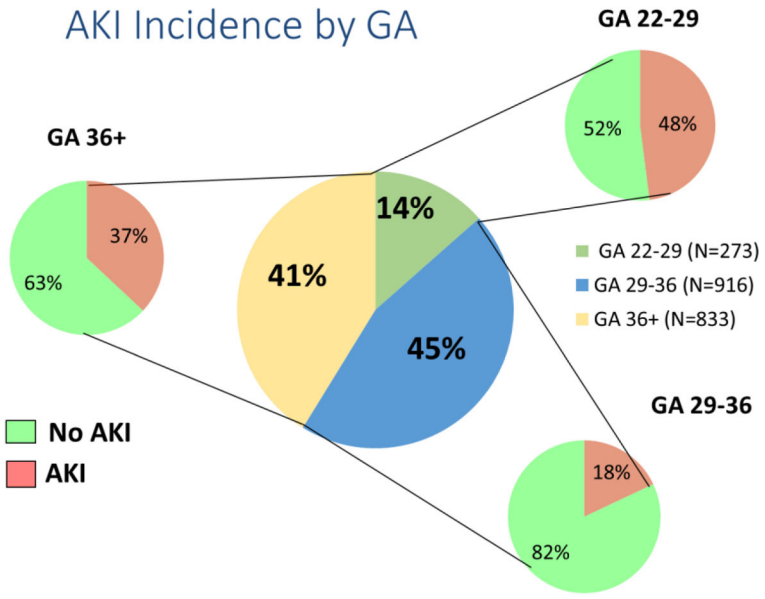

Figure 2. Schematic representation of gestational age distribution in the cohort

Gestational age (GA) is presented in weeks. AKI, acute kidney injury.

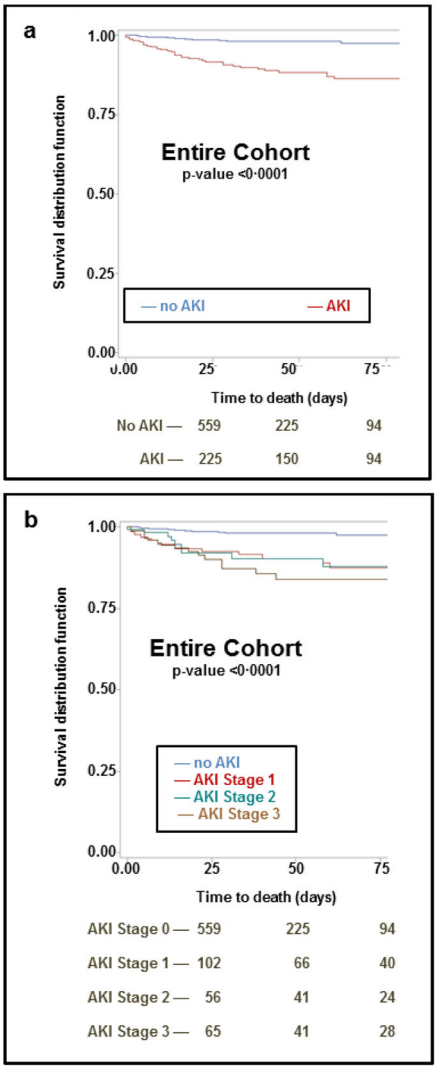

Figure 3. Acute kidney injury (AKI) and survival a)
Survival for entire cohort AKI vs no-AKI. **b)** Survival for entire cohort comparing no-AKI and the three stages of AKI.

Table 1

Acute Kidney Injury (any stage) by Urine Output and Serum Creatinine Criteria: N (% of total)

		SCr AKI status			
		Missing	**No**	**Yes**	**Totals****
UOP AKI status	Missing	140 *	177 (8·7%)	66 (3·3%)	243 (12·0%)
	No	469 (21·7%)	771 (38·1%)	258 (12·7%)	1498 (74·1%)
	Yes	92 (4·3%)	133 (6·6%)	56 (2·8%)	281 (13·9%)
	Totals**	561 (27·7%)	1081 (53·5%)	380 (18·8%)	2022 ** (100·0%)

N (% of total); UOP= Urine Output, SCr= Serum Creatinine, AKI= Acute Kidney Injury

* Excluded from all calculation because this 140 patients were lacking enough data for both UOP and SCr.

** Totals calculations exclude the 140 patients that were missing adequate UOP and SCr data.

Lancet Child Adolesc Health. Author manuscript; available in PMC 2018 November 01.

Table 2

Patients' Characteristics

	No AKI (n=1417)	AKI (n=605)	*P*-value
Infant Variables			
Gender (male)	795 (56·1%)	347 (57·4%)	0·12
Ethnicity			0·03
Hispanic	198 (14·0%)	60 (9·9%)	
Non-Hispanic	1004 (70·8%)	441 (72·9%)	
Unknown	215 (15·2%)	104 (17·2%)	
Race			0·07
White	777 (54·8%)	364 (60·2%)	
Black	271 (19·1%)	107 (17·7%)	
Other	369 (26·0%)	134 (22·1%)	
Site of delivery (outborn)	505 (35·6%)	349 (57·7%)	<0·0001
Gestational age			<0·0001
22 0/7 – 28 6/7 weeks	142 (10·0%)	131 (21·6%)	
29 0/7 – 35 6/7 weeks	748 (52·8%)	168 (27·8%)	
≥ 36 weeks	527 (37·2%)	306 (50·6%)	
Birthweight			<0·0001
≤ 1000 gm	112 (7·9%)	119 (19·8%)	
1001 – 1500 gm	238 (16·8%)	57 (9·5%)	
1501 – 2500 gm	552 (39·0%)	124 (20·6%)	
≥ 2501 gm	513 (36·3%)	302 (50·2%)	
Apgar 1 Minute[b]	7·00 (5·00, 8·00)	6·00 (3·00, 8·00)	<0·0001
Apgar 5 Minutes[b]	8·00 (7·00, 9·00)	8·00 (6·00, 9·00)	<0·0001
Reason for admission[a]			
Prematurity < 35 weeks	791 (55·8%)	263 (43·5%)	<0·0001
Respiratory symptoms	314 (22·2%)	150 (24·8%)	0·20
Respiratory failure	651 (45·9%)	281 (46·5%)	0·84
Sepsis evaluation	742 (52·4%)	274 (45·3%)	0·004
HIE	70 (4·9%)	48 (7·9%)	0·01
Seizures	33 (2·3%)	37 (6·1%)	<0·0001
Hypoglycemia	168 (11·9%)	50 (8·3%)	0·02
Hyperbilirubinemia	32 (2·3%)	29 (4·8%)	0·002
Metabolic evaluation	8 (0·6%)	12 (2·0%)	0·003
Trisomy 21	14 (1·0%)	9 (1·5%)	0·33
Congenital heart disease	34 (2·4%)	48 (7·9%)	<0·0001
Necrotizing enterocolitis	6 (0·4%)	15 (2·5%)	<0·0001
Omphalocele/Gastroschisis	32 (2·3%)	15 (2·5%)	0·76

	No AKI (n=1417)	AKI (n=605)	*P*-value
Need for surgical evaluation	47 (3·3%)	48 (7·9%)	<0·0001
Meningomyelocele	9 (0·6%)	8 (1·3%)	0·12
SGA	306 (21·6%)	117 (19·4%)	0·27
LGA	58 (4·1%)	40 (6·6%)	0·02
Maternal Variables			
Maternal age (years)	28·6 ± 6·2	28·3 ± 5·9	0·24
Infections			
Bacterial	120 (8·5%)	66 (10·9%)	0·08
Viral	35 (2·5%)	23 (3·8%)	0·10
Diabetes	203 (14·3%)	68 (11·2%)	0·06
Hypothyroidism	64 (4·5%)	33 (5·5%)	0·37
Chronic Hypertension	140 (9·9%)	38 (6·3%)	0·01
Kidney disease	12 (0·9%)	6 (1·0%)	0·75
Pre-eclampsia	220 (15·5%)	67 (11·1%)	0·01
Eclampsia	17 (1·2%)	8 (1·3%)	0·82
IUGR	136 (9·6%)	52 (8·6%)	0·48
Oligohydramnios	65 (4·6%)	33 (5·5%)	0·41
Polyhydramnios	39 (2·8%)	34 (5·6%)	0·002
Hemorrhage	40 (2·8%)	23 (3·8%)	0·25
Multiple Gestation	291 (20·5%)	67 (11·1%)	<0·0001
Assisted conception	112 (7·9%)	37 (6·1%)	0·003
Drugs used during pregnancy			
Steroids	563 (39·7%)	173 (28·6%)	<0·0001
ACE-inhibitors	0 (0·0%)	0 (0·0%)	na
NSAIDs	46 (3·2%)	16 (2·6%)	0·47
Antihypertensives	172 (12·1%)	44 (7·4%)	0·002
Illicit drugs	115 (8·1%)	49 (8·1%)	0·99
Tobacco	156 (11·0%)	64 (10·6%)	0·78
Alcohol	27 (1·9%)	9 (1·5%)	0·52
SSRIs	42 (3·0%)	17 (2·8%)	0·85
Intrapartum complications			
Nuchal cord	85 (6·0%)	40 (6·6%)	0·60
Meconium	142 (10·0%)	74 (12·2%)	0·14
Severe vaginal bleeding	58 (4·1%)	33 (5·5%)	0·18
Shoulder dystocia	13 (0·9%)	7 (1·2%)	0·62
Disposition			<0·0001
Discharged within 120 days	1156 (81·6%)	400 (66·1%)	
Still in NICU at ≥120 days	28 (2·0%)	53 (8·8%)	
Transfer convalescent care	200 (14·1%)	73 (12·1%)	

	No AKI (n=1417)	AKI (n=605)	*P*-value
Transfer escalated care	13 (0·9%)	20 (3·3%)	
Died in hospital	20 (1·4%)	59 (9·7%)	

*$P<0·05$

[a]Reason for admission - may be more than one

[b]Continuous variables shown by b are reported mean (25% IQR, 75% IQR) otherwise are reported by mean and sd.

Abbreviations: HIE=hypoxic ischemic encephalopathy; SGA=small for gestational age; LGA=large for gestational age; HTN=hypertension; IUGR=intra-uterine growth retardation; ACE=angiotensin converting enzyme; NSAID=non-steroidal anti-inflammatory drug; SSRI=serotonin uptake inhibitors

Table 3

Clinical Outcomes by Acute Kidney Injury Status.

	ANY AKI			AKI MAX Stage				
	NO (n=1417)	**YES (n=605)**	**p-value**	**0 (n=1417)**	**1 (n=281)**	**2 (n=143)**	**3 (n=181)**	**p-value**
Survived			<0·0001					<0·0001
Yes	1397 (98·6%)	546 (90·3%)		1397 (98·6%)	255 (90·7%)	133 (93·0%)	158 (87·3%)	
No	20 (1·4%)	59 (9·7%)		20 (1·4%)	26 (9·3%)	10 (7·0%)	23 (12·7%)	
LOS (Days)	19 (9, 36)	23 (10, 61)	<0·0001	19 (9, 36)	18 (9, 55)	30 (11, 79)	27 (13, 59)	<0·0001

Note that there were 140 enrolled patients with <2 serum creatinine measurements and no urine output data collected. Note also that among the subjects who did not die, 306 were transferred for convalescence or escalation of care.

AKI= Acute Kidney Injury, LOS= Length of stay expressed as median (25·75% IQR)

Table 4

Prediction Models for Clinical Outcomes.

	Crude	p-value	Adjusted	p-value
Mortality	OR=7·5 (4·5 – 12·7)	<0·0001	OR=4·6 (2·5 – 8·3) *	<0·0001
Length of Stay (Days)	Parameter Estimate 14·9 (11·6 – 18·1)	< 0·0001	Parameter Estimate *** 8·8 (6·1 – 11·5)	<0·0001

* Logistic model for mortality adjusted for Neonatal Height, Admission for Seizures, Admission for Congenital Heart Disease, Mode of Delivery, Neonatal Intubation, Neonatal Chest Compression, and Admission for Other Reasons

** Linear model for LOS adjusted for Gestational Age, Birthweight, Neonatal Intubation, Neonatal Chest Compression, Admission for Prematurity, Admission for Respiratory Symptoms, Admission for Respiratory Failure, Admission for NEC, Admission for Omphalocele, Maternal Multiple Gestation, Maternal use of NSAIDs, Neonatal Height, Neonatal Head Circumference, Neonatal APGAR of 5 minutes, and Admission for Other Reasons